CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

205552 Clinical Pharmacology Review

NDA	205552
Submission Date:	28th June 2013
Brand Name:	Imbruvica™
Generic Name:	ibrutinib
Formulation:	140 mg Capsules
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OCP Division:	Division of Clinical Pharmacology V
OND Division:	Division of Hematology Products
Applicant:	Pharmacyclics
Submission Type; Code:	0000/1
Proposed Dosing regimen:	MCL: 560 mg (4 x 140 mg capsules) once daily (b) (4)
Proposed Indication:	Original 1: Mantle cell lymphoma (MCL) (b) (4)

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1 EXECUTIVE SUMMARY

Ibrutinib is an irreversible Bruton's tyrosine kinase (BTK) inhibitor that binds to a cysteine residue (Cys-481) in the BTK active site. It is proposed for the treatment of patients with mantle cell lymphoma (MCL; Original NDA 1) [redacted] The applicant proposes oral dosing regimens of 560 mg once daily in MCL [redacted]

To support the approval of ibrutinib, the applicant submitted two pivotal clinical trials: a phase 2 trial (PCYC-1104-CA) in patients with MCL and a phase 1b/2 trial (PCYC-1102-CA) in patients with CLL. PCYC-1102-CA was an open-label trial in elderly treatment naïve (N=31) or relapsed/ refractory (N=82) CLL that evaluated ibrutinib at daily doses of 420 mg or 840 mg. Trial PCYC-1104-CA was an open label, non-randomized trial in patients with relapsed or refractory MCL (N=111) that evaluated ibrutinib at 560 mg daily. Original NDA 1 is for the MCL indication [redacted] Treatment with ibrutinib resulted in an ORR of 65.8% (95% CI: 56.2, 74.5) and a CR rate of 17.1% in the overall MCL study population. The safety database is small and does not include long term data. The median duration of treatment with ibrutinib was 8.3 months and the median dose intensity was 550 mg/day.

Pharmacokinetic data to support the clinical pharmacology program were submitted for the two pivotal trials and three additional trials (mass balance trial, CYP3A4 inhibitor trial and a dose-escalation trial). No exposure-response relationship was observed for effectiveness at the dose of 560 mg in MCL. No exposure-response relationship was observed for Grade 3 or 4 infection and infestation and Grade 3 or 4 neutropenia in the dose range of 420 - 840 mg in the pivotal phase 2 trials. The dose-response relationship for BTK occupancy and clinical response in the phase 1 dose escalation trial showed that maximum BTK occupancy and maximum response were achieved at doses of $\geq$ 2.5 mg/kg ($\geq$ 175 mg for average weight of 70 kg).

Ibrutinib is primarily metabolized by CYP3A4. No dose reduction is recommended for weak CYP3A4 inhibitors, but a dose reduction to 140 mg is recommended for concomitant use of a moderate CYP3A4 inhibitor. A dose recommendation could not be made for strong CYP3A4 inhibitors due to the 24-fold increase in exposure. Therefore, it is recommended that concomitant use be avoided for chronic CYP3A4 inhibitors and the dose of ibrutinib can be temporarily interrupted during the use of a short-term CYP3A4 inhibitor ($\leq$ 7 days). A 7 day interruption of ibrutinib dosing was supported by data from the pivotal trial where patients responded to therapy even when they required short term dose interruption during therapy. The concomitant use of strong CYP3A4 inducers should be avoided. There is insufficient data to recommend a dose of ibrutinib in patients with hepatic impairment. A PMR will be issued for the submission of the study report for the ongoing hepatic impairment trial.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology V, Pharmacometrics and Genomics have reviewed the information contained in NDA 205-552. This NDA is acceptable from a clinical pharmacology perspective. The adequacy of specific drug information is provided below:

Decision	Sufficiently Supported?	Recommendations and Comments
Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	Pivotal trials
Proposed dose for general population	☐ Yes ☒ No ☐ NA	The proposed doses are effective and appear to be safe given the limited data available. However, given what is known about the in vitro IC50, and the flat-exposure response seen between 2.5 mg/kg and 12.5 mg/kg a lower dose would likely be efficacious. See Section 2.2.4.4 for more information. Comment: 1. Evaluate lower doses of ibrutinib in future clinical development as data from the Phase 1 trial showed that maximum BTK occupancy and maximum response were achieved at doses of ≥ 2.5 mg/kg.
Proposed dose adjustment in specific patients or patients with comedications	☐ Yes ☒ No ☐ NA	Labeling Recommendations: 1. A dose reduction to 140 mg is recommended for concomitant use of a moderate CYP3A4 inhibitor PMR studies: 1. Submit final study report for trial evaluating the effect of a strong CYP3A4 inducer (rifampin) on ibrutinib exposure 2. Submit final study report for trial evaluating the effect of hepatic impairment on ibrutinib exposure
Pivotal bioequivalence studies	☒ Yes ☐ No ☐ NA	A formal bioequivalence trial was not performed to evaluate differences between the two clinical trial formulations used across studies. The to-be-marketed formulation (one of the clinical trial formulations) was used in >70% of the treatment cycles in the two pivotal trials.
Labeling	☒ Yes ☐ No ☐ NA	

1.2 POST MARKETING REQUIREMENTS

1. Submit the final study report for trial PCI-32765CLL1006 entitled, "An Open-Label, Multicenter, Pharmacokinetic Study of PCI-32765 in Subjects with Varying Degrees of Hepatic Impairment".
2. Submit the final study report for trial PCI-32765CLL1010 entitled, "An Open-Label, Sequential Design Study to Assess the Effect of Rifampin on the Pharmacokinetics of PCI-32765 in Healthy Subjects".

(b) (4)

1.3 COMMENTS TO THE APPLICANT

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

1.4 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Ibrutinib is an irreversible Bruton's tyrosine kinase (BTK) inhibitor that binds to a cysteine residue (Cys-481) in the BTK active site. It is proposed for the treatment of patients with mantle cell lymphoma (MCL) (b) (4) The applicant proposes oral dosing regimens of 560 mg once daily in MCL (b) (4)

Two pivotal clinical trials (a phase 1b/2 trial for CLL and a phase 2 trial for MCL) were submitted to support the proposed indication and dosing regimen. Pharmacokinetic data to support the clinical pharmacology program were submitted from the two pivotal trials and three additional trials (mass balance trial, CYP3A4 inhibitor trial and a dose-escalation trial).

Ibrutinib exposure increases with dose up to 840 mg. The median ibrutinib Tmax ranged from 1 to 2 hours and the mean elimination half-life ranged from 4 to 6 hours. The mean accumulation ratio observed at steady state ranged from 1 – 1.6. In a food effect cohort (sub-study) of trial 1102-CA, a high-fat meal increased ibrutinib exposure approximately 2-fold compared to when ibrutinib was administered after an overnight fast. In an oral mass balance trial, radioactivity recoveries in feces and urine were 81% (<1% unchanged ibrutinib) and 8%, respectively. The absolute bioavailability of ibrutinib has not been determined.

Ibrutinib is extensively metabolized and is primarily metabolized by CYP3A4. In a dedicated drug-interaction trial, concomitant ketoconazole (strong CYP3A4 inhibitor) increased ibrutinib Cmax 29-fold and AUC 24-fold. Based on preliminary clinical trial data and PBPK modeling, concomitant rifampin (strong CYP3A4 inducer) decreased the Cmax and AUC of ibrutinib by 14-fold and 13-fold, respectively. PBPK modeling predicted that moderate CYP3A4 inhibitors can increase ibrutinib exposure 6 - 9 fold and mild inhibitors can increase ibrutinib exposure 2-fold. In addition, a moderate inducer is predicted to decrease ibrutinib exposure 3-fold. A dedicated hepatic impairment trial is currently ongoing. The applicant reported that preliminary data suggest a 6-fold increase in exposures in moderate hepatic impairment (Child-Pugh B; N=3).

No exposure-response relationship was observed for effectiveness at the dose of 560 mg in MCL.

No exposure-response relationship was observed for Grade 3 or 4 infection and infestation and Grade 3 or 4 neutropenia in the dose range of 420 - 840 mg in the pivotal phase 2 trials. Dose-response relationship for BTK occupancy and clinical response in the phase 1 dose escalation trial showed that maximum BTK occupancy and maximum response were achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg).

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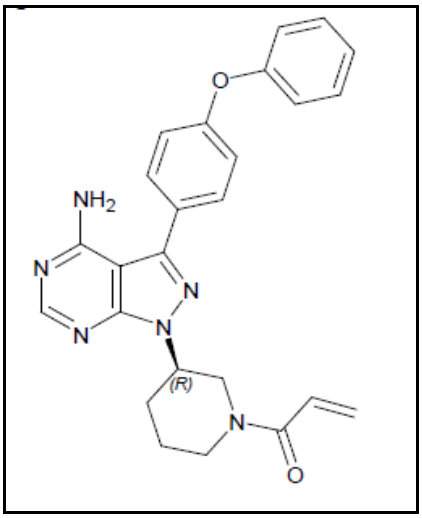
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

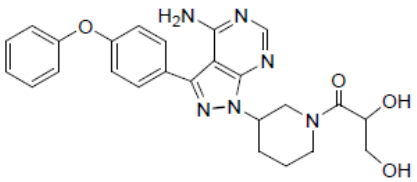
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Ibrutinib is planned to be available as 140 mg hard gelatin capsules for oral administration.

Figure 1: Structural Formula of Ibrutinib and its Active Metabolite (PCI-45227)



JNJ-54243761 (PCI-45227) = M37



Established names: Ibrutinib
Stereochemistry: The absolute configuration at the single stereocenter is (R).
Molecular Weight: 440.5 g/mole
Molecular Formula: $C_{25}H_{24}N_6O_2$
Partition coefficient (log P): 3.97 (pH=7)
Dissociation Constant (pKa): 3.74
Chemical Name: 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one
Melting Point Range: 149°C to 158°C
Solubility: Ibrutinib is insoluble in water (0.003 mg/mL)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Ibrutinib is an irreversible Bruton's tyrosine kinase (BTK) inhibitor (IC_{50}=0.46 nM) that binds to a cysteine residue (Cys-481) in the BTK active site. It is proposed for the treatment of patients with mantle cell lymphoma (MCL; Original NDA 1 (b) (4) who have received at least one prior therapy. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in several B-cell malignancies, including MCL and B-cell CLL. Ibrutinib is also

expected to inhibit Blk, Bmx/Etk, FGR, CSK and Txk (IC_{50}< 4 nM) to a lesser extent.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The applicant proposes oral dosing regimens of 560 mg once daily in MCL (b) (4) (b) (4)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical trials used to support dosing or claims?

To support the approval of ibrutinib, the applicant submitted two pivotal clinical trials; a phase 1b/2 trial (PCYC-1102-CA referred to as 1102-CA hereafter) in CLL and a phase 2 trial (PCYC-1104-CA referred to as 1104-CA hereafter) in MCL (**Table 1**).

1104-CA was an open label, non-randomized trial in patients with relapsed or refractory MCL (N=111) that evaluated ibrutinib at 560 mg daily. The primary efficacy endpoint was investigator assessed ORR. The key secondary efficacy endpoints were duration of response, time to response, PFS and overall survival. Treatment with ibrutinib resulted in an ORR of 65.8% (95% CI: 56.2, 74.5) and a CR rate of 17.1% in the overall study population.

(b) (4)

Table 1: Summary of the Pivotal Efficacy Trials

Study Number	Study Description	Treatment Groups	Primary Study Endpoint
PCYC-1104-CA (1104-CA)	Phase 2, open label, nonrandomized study in relapsed or refractory MCL (N=111)	Ibrutinib 560 mg/day	ORR

(b) (4)

Pharmacokinetic data are available for the two pivotal trials (intensive and sparse sampling) and three additional trials (intensive sampling). The three additional trials (**Table 2**) are a phase 1 dose-escalation trial, a mass balance trial and a drug interaction trial.

Table 2: Overview of Clinical Pharmacology Related Trials Submitted in the NDA

Study Number	Study Description	Treatment Regimen
PCYC-04753 (04753)	Phase 1, dose-escalation trial to determine MTD, PK and PD in patients with recurrent B-cell lymphoma (N=66)	Body Weight Based Cohorts: 1.25, 2.5, 5, 8.3 and 12.5 mg/kg/day for 28 on/ 7 off (35 day cycle) Continuous Dosing Cohorts: 8.3 mg/kg/day and 560 mg/day
PCI-2765CLL1002 (1002)	Phase 1 DDI healthy volunteer trial evaluating the effect of ketoconazole on the PK of Ibrutinib (N=18+3)	DDI Cohort (N=18): • Ibrutinib 120 mg on Day 1 and 40 mg on Day 7 • Ketoconazole 400 mg on Days 4 to 9 Exploratory Cohort (N=3): Ibrutinib 70 mg solution on Day 1 to determine dose for ADME trial
PCI-32765CLL1004 (1004)	Phase 1 mass-balance ADME healthy volunteer trial (N=6)	140 mg of ^{14}C-ibrutinib solution

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical trials?

The primary endpoint for the pivotal trials was overall response rate as determined by investigators & confirmed by an independent review committee. This endpoint has been used for previous approvals in MCL. Single agent bortezomib was FDA approved in December 2006 for MCL using a single arm phase 2 trial evaluating response rates.

BTK active-site occupancy was assessed in the three submitted trials with cancer patients. This PD marker was selected based on the mechanism of action of the drug (Refer to **Section 2.2.4.1** for further discussion).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Plasma samples from clinical trials were assessed for the parent drug (ibrutinib) and its metabolite, PCI-45227. Ibrutinib is an active moiety. PCI-45227 (M37) is an inhibitor of BTK, but is 15 times less potent compared to the parent. Ibrutinib is extensively metabolized to many metabolites. In the mass balance trial, ibrutinib and M37 combined were <10% of total radioactivity. Total radioactivity $AUC_{0\text{-last}}$ was 37-fold higher than that of ibrutinib in blood. However, other metabolites were not measured in other clinical trials.

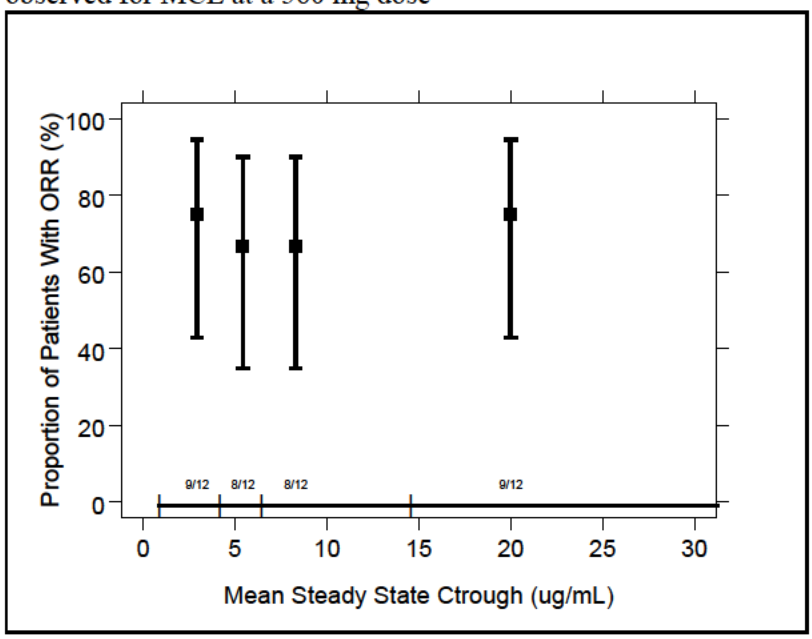
(b) (4)

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and PD marker?

There is no evidence of an exposure-response relationship for overall response rate (ORR) in the range of exposures observed following an ibrutinib dose 560 mg in mantle cell lymphoma (MCL) in 1104-CA (**Figure 2**). Steady state trough plasma concentrations were available from a total of 48 patients with MCL. In 1104-CA, trough concentrations were obtained on Days 1, 8, 15 and 22. Trough concentrations obtained on Day 8 or later were used to calculate the mean steady state trough concentrations used for exposure-response analyses.

Figure 2: No Exposure Response Relationship for Objective Response Rate (ORR) at Exposures observed for MCL at a 560 mg dose

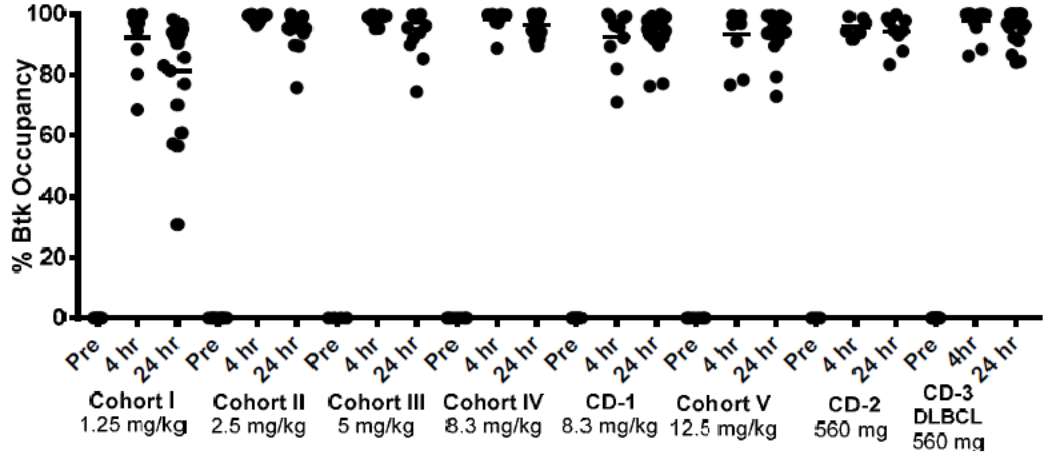


Dose-response relationships for BTK occupancy and clinical response in the phase 1 trial 04753 showed that maximum BTK occupancy and maximum response were achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg; **Figures 3 and 4**).

Trial 04753 evaluated ibrutinib daily doses of 1.25 to 12.5 mg/kg (actual doses of 80 - 1400 mg). Cohorts 1 - 5 received ibrutinib on 35-day treatment cycles (28 days on/ 7 days off). The doses of 8.3 mg/kg and 560 mg were also evaluated on a continuous dose schedule. As shown in **Figure 3**, maximum BTK occupancy was achieved at doses of 2.5 mg/kg (175 mg for the average 70 kg

body weight) and greater. Similarly, maximum clinical response (response rate) was also achieved at doses ≥ 2.5 mg/kg. BTK occupancy and clinical response rates were similar for continuous dosing (CD) and 35-day treatment cycle schedules. Patients with diffuse large B-cell lymphoma (DLBCL) had a lower response rate of 30%. For more details refer to the appendix in **Section 3.1**.

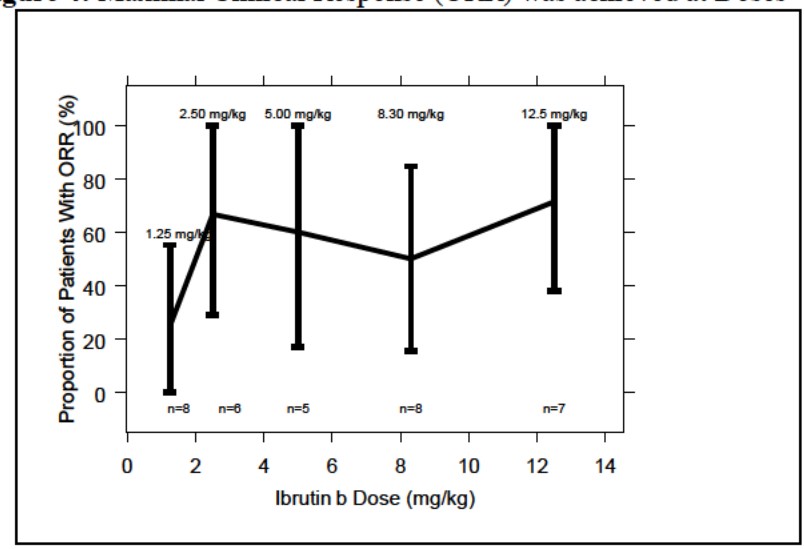
Figure 3: BTK Occupancy of > 90% at Doses ≥ 2.5 mg/kg in Trial 04753



Cohorts 1, II, III, IV and V received treatment in a 35-day treatment cycle and Cohorts CD-1,CD-2 and CD-3 received treatment as continuous dosing

Source: Applicant's Figure 10 in study-report-pcyc-04753.pdf

Figure 4: Maximal Clinical Response (ORR) was achieved at Doses > 2.5 mg/kg*.



*ORR for the CD-1,CD-2, CD-3 cohorts were, 67%, 66.7, and 30%, respectively

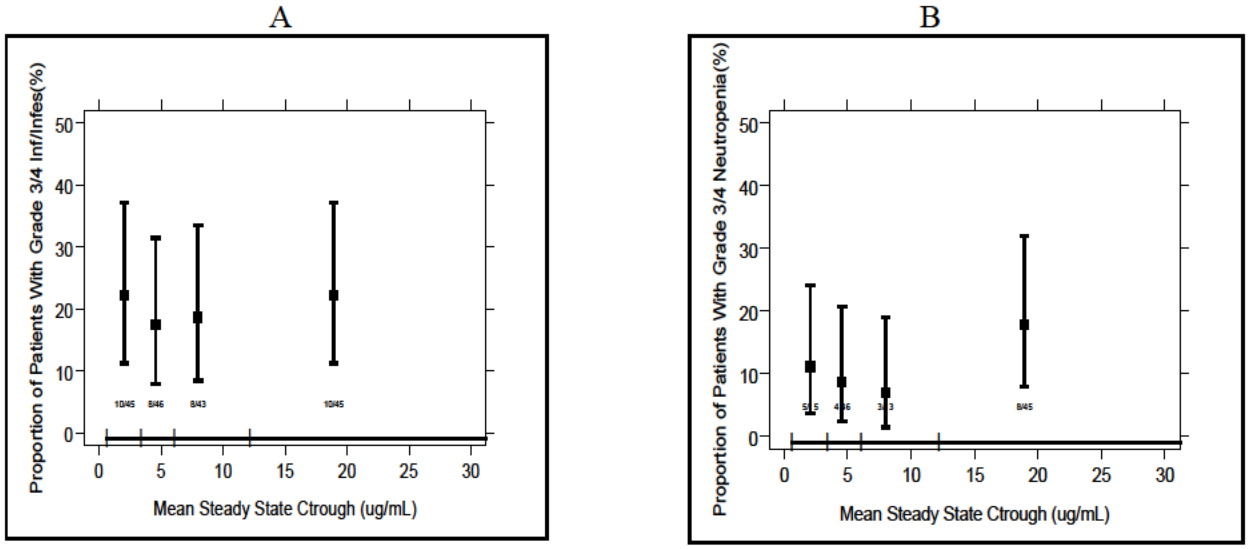
2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

There was no evidence of exposure-response relationships for Grade 3 or 4 infection and infestation and Grade 3 or 4 neutropenia observed in the range of exposures observed following

ibrutinib doses of 420 mg, 560 or 840 mg in the pivotal phase 2 trials.

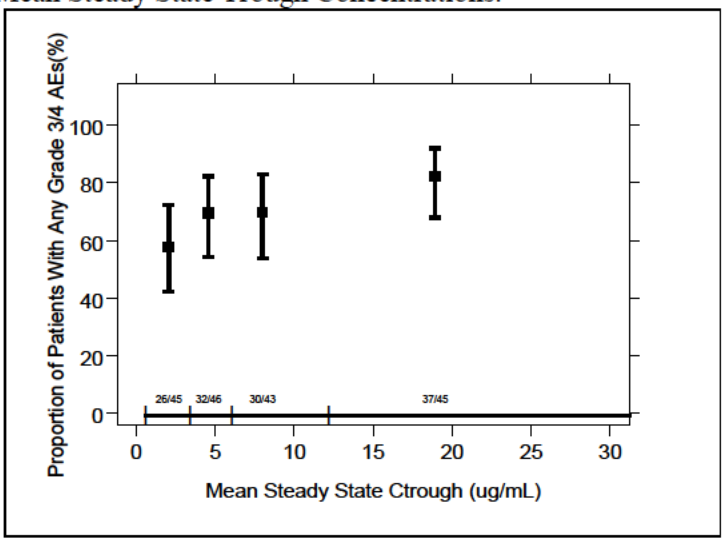
Steady state trough plasma concentrations were available from 48 patients with MCL and 110 patients with CLL. In 1104-CA, trough concentrations were obtained on Days 1, 8, 15 and 22. In 1102-CA trough concentrations were obtained on Days 1, 8 and 15. Trough concentrations obtained on Day 8 or later were used to calculate the mean steady state trough concentrations used for exposure-response analyses. Exposure safety analyses for ibrutinib were conducted using data from the 179 patients who were enrolled in the two pivotal phase 2 trials. The most frequent and important Grade 3 or higher (Grade 3+) adverse events were infections and infestations and neutropenia. Pharmacokinetic data were available from 125 patients from the phase 2 trials. The proportion of patients with Grade 3+ infections and infestations does not increase with increasing ibrutinib concentrations (**Figure 5**). Similarly Grade 3+ neutropenia did not increase with increasing ibrutinib concentration.

Figure 5: Proportion of Patients with Grade 3+ Infections and Infestations (A) and Grade 3+ Neutropenia (B) Does Not Increase with Increasing Mean Steady State Trough Concentrations



While an exposure response relationship for individual toxicities could not be identified (Grade 3+ neutropenia and Grade 3+ infections and infestations), there was a slight increase in the proportion of patients with any Grade 3+ adverse events with increasing mean steady state trough concentrations (**Figure 6**).

Figure 6: Proportion of Patients with any Grade 3+ Adverse Event Does Not Increase with Increasing Mean Steady State Trough Concentrations.



2.2.4.3 Does this drug prolong the QT or QTc interval?

The IC_{50} for inhibitory effect by ibrutinib on hERG channel current was 970 nM (427 ng/mL) and was 9600 nM (4229 ng/mL) for PCI-45227 (active metabolite). The non-clinical reviewer commented that ibrutinib can be considered a low-potency blocker of the hERG channel (Refer to non-clinical review).

A formal thorough QT trial has not been performed for ibrutinib. Formal ECG monitoring was performed in 2 single-arm trials (PCYC-04753 [n = 45] and PCYC-1102-CA [n = 67]). The QT-IRT evaluated the relationships between Δ QTcF and ibrutinib and PCI-45227 concentrations and did not observe an exposure-response relationship. QT-IRT has concluded that the submitted QTc data is inconclusive due to the following limitations in trial design:

- Baseline ECGs were not adequately collected. The applicant 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.

The QT/IRT is not proposing any labeling language and a PMR will be issued for the applicant to perform and submit the results of a thorough QT trial. The protocol was previously submitted and reviewed by QT-IRT. The applicant has stated that they plan to perform the trial in 2014.

2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant selected oral dosing regimens of 560 mg once daily in MCL (b) (4) The following can be considered regarding the dose selection of 560 (b) (4) mg daily:

- The IC50 for the inhibition of BTK by ibrutinib was 0.2 ng/mL (0.46 nM) in an in vitro protein kinase assay in which ibrutinib was incubated in purified kinase enzymes (see

Pharmacology/Toxicology review). Mean (range) steady-state PK trough concentrations of 9.2 µg/mL (0.6 – 68 µg/mL) were observed in the pivotal trials over the dose range of 420 to 840 mg.

- In the phase 1 dose escalation trial, full and sustained (> 90% at 24 hours) occupancy of the BTK active site was reached at ibrutinib doses ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg). Therefore, doses lower than the selected doses are expected to have sustained occupancy of the BTK active site in vivo with once daily dosing. In addition, the ORR was similar at doses of 2.5, 5, 8.3 and 12.5 mg/kg. The MTD was not reached in the dose escalation trial with doses of up to 12.5 mg/kg/day.
- The applicant states that 5/9 patients with MCL in the phase 1 trial received a daily dose of 560 mg and showed preliminary evidence of efficacy and tolerability. This led to the decision to evaluate only the 560 mg/day dose in 1104-CA.
- (b) (4)

Although the proposed dose (b) (4) acceptable based on the limited effectiveness and safety data in the limited (b) (4) MCL study population, the proposed doses are 2- to 3- fold higher than the lowest dose that resulted in maximum BTK occupancy and maximum response. Therefore, the applicant should consider exploring lower doses in future development programs.

(b) (4) In a sub-study performed as part of 1102-CA (N=16), a high-fat meal increased exposure about 2 fold compared to when the ibrutinib was dosed after an overnight fast. In the pivotal trials (1102-CA and 1104-CA), ibrutinib was given under the modified fasting conditions (b) (4). The modified fasting conditions may result in exposures higher than total fasting conditions, but lower than the 2 fold increase observed with a high fat meal (exposure may vary according to timing and content of meal). Considering the exposure response analyses, it is unlikely any potential differences in fasting conditions and modified fasting conditions would be meaningful. Therefore, we recommend that ibrutinib be dosed without regard to food. Please refer to **Section 2.5.4** for further discussion of food effect.

2.2.4.5 Do the exposure response relationships for efficacy and safety support the proposed dose adjustments for safety events?

Yes. In the proposed labeling, the applicant recommends a dose reduction in 140 mg increments for hematologic and non-hematologic adverse reactions. The minimum dose is (b) (4) and treatment will be discontinued if this dose is not tolerated. Based on **Figure 4**, dose decreases to 140 mg for safety events are not likely to reduce the effectiveness of ibrutinib.

This dose reduction plan was used in the pivotal trials. In the MCL trial 1104-CA, serious adverse events occurred in 62 patients (55.8%). Neutropenia, thrombocytopenia, anemia, and pneumonia were the most common Grade 3 and 4 treatment-emergent adverse events (TEAEs). Most were managed by dose interruptions. Doses were withheld for TEAEs in 44 (39.6%) patients and dose

reductions occurred in 16 (14.4%) patients. Discontinuations due to TEAEs occurred in 8 patients (7.2%).

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

Single dose PK

Single dose PK parameters (non-compartmental analysis) of ibrutinib are summarized (**Table 3)** using data from the dose escalation trial in patients with cancer. The first 5 cohorts evaluated body-weight based dosing (1.25 - 12.5 mg/kg/day) for 28 days with a 7 day rest period. Data from these cohorts was used to select the dose for continuous daily dosing (8.3 mg/kg or fixed 560 mg daily). One of the continuous dose cohorts was restricted to patients with diffuse large B-cell lymphoma (DLBCL) with ABC subtype. PK samples in Cycle 1 were collected on Day 1 at pre-dose and 0.5, 1, 2, 4, 6 and 24 hours post-dose.

The median ibrutinib and PCI-45227 Tmax ranged from 1 - 2 hours and the mean terminal $T_{1/2}$ from 4 - 7 hours (**Tables 3 and 4**). Inter-subject variability (CV %) for ibrutinib ranged from 58.5% to 136% for Cmax and 60.1% to 107% for $AUC_{0\text{-}24h}$. The CV% was high for both fixed dosing and body-weight based dosing. CV% for PCI-45227 ranged from 47.5% to 64.9% for Cmax and 40.6% to 61.8% for $AUC_{0\text{-}24h}$.The mean metabolite-to-parent ratios for PCI-4557 ranged from 0.7 - 3.4 with metabolite exposures exceeding parent in most cases. It is not clear why the metabolite exposures are lower in the DLBCL cohort, although the ibrutinib exposures are similar to the other 560 mg cohort. The Day 1 PK parameters observed in 1102-CA were similar to those seen in the dose escalation trial (**Table 5**).

Table 3: Summary of (Mean ± SD) Ibrutinib Pharmacokinetic Parameters after Single Dose Ibrutinib in Patients with Cancer in 04753

Treatment	Dose Range (mg)	N	Cmax (ng/mL)	$AUC_{0\text{-}24}$ (ng.h/mL)	[a]Tmax (hr)	$T_{1/2}$ (hr)	CV%	
							Cmax	$AUC_{0\text{-}24}$
1.25 mg/kg	40-160	7	36 ± 30.5 (3.2 – 92.8)	126 ± 105 (12.3 – 311)	1 (1-2)	[b]6.2± 2.6	84.8	83.2
2.5 mg/kg	40-320	9	90.4 ± 82.9 (18.3 – 253)	451 ± 395 (108 – 1256)	2 (0.6-4)	[b]5.9± 0.7	91.7	87.5
5 mg/kg	280-600	6	86.1 ± 117 (7.12 – 313)	372 ± 398 (87 – 1133)	2 (1-4)	ND	135.8	107
8.3 mg/kg	440-880	7	109 ± 63.5 (27.9 – 199)	547 ± 422 (189 – 1267)	1 (1-4)	[c]6.1	58.5	77.1
12.5 mg/kg	840-1400	7	383 ± 274 (17.4 – 701)	1445 ± 869 (106.4 – 2576)	2 (1-2)	[d]5.8± 3.7	71.6	60.1
Continuous Fixed	560	9	156 ± 141 (38.1 – 447)	780 ± 558 (229 – 1767)	2 (1-4)	[e]5.2± 1.5	90.6	71.5
Continuous 8.3 mg/kg	560 - 960	10	155 ± 126 (11.1 -388)	938 ± 729 (91.2 – 2285)	2 (1 -24)	[e]4.0± 0.8	81	77.7
DLBCL ABC Fixed Dose	560	9	141 ± 110 (19.9 – 303)	682 ± 500 (125 – 1681)	2 (1-6)	[c]6.1	77.9	73.4

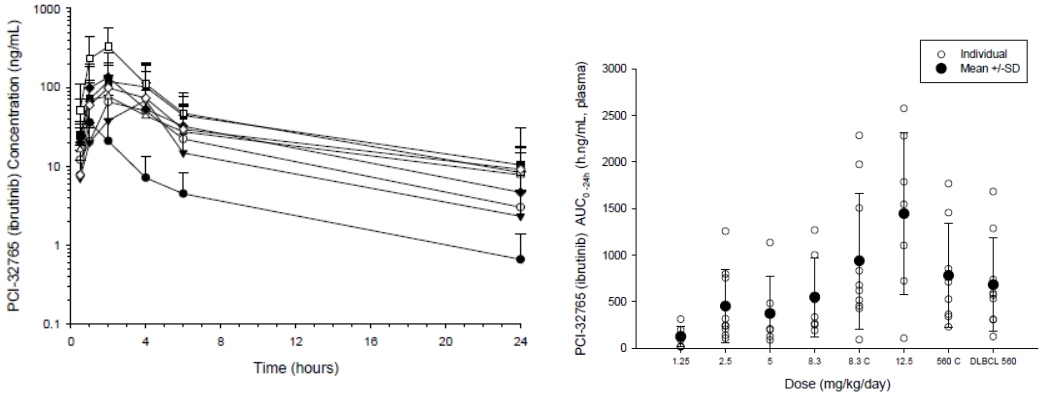
[a]Median (min - max); [b]N = 5; [c]N = 2 (SD not calculated); [d]N = 4; [e]N = 6; NA=Not assessable

Table 4: Summary of (Mean ± SD) PCI-45227 Pharmacokinetic Parameters after Single Dose Ibrutinib in Patients with Cancer in 04753

Treatment	N	Cmax (ng/mL)	AUC_{0-24} (ng.h/mL)	[a]Tmax (hr)	$T_{1/2}$ (hr)	CV% (AUC_{0-24})	M/P Ratio (AUC_{0-24})
1.25 mg/kg	7	33.8 ± 20.7	258 ± 145	1 (1-2)	[c]6.8 ± 1.4	56.2	2.7 ± 1.7
2.5 mg/kg	9	45.8 ± 22.5	475 ± 193	2 (2-4)	[d]6.5 ± 1.9	40.6	1.5 ± 0.8
5 mg/kg	6	60.7 ± 39.4	571 ± 285	2 (1-6)	[d]6.3 ± 1.1	49.9	2.4 ± 1.6
8.3 mg/kg	7	158 ± 75.1	1402 ± 711	2 (1-4)	[c]6.8 ± 1.6	50.7	3.4 ± 2.8
12.5 mg/kg	7	278 ± 135	2259 ± 1015	2 (1-2)	7.4 ± 2.2	44.9	1.9 ± 0.9
Continuous 560 mg	9	122 ± 67.9	[b]1314 ± 783	2 (1-4)	[e]6.5 ± 1.1	59.6	[b] 1.9 ± 1.0
Continuous 8.3 mg/kg	10	176 ± 97.4	1617 ± 884	2 (1-4)	[c]6.8 ± 1.6	54.7	2.4 ± 1.4
DLBCL 560 mg QD	9	66 ± 39.7	398 ± 246	2 (1-4)	[f]6.6	61.8	0.7 ± 0.5

[a]Median (min - max); [b]N = 8; [c]N = 5; [d]N = 3; [e]N = 6; [f]N = 2 (SD not calculated)

Figure 7: Concentration-Time Profile of Ibrutinib (left) and Plot of Individual and Mean (SD) Ibrutinib AUC_{0-24} (right) for the 8 Cohorts in 04753



Multiple Dose PK

Multiple dose PK (**Tables 5 and 6)** are available from the two pivotal trials. Daily doses of 420 and 840 mg were evaluated in 1102-CA and 560 mg daily was evaluated in 1104-CA. PK samples in Cycle 1 were collected at pre-dose and 0.5, 1, 2, 4, 6 and 24 hours post-dose on Days 1 and 8.

On Day 8, the median ibrutinib Tmax was 2 hours and the mean terminal $T_{1/2}$ ranged from 6 to 9 hours (similar to single dose). The mean accumulation ratio ranged from 1 to 1.6 following multiple doses. The CV% was 77 - 110% for Cmax and 71 - 85% for AUC_{0-24}. The PK appears linear between doses, but an analysis of dose linearity was not performed due to the limited dose range studied. The mean metabolite-to-parent ratios for PCI-4557 ranged from 0.97 - 2.7 on Day 1 (consistent with the dose-escalation trial data) and ranged from 1.02 - 2.8 on Day 8 (consistent with Day 1).

Table 5: Mean ± SD Pharmacokinetic Parameters on Days 1 and 8 at Ibrutinib Doses of 420 mg and 840 mg in Patients with CLL (1102-CA) and Ibrutinib 560 mg in Patients with MCL (1104-CA)

1102-CA								
Dose (mg)	**Day**	**N**	**Cmax (ng/mL)**	**AUC_{0-24} (ng.h/mL)**	**[a]Tmax (h)**	**$T_{1/2}$ (hr)**	**AR**	**AUC_{0-24} CV%**
420	1	50	123 ± 145	603 ± 542	2 (0.5 - 24)	[b]5.9 ± 2.4	NA	83.4
840	1	33	208 ± 166	[c]1184 ± 1056	2 (0.6 - 4.2)	[d]6.3 ± 2.6	NA	85.3
420	8	47	132 ± 129	[e]680 ± 517	2 (0.5-7)	[f]7.3 ± 3.9	[e]1.6 ± 1.2	71.1
840	8	32	221 ± 193	1246 ± 921	2 (0.5-4)	[g]7.4 ± 2.7	[f]1.2 ± 0.6	73.1
1104-CA								
560	1	48	147 ± 143	[h]802 ± 668	2 (0.8 - 23)	[j]5.9 ± 2.0	NA	83.2
560	8	45	164 ± 164	[i]953 ± 705	2 (0 - 4.1)	[k]8.5 ± 6.2	1.4 ± 08	74.0

[a]Median (min- max); [b]N=24; [c]N=32; [d]N=13; [e]N=45; [f]N=25; [g]N=22; [h]N=45; [i]N=43; [j]N=20; [k]N=21; NA= not assessable; AR= accumulation ratio

Table 6: PCI-45227 (Mean ± SD) Pharmacokinetic Parameters on Days 1 and 8 at an Ibrutinib Dose of 560 mg in Patients with MCL in 1104-CA

Day	**N**	**Cmax (ng/mL)**	**AUC_{0-24} (ng.h/mL)**	**[a]Tmax (h)**	**$T_{1/2}$ (hr)**	**AR**	**CV% AUC_{0-24}**
1	48	112 ± 54	[b]1052 ± 583	2 (0.9 - 6.1)	[d]6.9 ± 1.5	NA	83.2
8	45	122 ± 59	[c]1263 ± 707	2 (1.0 - 4.1)	[d]9.2 ± 3.7	1.4 ± 09	74.0

[a]Median (min- max); [b]N=46; [c]N=44; [d]N=28; NA= not assessable; AR= accumulation ratio

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The single dose exposures appear higher in patients compared to healthy volunteers (**Tables 3 and 7**), but this is based on cross-study comparison of different dose levels (140 mg in healthy volunteers compared to 2.5 mg/kg in patients). The single dose CV% for AUC were approximately 60% in healthy volunteer trials and 60 - 107% in patient trials. The higher exposure and CV% in patient trials may be due in part to the use of modified fasting conditions (dose taken at least 30 minutes before or at least 2 hours after a meal) for drug administration in patient trials compared to fasting conditions in healthy volunteer trials.

Single dose PK were available from two healthy volunteer trials: 1002 (ketoconazole DDI discussed in **Section 2.4.2.2**) and 1004 (mass balance discussed in **Section 2.2.5.5**). A single dose of 120 mg was used in 1002 as a capsule formulation and 140 mg was used in 1004 as a solution formulation. For the capsule formulation, the median Tmax was approximately 2 hours, the mean half-life ($T_{1/2}$) was approximately 8 hours, and the CV% for AUC was about 59%. The Cmax appears higher and the Tmax shorter for the solution formulation, but the AUC appears to be in the same range between the capsule and the solution.

Table 7: Pharmacokinetic Parameters of Single Dose Ibrutinib in Healthy Volunteers

Trial formulation	Dose (mg)	N	Cmax (ng/mL)	AUC_{0-24} (ng.h/mL)	Tmax (hr)	$T_{1/2}$ (hr)	CV%	
							Cmax	AUC
1002 (Capsule)	120	18	11.8 ± 6.7	63.8 ± 37.3	1.8 (1.0 – 3.0)	8.2 ± 3.2	56.5	58.5
1004 (solution)	140	6	37.1 ± 22.4	61.5 ± 39.2	0.5 (0.5 – 1.5)	3.1 ± 0.8	60.4	63.7

PK parameters presented as Mean ± SD except Tmax is presented as Median (min- max)

2.2.5.3 What are the characteristics of drug absorption?

The median Tmax of ibrutinib is approximately 1 - 2 hours. In a food effect sub-study of 1102-CA, a high-fat meal increased ibrutinib exposure approximately 2-fold compared to when ibrutinib was administered after an overnight fast (**Table 25**).The absolute bioavailability of ibrutinib has not been evaluated but is likely low due to extensive first pass metabolism. The bioavailability based on AUC of a solution formulation compared to a capsule formulation appeared comparable (**Table 7**) which may suggest that absorption from the gastrointestinal (GI) tract may not be the limiting factor to the bioavailability. In addition, mostly oxidative metabolites were found in feces in the mass balance trial with minimal parent drug (0.77% of total), suggesting absorption of ibrutinib from the GI tract is near complete (fraction absorbed, fa, was close to 1). Ibrutinib is not a substrate of P-gp, in vitro. Therefore, P-gp is unlikely to affect its absorption.

2.2.5.4 What are the characteristics of drug distribution?

Plasma Protein Binding: Ibrutinib is highly bound (mean of 97.2 - 98 %) to plasma proteins and PCI-45227 is 91% bound, in vitro (studies FK10373, FK10375, 13-044-Hu-X-PB). Protein binding of ibrutinib was concentration independent (50 - 5000 ng/mL). Ibrutinib protein binding was found to be 97.7% in the mass balance trial 1004 and 97.5 - 98.3% in the drug interaction trial 1002. At 150 ng/mL, it was found to bind to human serum albumin (HSA) 96% (4.3% HSA solution) and to human α1-acid glycoprotein (AAG) 24 - 76% (0.05 – 0.2 % AAG solution; Study FK10375). HSA binding was only evaluated at one concentration and it is not clear if the binding is dependent on amount of HSA similar to AAG. Therefore, it would be pertinent to evaluate protein binding in the ongoing hepatic impairment trial.

Blood to Plasma Ratio: In vitro, the whole blood to plasma ratio for ibrutinib was approximately 0.7 - 0.8 at concentrations of 100 – 500 ng/mL (study FK10375). In the human mass balance trial, the mean whole blood to plasma ratio for total radioactivity was approximately 0.7.

Tissue Distribution: The apparent volume of distribution (Vd) based on population PK analysis was approximately 10 000 L, which may suggest that ibrutinib is extensively distributed to peripheral tissues. However, the Vd may be overestimated if the bioavailability of ibrutinib is low. An absolute bioavailability study has not been performed, but ibrutinib likely has low bioavailability.

Transporter Proteins:

Ibrutinib is not a substrate of P-gp (net flux ratio of 0.13), but PCI-45227 is a substrate (net flux ratio of 2), in vitro. In addition, ibrutinib is an inhibitor of P-gp with an IC_{50} of 2.15 μg/mL but PCI-45227 is not.

Caco-2 cells and MDR1-MDCK cells were used to evaluate whether ibrutinib and PCI-45227 are substrates and/or inhibitors of P-gp (studies 10-017-V-X-ADMET and 07-151-MDCK-X-TI). The I/Ki (I based on steady-state Cmax of 122 ng/mL at the 560 mg dose) was approximately 0.06. Based on the I/Ki of < 0.1, systemic ibrutinib is unlikely to have a potential to inhibit P-gp. However, it may have an effect on P-gp substrates in the GI tract due to higher local concentrations after an oral dose. The calculated mean gut luminal inhibitor concentration at proposed dose of 560 mg divided by IC_{50}, assuming the drug is taken with 250 mL water, was greater than 10. PBPK software was used to simulate ibrutinib drug absorption kinetics and luminal drug concentration-time profiles for each segment of the GI tract (Refer to the appendix in **Section 3.2** for more details). Ibrutinib is predicted to be quickly absorbed with absorption generally completed in 2.5 hours. Therefore, assuming ibrutinib can inhibit P-gp in the GI tract in vivo, the potential for an interaction could be minimized by staggering the dose of ibrutinib and a P-gp substrate by at least 2.5 hours.

The effect of ibrutinib on other transporters has not been evaluated. A comment will be sent to address the evaluation of the inhibition potential of ibrutinib on other transporters such as BCRP, OATP1B1/OATP1B3, OCT2, OAT1 and OAT3.

2.2.5.5 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

Ibrutinib is primarily metabolized and excreted through the feces (80.6%). The renal route is a minor elimination pathway of ibrutinib-related material (7.8%) and renal clearance of unchanged ibrutinib is negligible (<0.004 L/hr).

In the mass balance trial, six healthy male volunteers received 140 mg of oral ^{14}C-labeled ibrutinib (1480 kBq). The dose was given after an overnight fast of at least 8 hours. The formulation was a 30% hydroxypropyl-β-cyclodextrin solution with ibrutinib 5 mg base eq/mL with a radioactivity concentration of 52.9 kBq/mL. A 70 mg oral solution was assessed in three volunteers in the drug interaction trial 1002 (volunteers were in an exploratory cohort separate from the drug interaction cohort) before use in this mass balance trial. The solution formulation had a 2 fold higher ibrutinib Cmax with no difference in AUC compared to the capsule formulation used in the DDI.

Concentrations of ibrutinib and the metabolite PCI-45227 and total radioactivity (^{14}C) were measured in blood, plasma and urine. Metabolic profiling was performed on selected samples.

- Blood samples for blood and plasma concentrations and total radioactivity were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48 and 72 hours post-dose. Additional samples for total radioactivity were collected every 24 hours from Day 5 to 8.
- Blood samples for metabolite profiling were collected 1, 2, 4, 8, 12, 24 and 72 hours post-dose.

- ❖ A pre-dose blood sample was collected for determination of ibrutinib protein binding and assessing total protein, albumin and α1-acid glycoprotein.
- ❖ Urine samples for concentration and total radioactivity were collected pre-dose and at the following time-intervals: 0 - 2, 2 - 4, 4 - 8, 8 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120, 120 - 144 and 144 - 168 hours post-dose. Urine samples collected over a 24 hour time interval from Day-1 were used for determination of urine creatnine and GFR.
- ❖ Fecal samples were collected pre-dose (Days -1 to 1) and per stool up to 168 hours post-dose.
- ❖ A baseline pharmacogenomic blood sample was collected for CYP2D6, CYP3A4 and CYP3A5 genotyping.

Plasma concentrations were analyzed using a validated LC-MS/MS method and blood and urine samples used assay methods that are not validated as discussed in **Section 2.6.4**. Liquid scintillation was used for assessment of radioactivity in blood, plasma, urine and feces.

Blood and Plasma:

The total radioactivity Cmax was 15 fold higher and AUC was 100-fold higher than that of ibrutinib in blood. Ibrutinib and PCI-45227 combined constituted less than 10% of total circulating radioactivity (**Figure 8**).

The PK parameters reported for blood and plasma were similar for both ibrutinib and PCI-45227, but the Cmax and AUC for total radioactivity were approximately 50% higher in plasma compared to blood. The mean blood to plasma concentration ratio of total radioactivity at Tmax was approximately 0.7.

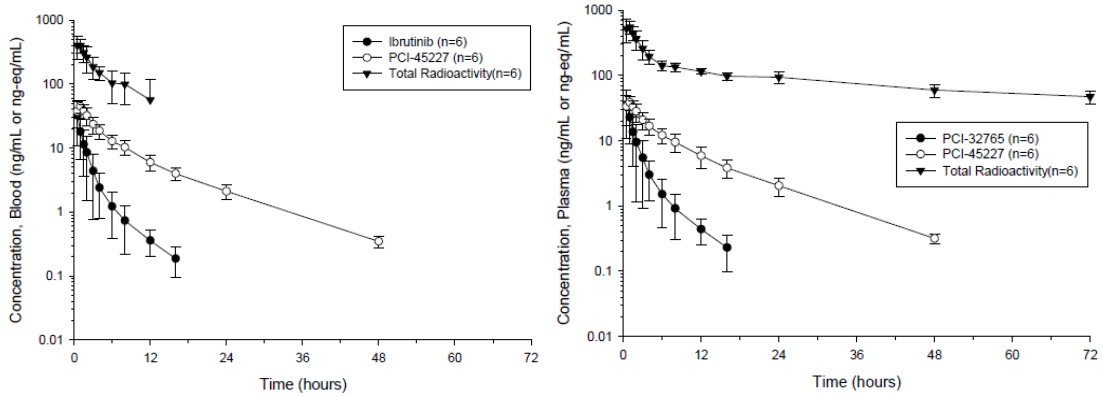
The mean half-lives were 3 hours for ibrutinib and 8 hours for PCI-45227. The total radioactivity half-life was 26 hours in blood and 47 hours in plasma (the applicant attributes the difference in blood and plasma values for total radioactivity to fewer available time-points for blood samples).

Table 8: Mean (SD) Pharmacokinetic Parameters of Ibrutinib and PCI-45227 and Total Radioactivity in Blood and Plasma Following a Single Oral Administration of 140 mg ^{14}C-Ibrutinib

Parameter	Ibrutinib Blood	Ibrutinib Plasma	PCI-45227 Blood	PCI-45227 Plasma	Total Radioactivity in Blood	Total Radioactivity in Plasma
C_{max} (ng/mL)	33.9 (19.1)	37.1 (22.4)	49.6 (9.34)	43.5 (9.09)	480 (72.5)[b]	634 (87.9)[b]
T_{max} (h)[a]	0.52 (0.50 – 1.50)	0.52 (0.50 – 1.50)	0.78 (0.50 – 1.50)	0.78 (0.50 – 1.50)	0.78 (0.50 – 1.50)	0.77 (0.50 – 1.50)
T_{last} (h)	17.34 (3.26)	17.34 (3.26)	56.01 (12.39)	56.01 (12.39)	11.34 (6.89)	72.03 (0.03)
AUC_{24} (ng.h/mL)	NA	NA	248 (50.3)	227 (56.0)	NA	3690 (434)[c]
AUC_{last} (ng.h/mL)	52.0 (32.9)	61.5 (39.2)	280 (55.0)	257 (61.5)	1932 (1054)[c]	6821 (908)[c]
AUC_{∞} (ng.h/mL)	59.6 (31.6)	70.5 (37.8)	283 (54.7)	259 (60.7)	6173 (7076)[c]	10107 (2123)[c]
$t_{1/2}$ (h)	3.33 (0.98)	3.14 (0.81)	8.45 (0.84)	8.37 (0.88)	25.79 (35.93)	47.25 (11.60)
Vd/F (L)	14385 (9102)	11038 (5485)			708 (154)	941 (161)
CL/F (L/h)	2825 (1258)	2443 (1188)			46.3 (38.7)	14.2 (2.49)
CL_R (L/h)	0.00365 (0.00156)					

[a] Median (range); [b]ng.eq/mL; [c] ng.eq h/mL; NA=not applicable
Source: Applicant's Table 2 in study-report-pci-32765cll1004.pdf

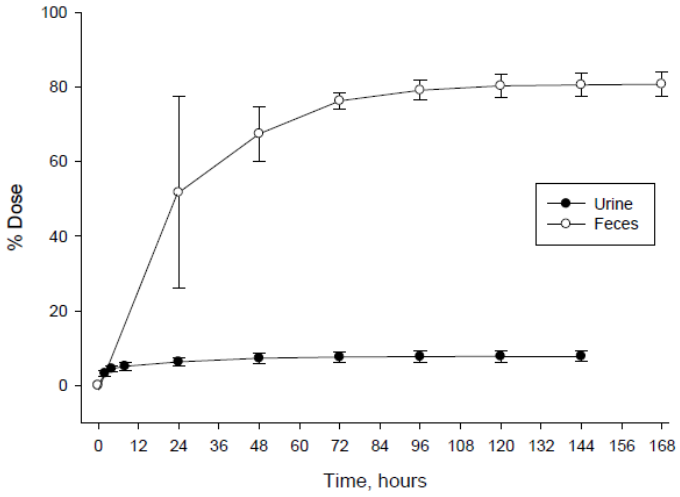
Figure 8: Mean (SD) Ibrutinib and PCI-45227 Concentration- and Total Radioactivity -Time Profiles in Blood and Plasma Following a Single Oral Administration of 140 mg ^{14}C-Ibrutinib



Source: Applicant's Figure 3 on Page 31 of study-report -pci-32765cll1004.pdf

Urine and feces: Ibrutinib concentrations were measurable in urine up to 2 hours after dosing in 5 volunteers and in only 1 volunteer between 2 and 4 hours (mean of 0.000176% of total dose). PCI-45227 was measurable in urine in all subjects through 72 hours after dosing (mean of 0.12% of total dose). Approximately 88.5% of radioactivity was recovered in urine and feces over 168 hours (**Figure 9**). The mean cumulative excretion of radioactivity in urine accounted for 7.81±1.43% of the dose and 80.6% in feces (ibrutinib only accounted for 0.77% of the administered dose in feces).

Figure 9: Mean (SD) Cumulative Excretion of Total Radioactivity in Urine and Feces Following Single Oral Administration of 140 mg ^{14}C-Ibrutinib



Source: Applicant's Figure 4 on Page 32 of study-report -pci-32765cll1004.pdf

2.2.5.6 What are the characteristics of drug metabolism?

Ibrutinib is primarily metabolized by CYP3A4. The main circulating moieties in blood and plasma were M21, M25, M34, M37 (PCI-45227) and ibrutinib. Ibrutinib and the active metabolite, PCI-45227, accounted for less than 10% of total radioactivity in the mass balance

trial. Ibrutinib likely undergoes significant first pass metabolism with unchanged drug as <1% of the administered dose in feces. In vitro turnover in human microsomes was rapid with 66% metabolized within 10 minutes.

Metabolic Profiling and Identification

Based on the metabolic profiling of samples from the mass balance trial 1004 (report FK 10267), ibrutinib is extensively metabolized. The main circulating moieties in blood and plasma were M21 (sulphate conjugate of M35), M25 (oxidation to a carboxylic acid), M34 (reduction to a primary alcohol), PCI-45227 (M37) and ibrutinib (**Table 9** shows the plasma concentrations observed). The main metabolites identified in feces were M11 (2.6% of administered dose), M17 (3.8%), M20 (7.1%), M24 (2.0%), M25 (6.1%), M29 (2.9%), M34 (9.1%), M36 (2.9%) and M37 (2.9%). The main metabolites identified in urine were M7, M17, M20, M24, M25, M29 and M34.

Table 9: Ibrutinib and its Metabolites in Human Plasma after a Single Dose 140 mg ^{14}C-ibrutinib

	Ibrutinib and Metabolite Concentration (ng/mL)								
Time (h)	M11	M21[c]	M25	M29	M34[d]	M37	M39	M40	Ibrutinib
1[a]	NA	102.3	68.1	NA	47.7	41.9	NA	NA	33.5
2[a]	NA	78.4	36.9	NA	33.3	32.0	NA	NA	26.9
4[a]	NA	NA	NA	NA	NA	28.2	NA	NA	NA
8[b]	ND	LOD	LOQ	ND	LOD	LOQ	LOD	LOD	LOQ
24[b]	ND	LOD	LOD	ND	LOD	LOD	LOD	LOD	LOD
72[b]	ND	ND	ND	ND	ND	ND	ND	ND	LOD

[a]Mean data from 6 subjects; [b]Samples pooled from 6 subjects; [c]Co-elution with M20 and M24; [d]Co-elution with M31 and M35; Values determined by UPLC analysis
Source: Applicant's Table 2 in FDAResponse-Metabolites_082813.pdf

(b) (4)

Figure 10: Proposed Metabolic Pathways for Ibrutinib Based on Metabolites Observed in 1004

Source: Applicants Figure 8 in pharmkin-written-summary.pdf

2.2.5.7 What are the characteristics of drug excretion?

Elimination: Ibrutinib is primarily metabolized and excreted through the feces (80.6%) mostly as metabolites (0.77% unchanged drug). The renal route appears to be a minor elimination pathway (7.8%) as determined by the mass balance trial discussed in **Section 2.2.5.5**.

Clearance: Apparent clearance (CL/F) in patients estimated using population PK analyses is 1060 L/h. The apparent steady-state peripheral Vd is estimated as 9620 L.

Half-life: The mean elimination half-life of ibrutinib was 4 - 6 hours (Refer to **Section 2.2.5.1**). Minimal accumulation was observed with daily dosing (accumulation ratio of 1 - 1.6 fold).

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity?

The exposure of ibrutinib increased with increasing dose from 420 – 840 mg but, the applicant did not perform dose proportionality assessments for the flat dosing regimen as the dose range was limited. The applicant did not make a formal dose proportionality assessment in the dose escalation trial that used body-weight based dosing, but the dose normalized Cmax and AUC did not suggest non-linearity (**Table 10**). The applicant's population PK model assumes dose linearity and in this model the PK was described using a standard linear two-compartment model

with sequential zero-first order model and a lag time. Linear regression of data from the dose-escalation trial using actual doses had R^2 of 0.3 for these mg/kg cohorts with large variability as shown in **Figure 11**. Dose proportionality could not be assessed for single doses in the healthy volunteer trials as solution was used in one trial and capsules were used in another, with both only evaluating one dose level.

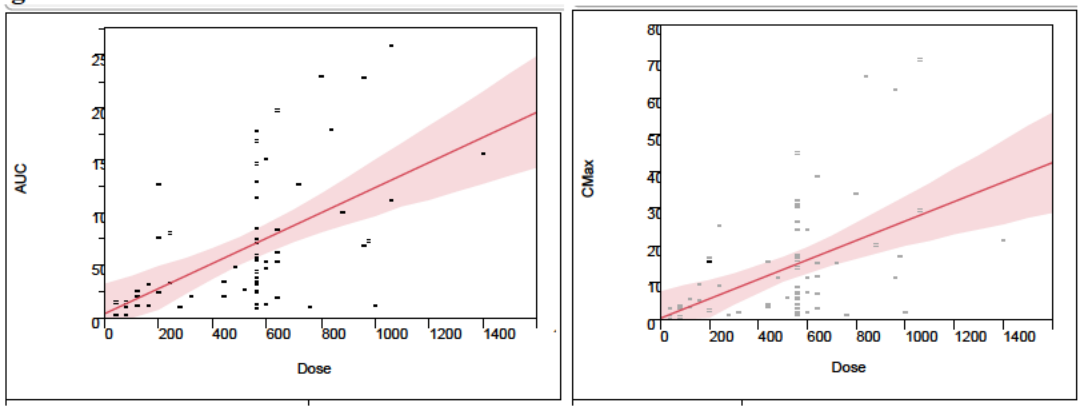
Table 10: Ibrutinib Mean and Dose-Normalized PK Parameters in 04753

Treatment	N	Dose Range mg	C_{max} ng/mL	DN_C_{max} ng/mL	AUC_{0-24} ng.h/mL	DN_AUC_{0-24} ng.h/mL
1.25 mg/kg/day	7	40-160	36.0	182 (106)	126	641 (381)
2.5 mg/kg/day	9	40-320	90.4	277 (194)	451	1411 (1042)
5 mg/kg/day	6	280-600	86.1	93.3 (115)	372	417 (383)
8.3 mg/kg/day	7	440-880	109	98.6 (57.7)	547	462 (280)
12.5 mg/kg/day	7	840-1400	383	217 (170)	1445	793 (504)
Continuous Fixed Dose	9	560	156	156 (141)	780[a]	780 (558)[a]
Continuous 8.3 mg/kg/day	10	560-960	155	129 (104)	938	776 (581)
DLBCL ABC Subtype Fixed Dose	9	560	141	141 (110)	682	682 (500)

DN = dose normalized to 560 mg
[a] n=8

Source: Applicant's Table 3 in summary-clin-pharm.pdf

Figure 11: AUC and Cmax versus Actual Dose in 04753



2.2.5.9 How do the PK parameters change with time following chronic dosing?

Mean accumulation ratios of < 2 were observed at steady-state compared to single dose exposures. The clearance appears to be the same after a single dose as with multiple doses. The PK variability was high for both single and multiple dose PK (see **Tables 3 and 5)**.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

High PK variability was observed in both the healthy volunteer (CV of 60%) and patient trials (CV of 60 - 107%). The higher CV% in patients may be due in part to the use of modified fasting

conditions. However, high variability was also observed in the healthy volunteers using an overnight fast before dosage administration.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Hepatic impairment increases ibrutinib exposure. Preliminary data from an ongoing Trial PCI-32765CLL1006 (1006) in patients with moderate hepatic impairment (Child-Pugh B; N=3) shows a 6 fold increase in exposure when compared to mean exposures in patients with normal hepatic function. As this is preliminary data and the patient characteristics have not been submitted, we cannot make conclusions about the exposure of ibrutinib in hepatic impairment. Ibrutinib should be avoided in patients with hepatic impairment.

No patients with hepatic impairment were enrolled in the pivotal trials. The applicant is currently evaluating the effect of hepatic impairment on the PK of ibrutinib in 1006. The applicant stated that preliminary data in patients with moderate hepatic impairment (Child-Pugh B; N=3) shows a 6 fold increase in exposure when compared to mean exposures in patients with normal hepatic function (cross-study comparison; in healthy volunteer trial at the dose of 120 mg the mean Cmax was 11.8 ng/mL and mean AUC was 63.8 ng*hr/mL). One of the three patients in the mild impairment group had higher exposures than those in the moderate hepatic impairment group (**Table 11**). As this is preliminary data and the patient characteristics have not been submitted, we cannot make conclusions about the exposure of ibrutinib in mild hepatic impairment. The trial is still ongoing and a PMR will be issued for the submission of the final study report.

Table 11: Preliminary PK data of Ibrutinib after a Single 140 mg Oral Dose in Fasted Conditions in Mild (CP-A) and Moderate (CP-B) Hepatic Impaired Patients (PCI-32765CLL1006)

	Hepatic Impaired Population			
	CP-A (n=3)		CP-B (n=3)	
	AUC_{last} (ng.h/mL)	C_{max} (ng/mL)	AUC_{last} (ng.h/mL)	C_{max} (ng/mL)
1	156	17.2	448	13.9
2	948	109	570	49.6
3	158	53.0	539	25.3

Source: Applicants Table 2 in response-info-request-20130718.pdf

Physiologic based pharmacokinetic (PBPK) modeling (**Section 3.2**) over predicted the effect of hepatic impairment. The PBPK model predicted mean exposure changes of 4.7-, 14- and 21-fold in mild, moderate, and severe hepatic impaired patients, respectively. The model over-predicted the effect in moderate impairment when compared to preliminary data in patients in the dedicated trial (14- versus 6 fold). Therefore, labeling recommendations cannot be made using the

predicted PBPK data.

The applicant does not provide any recommendations regarding hepatic impairment in the proposed label. A significant change in exposure (>6 fold) is expected in patients with severe hepatic impairment as ibrutinib is extensively metabolized and up to a 30 fold increase in exposure was observed with the use of a strong CYP3A4 inhibitor. We currently have insufficient data to make dosing recommendations in patients with hepatic impairment.

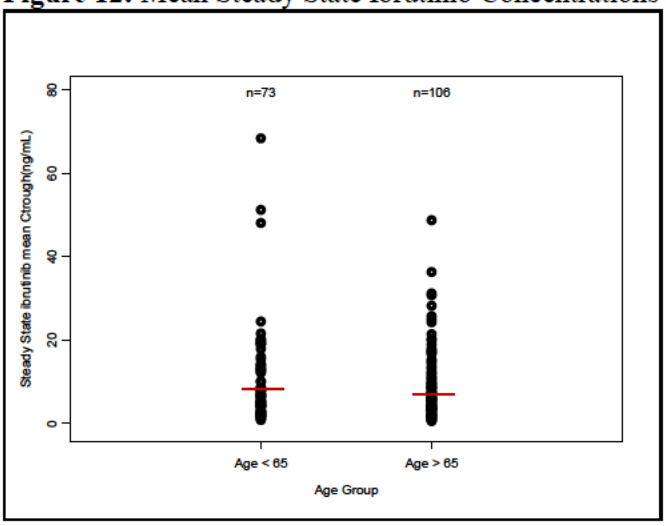
2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Population pharmacokinetic (Pop PK) analyses were performed using plasma concentration data from 245 subjects from the phase 1 dose escalation trial and the two phase 2 trials. The PK of ibrutinib was described using a standard linear two-compartment model with sequential zero-first order model and a lag time. Patient covariates such as age (range: 37 - 84 years), weight (range: 40.6 - 146.2 kg), creatinine clearance (range: 24.6 - 212 mL/min) and gender were not found to have a meaningful influence on the clearance of ibrutinib.

2.3.2.1 Elderly

Pop PK analysis showed that age in the range of 37 - 84 years had no meaningful influence on the clearance of ibrutinib. In addition, no difference was observed in the steady-state ibrutinib exposures in patients > 65 years old compared to those < 65 years old (**Figure 12**).

Figure 12: Mean Steady State Ibrutinib Concentrations Stratified by Age



2.3.2.2 Pediatric patients

Safety and effectiveness of ibrutinib have not been established in pediatric patients.

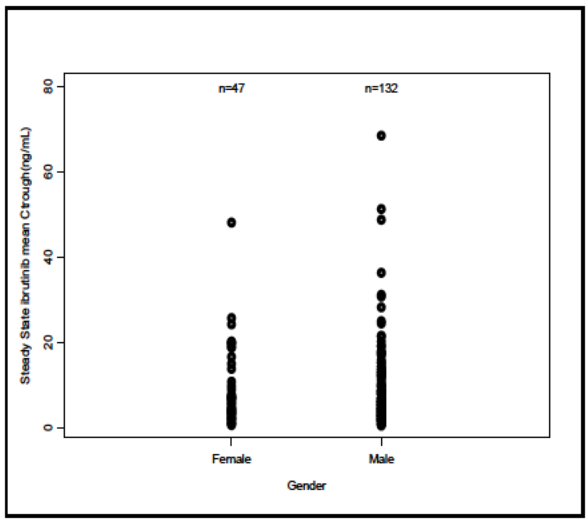
2.3.2.3 Body weight

Weight had no meaningful influence on the clearance of ibrutinib, but had influence on volume of distribution. This influence on volume of distribution does not seem to have any meaningful impact on the exposure to ibrutinib. Refer to appendix in **Section 3.1** for more details.

2.3.2.4 Gender

Population pharmacokinetic (Pop PK) analysis showed that gender had no meaningful influence on the clearance of ibrutinib. The mean steady-state trough concentrations stratified by gender are shown in **Figure 13**.

Figure 13: Mean Steady State Ibrutinib Concentrations Stratified by Gender



2.3.2.5 Race

The majority (N=221; 90%) of those included in the Pop PK analysis were white. No effect of race on ibrutinib PK was observed when comparing whites versus those of other races (all other races were grouped together due to limited numbers). The assessment of the effect of race on ibrutinib PK cannot be clearly interpreted due to the limited numbers in other races.

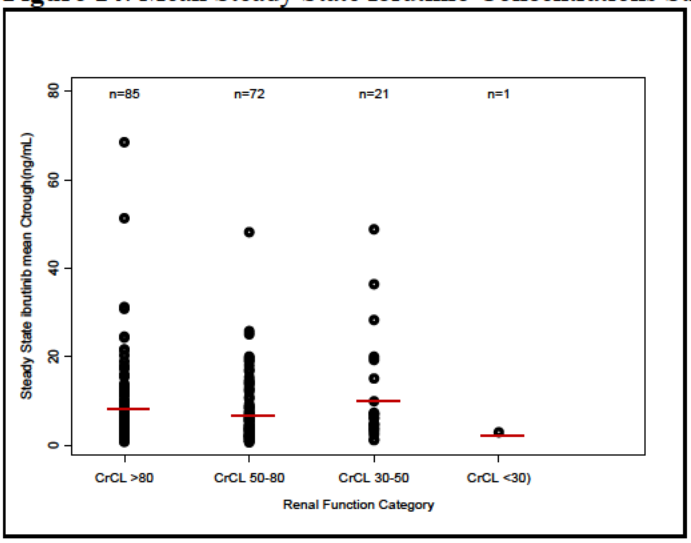
2.3.2.6 Renal impairment

Approximately 8% of radioactivity was detected in urine in the mass balance trial (Refer to **Section 2.2.5.5**) suggesting that the renal route is a minor elimination pathway. Pop PK analysis showed that creatinine clearance (CrCl) in the range of 24.6 - 212 mL/min had no meaningful influence on the clearance of ibrutinib.

A dedicated renal impairment trial has not been conducted. However, the pivotal trials had 40.8% of patients with a CrCl of 60 - 90 mL/min (mild impairment) and 21.2% of patients with a

CrCL of 30 - 60 mL/min (moderate impairment). In population PK analyses, CrCl was not found to have an impact on the exposure of ibrutinib for CrCl > 30 mL/min (**Figure 14)**. It can be concluded that mild and moderate renal impairment do not affect the exposure of ibrutinib. Ibrutinib has not been evaluated in patients with CrCl < 30 ml/min. No dose adjustments are recommended in patients with renal impairment.

Figure 14: Mean Steady State Ibrutinib Concentrations Stratified by Status of Renal Function



2.3.2.7 Hepatic impairment

Hepatic impairment increases ibrutinib exposure. Preliminary data from an ongoing Trial 1006 in patients with moderate hepatic impairment (Child-Pugh B; N=3) shows a 6 fold increase in exposure when compared to mean exposures in patients with normal hepatic function. As this is preliminary data and the patient characteristics have not been submitted, we cannot make conclusions about the exposure of ibrutinib in hepatic impairment. Ibrutinib should be avoided in patients with hepatic impairment.

2.3.2.8 Pharmacogenomics

CYP2D6 (b) (4) Exposure

In the mass balance trial (n = 6), the mean ibrutinib and the active metabolite PCI-45227 AUCs were 10% and 29% higher, respectively in CYP2D6 poor metabolizers (PMs, N=2) compared with the mean AUCs in CYP2D6 extensive metabolizers (EMs, N=4).

Ibrutinib is metabolized (b) (4) enzymes CYP3A4/5 and to a lesser extent by CYP2D6, in vitro (Refer to **Section 2.4.2.1**). Information regarding PCI45227 metabolism was not provided. No dedicated pharmacogenomic study was conducted to explore the role of CYP450 (b) (4) on ibrutinib PK. Limited genotyping data from only six healthy male volunteers is available from the mass balance trial (**Section 2.2.5.5**) which pre-specified that two of the six volunteers enrolled should be CYP2D6 PMs.

To screen [redacted] germline DNA was isolated from peripheral blood cells and CYP2D6 genotyping was performed using the [redacted] assay. In addition, [redacted] CYP3A were analyzed with the Affymetrix DMET Plus. The CYP2D6 variants assessed and the criteria used for CYP2D6 genotype-derived phenotype assignment for the [redacted] assay are listed in **Table 12**.

Table12: CYP2D6 Variants Assessed in 1004 [redacted]

	*1	*2	*3	*4	*5	*6	*7	*8	*9	*10	*12	*14	*17	*29	*41	*1XN or *2XN
*1	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	UM
*2		EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	EM	UM
*3			PM	PM	PM	PM	PM	PM	IM	IM	PM	PM	IM	IM	IM	NK[1]
*4				PM	PM	PM	PM	PM	IM	IM	PM	PM	IM	IM	IM	NK[1]
*5					PM	PM	PM	PM	IM	IM	PM	PM	IM	IM	IM	NK[1]
*6						PM	PM	PM	IM	IM	PM	PM	IM	IM	IM	NK[1]
*7							PM	PM	IM	IM	PM	PM	IM	IM	IM	NK[1]
*8								PM	IM	IM	PM	PM	IM	IM	IM	NK[1]
*9									IM	IM	IM	IM	IM	IM	IM	NK[1]
*10										IM	IM	IM	IM	IM	IM	NK[1]
*12											PM	PM	IM	IM	IM	NK[1]
*14												PM	IM	IM	IM	NK[1]
*17													IM	IM	IM	NK[1]
*29														IM	IM	NK[1]
*41															IM	NK[1]

[1]In rare cases, duplicated alleles are reduced activity or null activity alleles, and individuals with this type of duplicated allele may have decrease in metabolism of some drugs.

Source: Applicant's Tables 2 in stats-methods-pci-32765cll1004.pdf

The genotyping and PK data for the six healthy volunteers are listed in **Table 13**. The mean ibrutinib and PCI-45227 AUCs were 10% and 29% higher in PMs (N=2) compared with the mean AUCs in EMs (N=4).

Table 13: Summary of Exposure for each Patient based on CYP2D6 Phenotype in 1004

CYP2D6 Genotype	CYP2D6 Phenotype	**Ibrutinib**		**PCI-45227**	
		Cmax (ng/mL)	AUC_{last} (ng*h/mL)	Cmax (ng/mL)	AUC_{last} (ng*h/mL)
*5/*5	PM	60.7	77.2	39.6	245
*4/*4	PM	29.6	53.9	59.4	360
*1/*4§	EM	13.0	32.3	44.0	268
*1/*4§	EM	14.5	20.2	31.5	207
*2/*41§	EM	65.2	131	43.9	275
*1/*1	EM	39.4	54.7	42.8	185

§: Heterozygous carriers such as *1/*4, *2/*41 are considered intermediate metabolizers (IM) by some CYP2D6 phenotype prediction methods (PMID: 18202689).

It does not appear that PMs have significantly higher ibrutinib exposures compared to EMs, and no exposure-response relationship for safety was observed in the dose range of 420 – 840 mg in the pivotal clinical trials. However, the genotyping data is too limited to draw conclusions.

Concerning CYP3A, all patients had the same genotype. The 6 volunteers were CYP3A4 wild type (CYP3A4*1/*1) and homozygous variants for CYP3A5*3C, the non-active form of CYP3A5 (CYP3A5*3C/*3C).

2.3.2.9 Pregnancy and lactation

The safety and effectiveness of ibrutinib have not been established in pregnancy and in lactating women.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

CYP3A4 inhibitors and inducers have an effect on ibrutinib exposures. Refer to **Section 2.4.2.2** for details. The effects of extrinsic factors such as herbal products, diet, smoking and alcohol use on the dose-exposure and/or dose-response for ibrutinib were not assessed in a formal study.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

A dose reduction to 140 mg daily is recommended when ibrutinib is co-administered with a moderate CYP3A4 inhibitor. Refer to see **Section 2.4.2.2** for details.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes, ibrutinib is a CYP3A4 substrate. In vitro studies in microsomes and recombinant CYP450s identified CYP3A4 as the major CYP enzyme involved in the metabolism of ibrutinib with minor involvement of CYP2D6. It was not a substrate of CYP1A2, 2A6, 2B6, 2C8, 2C9 or 2C19 (Studies 2-013-Hu-X-MT, 07-153-Hu-X-MTI, 12-013-Hu-X-MT, 11-041-Hu-X-MTI and 12-014-Hu-X-MT). Recombinant CYP3A4 and CYP3A5 showed higher intrinsic clearance (Vmax/Km ratio at least 20-fold higher) than CYP2D6.

2.4.2.2 Is the drug a substrate of CYP enzymes?

Yes, ibrutinib is a CYP3A4 substrate.

<u>Effect of CYP3A4 Inhibitors and Inducers</u>

Based on geometric mean ratios, a 29-fold increase in Cmax and a 24-fold increase in AUC were observed when ibrutinib was co-administered with ketoconazole as compared with ibrutinib administered alone. Preliminary data from a dedicated trial, showed that rifampin caused a 14 fold decrease in Cmax and a 12.5 fold decrease in AUC (observed mean Cmax and AUC ratios for rifampin were 0.07 and 0.08, respectively). A PBPK model predicted a 5.5 - 8.6 fold increase in ibrutinib AUC with the use of a moderate inhibitor and a 2 fold increase with the use of a

weak inhibitor. A 2.6-fold decrease (AUC ratio of 0.38) in AUC was predicted for a moderate inducer.

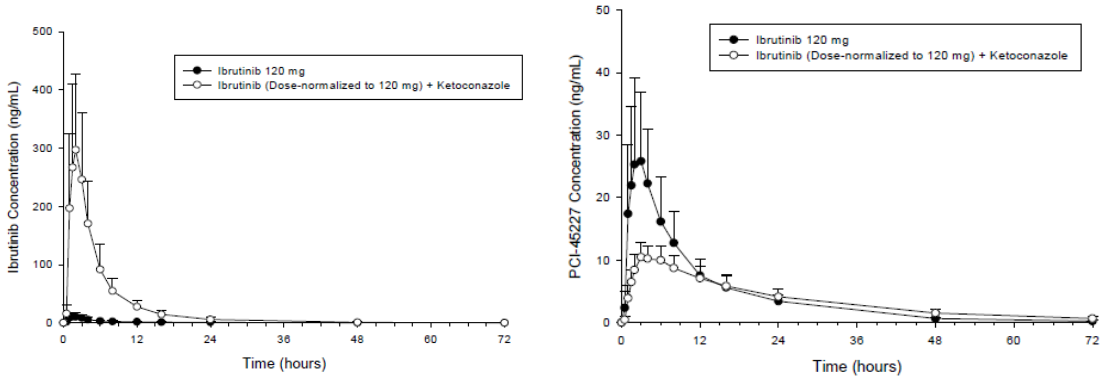
1002 was an open-label, sequential design trial to assess the effect of ketoconazole on the pharmacokinetics of ibrutinib in 18 healthy volunteers. Each volunteer received a single oral dose of ibrutinib 120 mg (3 X 40 mg) alone on Day 1 (Period 1) and ibrutinib 40 mg in combination with ketoconazole on Day 7 (Period 2). Ketoconazole 400 mg (2 X 200mg) was dosed once daily on Days 4 – 9 (dosed 1 hour before ibrutinib on Day 7). Ibrutinib was dosed after an overnight fast and fasting was continued until 4 hours post-dose. PK blood and urine samples for ibrutinib and PCI-45227 were collected pre-dose and up to 72 hours post-dose. A ketoconazole PK sample was collected 2 hours after ketoconazole dose on Day 7 of Period 2. Additional blood samples were collected on Day 1 for protein binding and pharmacogenomics assessment. None of the volunteers were CYP2D6 poor metabolizers.

Based on the geometric mean, a 29-fold increase in Cmax and a 24-fold increase in AUC_{last} were observed when ibrutinib was co-administered with ketoconazole as compared with ibrutinib administered alone. The mean ibrutinib concentration time profile is shown in **Figure 15** and the geometric mean ratios for AUC and Cmax are presented in **Table 14**. The mean metabolite (PCI-45227) to parent ratios decreased from 2.64 to 0.05 for Cmax and from 4.34 to 0.13 for AUC_{24} with the use of ketoconazole.

Table 14: Dose-Normalized Ibrutinib Geometric Mean Ratio Comparing Ibrutinib Alone and in Combination with Ketoconazole

Parameter	Group	N	DN Geometric Mean	Ratio (90% CI)
Cmax(ng/mL)	I+K	18	285.49	28.5 (24.0, 34.0)
	I		10.00	
AUClast(h*ng/mL)	I+K	18	1463.43	23.9 (19.0, 30.1)
	I		61.16	
AUCinf(h*ng/mL)	I+K	12	1859.52	26.2 (20.0 - 34.4)
	I		70.97	

Figure 15: Dose-Normalized Mean (SD) Ibrutinib and PCI-45227 Concentration-Time Profiles Following Oral Administration of Ibrutinib Alone and in Combination with Ketoconazole



Source: Figures 1 and 2 from Pages 32 and 33 in study-report -pci-32765cll1002.pdf

Individual ketoconazole concentrations ranged from 231 to 15800 ng/mL, with two volunteers

with low ketoconazole concentrations of 352 and 231 ng/mL. Paradoxically, these two volunteers had ibrutinib AUC values that were 80% lower than the mean values both when dosed alone and with ketoconazole.

A dedicated trial evaluating the effect of moderate and weak CYP3A4 inhibitors has not been performed and the applicant submitted a physiological based pharmacokinetic (PBPK) model (SimCYP) to predict their effects. Dr. Ping Zhao and Dr. Yuzhuo Pan reviewed the model and conducted additional analyses (Detailed in the appendix in **Section 3.2**). Preliminary results of PCI-32765CLL1010 (1010) evaluating the effect of rifampin (strong CYP3A4 inducer) on ibrutinib exposure were summarized (final study report will be requested as a PMR) and included as part the PBPK report. In addition, the PBPK model was used to predict the effects of weak and moderate CYP3A4 inducers. PBPK modeling of ibrutinib followed three steps:

Step 1 - Model Building: The model was built using data from in vitro phenotyping studies and in vivo PK studies. This step did not use any known clinical DDI data.

Step 2 - Model Verification: The model was verified using data from the clinical DDI studies evaluating the effect of a strong CYP3A4 inhibitor and inducer. The trials included were 1002 (ketoconazole 400 mg QD combined with single dose ibrutinib) and 1010 (rifampin 600mg QD combined with single dose ibrutinib).

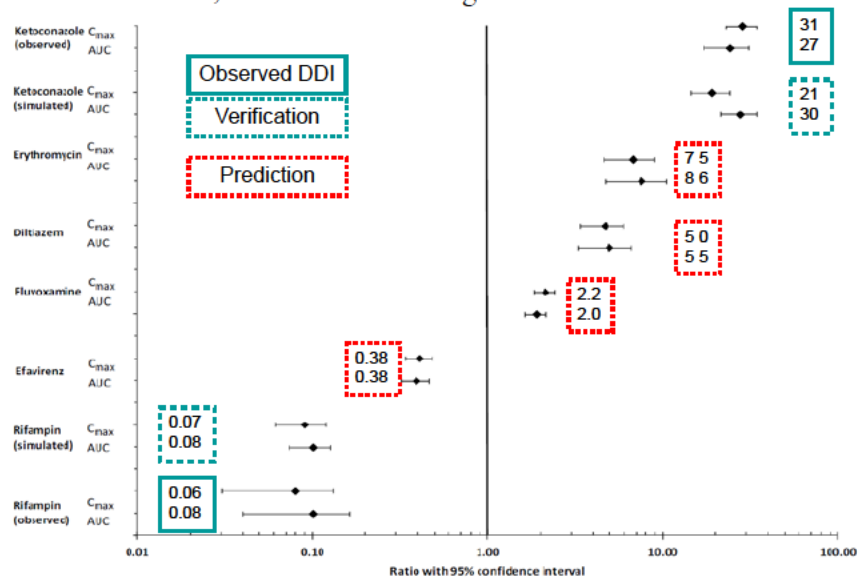
Step 3 - Model Predictions: The applicant conducted simulations to predict the effect of moderate CYP3A4 inhibitors (diltiazem and erythromycin), a weak CYP3A4 inhibitor (fluvoxamine), and a moderate CYP3A4 inducer (efavirenz) on ibrutinib exposure. The reviewer also simulated the effect of another strong CYP3A4 inhibitor ritonavir (time dependent inhibitor) and another moderate CYP3A4 inhibitor fluconazole.

To explore labeling options, the reviewer conducted additional simulations using the applicant's model in order to predict the following:

- the effect of dose staggering and/or dose reduction on ibrutinib exposure following concurrent use with strong or moderate CYP3A4 inhibitors
  - Scenario 1 - Ibrutinib 2 hours before inhibitor
  - Scenario 2 - Ibrutinib + inhibitor at the same time
- the effect of dose doubling or no dose adjustment on ibrutinib exposure following concurrent use with a strong or a moderate CYP3A4 inducer, respectively.

As shown in **Figure 16**, the effects of a strong CYP3A4 inhibitor and inducer were well predicted using the PBPK model (comparing the prediction results to actual clinical trial data). The predicted and observed mean AUC ratios (AUCR = with/without ketoconazole) for ketoconazole were 27 and 30, respectively. The predicted and observed mean AUC ratios for rifampin were 0.08 and 0.08, respectively. Therefore, the model could be used to predict the effect of moderate and weak CYP3A4 inhibitors and inducers.

Figure 16: Simulated and Observed Ibrutinib Cmax Ratios and AUC Ratios with 95% Confidence Intervals of Weak, Moderate and Strong Inhibitors and Moderate and Strong Inducers of CYP3A4



Source: Modified from Applicant's Figure 14 in 13-040-hu-po-pbpk-fk10387-report.pdf

Using the results for the dedicated trials, the predications from the PBPK model and information on exposure response the following considerations were made:

- The exposure response analyses (**Sections 2.2.4**) suggested that exposure changes to a range seen with 140 mg ibrutinib alone may be efficacious. In addition, exposures observed with 840 mg may be acceptable as safety data is available at this dose. The margin of exposures seen with 140 - 840 mg ibrutinib when dosed alone was considered for making dosing recommendations regarding the use of concomitant CYP3A4 modulators.
- The dose could only be reduced to 140 mg as this is the lowest capsule strength available.
- Dose reductions of ibrutinib and/or dose staggering in the presence of a strong or moderate CYP3A4 inhibitor were considered. A dose staggering approach was considered as a possibility as ibrutinib undergoes extensive first-pass metabolism and the greatest effect of CYP3A4 is expected to be near the time of dose administration. However, a dose staggering approach was predicted (by PBPK) to likely only be effective for inhibitors that were not time-dependent and did not have significant accumulation with multiple doses such as ketoconazole (**Table 15**). The dose staggering approach did not seem feasible as the label would need to specify which specific inhibitors are time-dependent or likely to accumulate.
- Since ibrutinib is likely to be given chronically in a patient population that is older, it is likely that the use of antibiotics and other CYP3A4 inhibitors may be needed during ibrutinib therapy. Therefore, an approach was considered to hold the dose of ibrutinib for short term use of CYP3A4 inhibitors that are not chronically administered. This was deemed a reasonable approach as patients in the pivotal trials still responded to therapy even when they required short term dose interruption during therapy (please consult the **Clinical Review** for further details on dose reductions and interruptions). Doses were withheld for treatment-emergent adverse events in 44 (39.6%) patients. Dose withholding was defined as missing doses for ≥ 7 consecutive days.

- A dose increase was considered with the use of strong and moderate CYP3A4 inducers. A simulation (**Table 16**) was performed to compare the exposure that would result from a dose increase to 1120 mg (double) or keeping a 560 mg dose with concomitant use of moderate or strong CYP3A4 inducers. The goal was to ensure the resulting exposures would not be lower than exposures observed at a 140 mg dose which is the dose that may still be efficacious as supported by the exposure response analysis for efficacy. We only considered dose increases to 1120 mg (double dose) as the highest dose given in the dose escalation trial 04753 was 1400 mg in the 12.5 mg/kg dosing cohort and absorption or dose-linearity data are not available at higher doses. The simulation showed that even with double the dose when using a strong CYP3A4 inducer the exposures observed would still be lower than when ibrutinib 140 mg is dosed alone. For concomitant administration of a moderate inducer, an ibrutinib dose increase to 1120 mg could result in exposures seen at the proposed doses and the use of the proposed doses would still result in higher exposures than those observed at the dose at the 140 mg dose (**Table 16**).

Table 15: Summary of Simulated Data for the Effect Dose Staggering on Ibrutinib Exposures when Ibrutinib 560 mg is Concomitantly Used With CYP3A4 Inhibitors

CYP3A4 inhibitor and dosing regimen	Inhibition mechanism	Ibrutinib dosing in relation to inhibitor dosing*				Does dose staggering have effect?
		Scenario 1 2 hrs. before inhibitor		Scenario 2 Co-administration		
		Ibrutinib exposure ratio (with/without inhibitor)				
		AUC	Cmax	AUC	Cmax	
Ketoconazole 400 mg QD	Strong, reversible	5.1	3.1	29	21	Yes
Ritonavir 100 mg BID	Strong, TDI**	39	23	40	24	No
Diltiazem, 120 mg BID	Moderate, TDI**	4.0	3.9	4.2	4.1	No
Erythromycin, 500 mg TID	Moderate, TDI**	6.9	6.6	7.0	6.4	No
Fluconazole, 200 mg QD	Moderate, reversible	4.3	3.9	5.5	5.3	slightly

*: Another scenario when ibrutinib is given 2 hr after inhibitor showed no difference compared to scenario 2 for all inhibitors

**: TDI: time dependent inhibitor

Table 16: Summary of Simulated Data Comparing a Dose Increase to 1120 mg (Double) or Keeping a 560 mg Dose with Concomitant CYP3A4 inducers Compared to Ibrutinib140 mg Alone

Interacting Drug	Mechanism	Ibrutinib exposure ratio (1120 mg with inducer vs. 140 mg no inducer)		Exposure ratio vs. 140 mg above 1?
		AUC	Cmax	
Rifampin	Strong	0.6	0.5	No
Efavirenz	Moderate	3.2	3.2	Yes
Interacting Drug	Mechanism	Ibrutinib exposure ratio (560 mg with inducer vs. 140 mg no inducer)		Exposure ratio vs. 140 mg above 1?
		AUC	Cmax	
Rifampin	Strong	0.3	0.3	No
Efavirenz	Moderate	1.6	1.6	Yes

With the above listed considerations, the following recommendations were made:

CYP3A4 Inhibitors

- A 2 fold increase in exposure with a weak CYP3A4 inhibitor was considered within the acceptable margins and a dose reduction is not deemed necessary.
- A dose reduction to 140 mg daily is recommended with a concomitant moderate CYP3A4 inhibitor if co-administration cannot be avoided. This dose adjustment is likely to result in exposures within an acceptable range considering the upper bound of the 840 mg dose and the predicted exposure change of 5.5 - 8.6.
- Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended.
- For strong CYP3A inhibitors that are for short-term use (treatment for 14 days or less) ibrutinib therapy can be interrupted until the CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, conivaptan) is no longer needed.

CYP3A4 Inducers

- Since a moderate inducer is predicted to decrease exposures 2.6 fold, any decrease in exposure with the concomitant use of weak CYP3A4 inducers are likely in an acceptable margin and a dose increase may not be necessary.
- In addition, a dose adjustment with the use of moderate inducers is not necessary as it would result in exposures above those at the 140 mg dose when ibrutinib is dosed alone.
- However, the use of concomitant strong CYP3A4 inducers should be avoided as a dose adjustment cannot be recommended.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Based on in vitro studies, ibrutinib and PCI-45227 are unlikely to inhibit any major CYPs or induce CYP 1A2, 2B6 or 3A4 at clinically relevant doses.

As a CYP inhibitor:

Based on in vitro studies (06-029-Hu-X-CYP and 10-016-Hu-X-CYP), ibrutinib and PCI-45227 are unlikely inhibitors of any of the major CYPs in humans at clinically relevant doses. The inhibition potentials of ibrutinib (0.0044 - 44.0 µg/mL) and PCI-45227 (0.014 - 47.5 µg/mL) were evaluated at a single probe substrate concentration in human hepatic microsomes. The I/Ki was calculated using the ibrutinib Cmax of 164 ng/mL and the PCI-45227 Cmax of 122 ng/mL reported on Day 8 for the 560 mg daily dose in patients (**Table 17**).

In vitro, Ibrutinib was not an inhibitor of CYP1A2 and CYP2E1 and showed no time-dependent inhibition of CYP3A4. It was a weak inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 in vitro. PCI-45227 was not an inhibitor of CYP1A2, CYP2C19, CYP2E1 and CYP3A4/5. It was a weak inhibitor of CYP2B6, CYP2C8, CYP2C9 and CYP2D6 in vitro, however, the estimated I/Ki values were < 0.1.

Table 17: Summary of CYP Enzyme Inhibitory Potential (I/Ki) of Ibrutinib and PCI-45227

CYP Enzyme	Substrate (Concentration in µM)	Ibrutinib		PCI-45227	
		Ki (µg/mL)	[I]/Ki	Ki (µg/mL)	[I]/Ki
1A2	Ethoxyresorufin (1)	[a] > 44	NC	[b]NC	NC
2B6	Bupropion (100)	2.1	0.08	4.04	0.03
2C8	Paclitaxel (10)	5.3	0.03	7.84	0.02
2C9	Diclofenac (10)	2.6	0.06	13.8	0.009
2C19	Omeprazole (0.5)	2.9	0.06	[a] > 47.5	NC
2D6	Dextromethorphan (5)	5.5	0.03	18.1	0.007
2E1	Chlorzoxazone (100)	NC	NC	NC	NC
3A4/5	Midazolam (5)	5.3	0.03	NC	NC
3A4/5	Testosterone (50)	4.4	0.04	[a] > 47.5	NC

[a] IC_{50} reported ; NC – not calculated; Phenacetin 10 µM used as substrate;

As a CYP inducer:

Based on an in vitro study 10-075-HU-X-INDC, ibrutinib and PCI-45227 are unlikely inducers of CYP1A2, CYP2B6 or CYP3A4.

- In cultured human hepatocytes where the positive controls caused anticipated increases in CYP enzyme expression, ibrutinib and PCI-45227 (at concentrations up to 10 µM) did not cause significant increases (on average ≤ 2.0-fold increase and ≤ 20% of positive control CYP inducer) in CYP1A2, CYP2B6 or CYP3A4/5 activity.
- Ibrutinib (0.5 - 10µM) increased CYP1A2 mRNA levels > 2 fold but the increase was < 20% of omeprazole in hepatocytes.
- PCI-45227(10µM) increased CYP1A2 mRNA levels an average of 3.75 fold for CYP2B6 and 6.7 fold for CYP3A4. The applicant argues that in both cases this was driven by one high

value out of the 3 samples tested in each case. For CY2B6 mRNA levels, one hepatocyte preparation showed an 8.79 fold increase, but the other 2 samples had < 2 fold increase. For CYP3A4 mRNA levels, one hepatocyte preparation showed an 18.4 fold increase in one hepatocyte preparation, but the other 2 samples had < 2 fold increase.

2.4.2.4 Are other metabolic/transporter pathways important?

Ibrutinib is not a substrate of P-gp, in vitro, but is a weak inhibitor of P-gp with an IC_{50} of 2.15 µg/mL. Based on an I/Ki of < 0.1, systemic ibrutinib is the unlikely to have a potential to inhibit P-gp in humans. However, it may have an effect on P-gp substrates in the GI tract due to higher local concentrations after an oral dose. A PBPK model predicted that staggering the dose of ibrutinib and an oral P-gp substrate by at least 2.5 hours could minimize the potential for an interaction. PCI-45227 is not a substrate or inhibitor of P-gp. Refer to **Section 2.2.5.4** for more details.

Other transporters have not been evaluated. Considering the significant increase in exposure with CYP3A4 inhibition, transporter interactions affecting ibrutinib as a substrate should be of minimal concern. However, a comment will be sent to address the evaluation of the inhibition potential of ibrutinib and its metabolites on other transporters such as BCRP, OATP1B1/OATP1B3, OCT2, OAT1 and OAT3.

2.4.2.5 Are there any other in vivo drug-drug interaction studies?

No.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Ibrutinib [redacted] (b) (4) low solubility, but high permeability characteristics (For more information refer to the ONDQA Quality Review). [redacted] (b) (4)

Solubility: Although its solubility increases with decreasing pH, ibrutinib can be classified as slightly soluble or practically insoluble in aqueous media (**Table 18**). It is soluble in some organic solvents, but the solubility is solvent dependent (**Table 19**).

Table 18: Solubility of Ibrutinib in Different Aqueous Media Across the pH Range of 3 - 8

Solvent	Solubility in mg/mL Solution	pH of Solution	USP Definition
Purified Water	0.003	~5.5	Practically insoluble
0.1 N HCl	2	1.2	Slightly soluble
60:40 Water: Acetonitrile (H_2O:CH_3CN)	7	NA	Slightly soluble
0.5% DMSO in 60:40 H_2O:CH_3CN	6	NA	Slightly soluble
0.2% Formic Acid	0.06	3	Practically insoluble
0.1% Trifluoroacetic acid	0.25	1.9	Very slightly soluble
10 mM Ammonium acetate	0.003	4.5	Practically insoluble
10 mM Ammonium acetate	0.003	6	Practically insoluble
100 mM Ammonium acetate	0.003	8	Practically insoluble
0.3% Sodium lauryl sulphate	1.1	6.8	Slightly soluble

NA = Not applicable

Source: Applicant's Table 2 in pharmaceutical-development-ds.pdf

Table 19: Solubility of Ibrutinib in Various Organic Solvents

Solvent	Solubility in mg/mL Solution	Ph. Eur./USP Definition
Methanol	39	Soluble
Acetone	50	Soluble
Ethanol	19	Sparingly soluble
2-Propanol	9	Slightly soluble
Acetonitrile	16	Sparingly soluble
Dichloromethane	>300	Freely soluble
Ethyl Acetate	23	Sparingly soluble
Hexane	0.0051	Practically insoluble
Heptane	0.0049	Practically insoluble
N,N-Dimethylformamide (DMF)	>500	Freely soluble
Dimethyl Sulfoxide (DMSO)	>500	Freely soluble
Tetrahydrofuran (THF)	>300	Freely soluble

Source: Applicant's Table 1 in pharmaceutical-development-ds.pdf

Permeability: Ibrutinib is a not a substrate of p-gp, in vitro. Studies performed using Caco-2 cell monolayers indicated that ibrutinib is likely to have a high apparent permeability. Atenolol 10 µM, propranolol 10 µM and talindolol 10 µM were used as controls. The apparent permeability from the apical to the basolateral side for ibrutinib 10 µM was 57.9×10^{-6} cm/s with an efflux ratio of 0.13 which is <1 **(Table 20)**.

Table 20: Permeability of Ibrutinib in Caco-2 Monolayers

P-gp Inhibitor	Papp (AB) * 10^{-6} cm/sec (Mean ±SD)	Papp (AB) * 10^{-6} cm/sec (Mean ±SD)	Efflux Ratio (ER)
Without	57.9 ± 1.09	7.55 ± 1.01	0.13
With Verapamil	46.1 ± 0.185	4.33 ± 0.584	0.094

2.5.2 What is the composition of the to-be-marketed formulation?

The planned commercial drug product is formulated as an immediate release 140 mg hard gelatin capsule. The composition is summarized in **Table 21**.

Table 21: Composition of Ibrutinib 140 mg Capsule

Component	Quality Reference	Function	Quantity/Unit Dose (mg/capsule)
Ibrutinib	In house specification	Active pharmaceutical agent	140 [a]
Microcrystalline cellulose Croscarmellose sodium Sodium lauryl sulfate Magnesium stearate[b]	NF, Ph. Eur., JP NF, Ph. Eur., JP NF, Ph. Eur., JP NF, Ph. Eur., JP		(b) (4)
Size 0, white, opaque, hard gelatin capsule with black "ibr 140 mg" print [c]	In house specification	Capsule shell	1 capsule
		Total	330.0

Source: Applicant's Table 1 in drug-product-desript-comp-dp.pdf

2.5.3 What moieties should be assessed in bioequivalence studies?

The parent compound ibrutinib and its active metabolite PCI-45227 (15 X less potent) are both active moieties and should be assessed in bioequivalence studies.

2.5.4 Is the to-be-marketed formulation the same as the clinical trial formulation and if not, is there bioequivalence data to support the to-be marketed formulation?

(b) (4)

(**Table 22**).

Table 22: Composition of 140 mg (b) (4) Ibrutinib Formulations

			(b) (4)			(b) (4)
Component	**Function**	**Quality Standard**	**Quantity % w/w**	**Quantity / Unit (mg/capsule)**	**Quantity % w/w**	**Quantity /Unit (mg/capsule)**
Ibrutinib	Active Pharmaceutical Ingredient	Manufacture's Specification	(b) (4)	140.0 [a]	(b) (4)	140.0 [a]
Microcrystalline cellulose	(b) (4)	NF, Ph. Eur.		(b) (4)		(b) (4)
Croscarmellose sodium		NF, Ph. Eur.				
Sodium lauryl sulfate		NF, Ph. Eur.				
Magnesium stearate		NF, Ph. Eur.				
Size 0, gray, opaque, hard gelatin capsule		Manufacture's Specification	NA	1 capsule	NA	1 capsule
Total						(b) (4)

[a] The ibrutinib quantity per capsule is adjusted based on its purity
Source: Applicant's Table 2 in summary-biopharm.pdf

A formal bioequivalence trial was not performed to compare the formulations manufactured at the two sites. However, PK comparisons were performed for the two formulations in 1102-CA. On Day 1, the mean Cmax was 59% higher and AUC_{0-24} was 24% higher for the (b) (4)

formulation compared to the [redacted] formulation. On Day 8 (steady-state), the mean Cmax was 22% higher and AUC_{0-24} was 19% higher for the [redacted] formulation compared to the [redacted] formulation (**Table 23**).

Table 23: Ibrutinib PK Comparisons of 420 mg Dosed as the [redacted] Formulation or the [redacted] Formulation in 1102-CA

Formulation	Day	N	Cmax (ng/mL)	[a]%↑ Cmax	AUC_{0-24}(ng.hr/mL)	[a]%↑ AUC_{0-24}
[redacted]	1	88	98.8	NA	560	NA
	8	82	116	NA	642	NA
	1	88	157	58.9	695	24.1
	8	82	141	21.6	764	19.0

[redacted]

Although both the formulations were used in the pivotal trials, patients received the TBM formulation in the majority of treatment cycles (**Table 24**). Each patient may have received either one or both of the formulations during the duration of treatment. The applicant argues that a formal BE trial is unnecessary and that the safety and efficacy in the phase two trials support the use of the [redacted] formulation as >70% of the treatment cycles used this TBM formulation.

Table 24: Percentage of Cycles of Exposure by Formulation

Study	Capsule Strengths (mg)	[redacted]	
PCYC-04753[a]	40/140/200	9%	91%
PCYC-1102-CA (Relapsed/Refractory 420 mg cohorts)	140	72%	28%
PCYC-1104-CA	140	87%	13%
PCI-32765CLL1002[b]	40	0%	100%
PCI-32765CLL1004[b]	Not applicable, solution formulation		

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

In a sub-study of 1102-CA, a high-fat meal increased ibrutinib exposure approximately 2 fold compared with ibrutinib administration under fasting conditions in steady-state conditions. The CV% for AUC_{last} were similar with 58.3% in the fasted arm and 58.1% in the fed arm.
Each patient received ibrutinib 420 mg dosed either after an overnight fast or with a high fat high calorie breakfast (800 – 1000 calories with 50% from fat) in a cross-over fashion on Day 8 and 15 depending on the randomization schedule (AB or BA). PK samples were collected pre-dose

and at 0.5, 1, 2, 4, 6 and 24 hours post-dose. The PK parameters are summarized in **Table 25**.

Table 25: PK Parameters (Mean ± SD) of Ibrutinib after 420 mg Dosed after an Overnight Fast or after a High Fat Meal in 1102-CA

Group	N	[a]Tmax (hr)	$T_{1/2}$	Cmax (ng/mL)	AUC_{0-24} (hr.ng/mL)	Geo Mean Ratio (90% CI)	
						Cmax	AUC_{0-24}
Fasted	15	1.9 (1.0 - 4.1)	[b]11.3 ± 9.6	51.7 ± 46.7	485 ± 265	Reference	Reference
Fed	16	3.9 (1.1 – 6.0)	[c]4.5 ± 0.76	120 ± 95.4	864 ± 402	2.2 (1.6-3.1)	1.7 (1.3 – 2.3)
[e]Modified Fasted	16	2.0 (1.0 - 4.0)	[d]5.58 ± 1.23	86.3 ± 63.0	546 ± 364	N/A	NA

[a]median(range); [b] N=9; [c]N=4; [d]N=6; [e]non-standardized and uncontrolled; NA=not applicable

In addition, samples were evaluated on Day 1 to assess the effect of modified fasting conditions. This part of the trial was not controlled for standardized meals or specific timing. Patients were given the instruction to take the drug at least 30 minutes before and 2 hours after a meal. The CV% was 66% in the modified fasting group. The mean exposures appear higher for the modified fasting conditions compared to the fasted group. However, due to accumulation of up to 1.6 fold expected by Day 8 (fasted group PK sampling at steady state) comparison of PK cannot be made directly as the PK in the modified fasting group was collected on Day 1. Due to lack of exposure response for safety in the dose range of 420- 840 mg, we recommend that ibrutinib be dosed without regards to food.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

The ONDQA Biopharmaceutics reviewer concluded that the proposed dissolution method QCM-164 and acceptance criterion are acceptable on an interim basis. A Tween 20 dissolution method QCM-168 is deemed superior to the SLS dissolution method QCM-164 but, limited GMP QC data and no GMP QC-stability testing data are available for the drug product tested with the QCM-168. Therefore, a PMC will be issued for the collection of additional dissolution profile data (n=12) using the QCM-168 method. Refer to the ONDQA Biopharmaceutics review for more details.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured appropriately in the clinical pharmacology and biopharmaceutics studies?

Yes. All the submitted clinical pharmacology related studies analyzed samples for ibrutinib and the active metabolite PCI-45227. Ibrutinib and PCI-45227 (M37) only made up 10 percent of the exposure of total radioactivity in the mass balance trial. Other metabolites were not measured in other trials. The main circulating entities in rat plasma were M15, M5 and M37, in contrast the main circulating entities in humans were M21, M25, M34, M37 and unchanged drug. The mass balance trial was a single dose trial, therefore the steady-state concentrations of each metabolite and the contribution of each to the overall exposure is unknown.

2.6.2 Which metabolites have been selected for analysis and why?

PCI-45227 was evaluated in the trials because it is an active metabolite. It is a less potent inhibitor of BTK compared to the parent drug (15 X less potent).

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Ibrutinib is highly bound to human plasma proteins (98%). The total concentration of ibrutinib in plasma was measured in the clinical trials. Although protein binding was independent of varying concentrations of ibrutinib, the binding varied with changing concentrations of human α1-acid glycoprotein. It is unclear if binding would vary with different amounts or concentrations of human serum albumin (binding was only evaluated at one concentration; Refer to **Section 2.2.5.4**). Therefore, protein binding should be assessed in the ongoing hepatic impairment trial.

2.6.4 What bioanalytical methods are used to assess concentrations?

Ibrutinib and PCI-45227 were measured using LC/MS/MS. The method validation reports are included for the methods used for plasma PK analysis. The analyses of blood and urine samples for the mass balance trial were not validated and have no method validation reports available. Profiling and identification of metabolites of [^{14}C]-ibrutinib in the mass balance trial were determined by (b) (4) analysis with radio-detection and mass spectrometry methods.

In 2008, a bioanalytical method for ibrutinib and PCI-45227 was validated at (b) (4) ((b) (4)-622021 [08-086-Hu-Z-BMV]). In 2011, a bioanalytical method for ibrutinib and PCI-45227 was validated at (b) (4) (AV11-PCI32765-01[10-088-Hu-ZBMV]). In 2012, a bioanalytical method for ibrutinib and PCI-45227 was validated at (b) (4) (BA10267[12-071-Hu-Z-BMV and BA10283[12-153-Hu-Z-BMV]). The (b) (4) method was thereafter transferred to (b) (4) and subsequently validated (BA10400[JNJ-2119;12-104-Hu-Z-BMV] and BA10399[JNJ-2120; 12-156-Hu-Z-BMV]).

The (b) (4) method was used in 04753 and 1102-CA, (b) (4) Method was used for 1104-CA and in the food effect cohort of 1102-CA and the (b) (4) method was used for 1002 and 1004. Details of these methods are discussed in **Section 2.6.5.**

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The LC/MS/MS methods developed are discussed in **Section 2.6.4**. The concentration ranges, correlation coefficients and inter assay precision and accuracy for the analytes are summarized for each method in **Table 26**. Results for ibrutinib and PCI-455227 were calculated using peak area ratios of analyte to internal standard and calibration curves were generated using a weighted ($1/x^2$) linear least-squares regression.

The mean Cmax values for doses of 8.3 mg/kg and 560 mg were above the upper limit of the calibration curve. In addition, exposures observed in the ketoconazole trial were up to 30 fold higher. The ketoconazole interaction trial 1102 used the (b) (4) Method for analysis. The (b) (4) method included dilution integrity of up to 20X, which was sufficient for PK analysis in this trial as ibrutinib was only used at a 40 mg dose when used in combination with ketoconazole.

Table 26: LC/MS/MS Analytical Methods for Ibrutinib and PCI-45227

(b) (4)


(b) (4)


(b) (4)


(b) (4)

3 APPENDICIES

3.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA 205552
Submission Number (Date)	June 28, 2013
Compound	Ibrutinib
Dosing regimen	560 mg QD (Mantle cell lymphoma)
Clinical Division	DHP
Primary PM Reviewer	Bahru A Habtemariam, Pharm.D.
Secondary PM Reviewer	Anshu Marathe, PhD.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

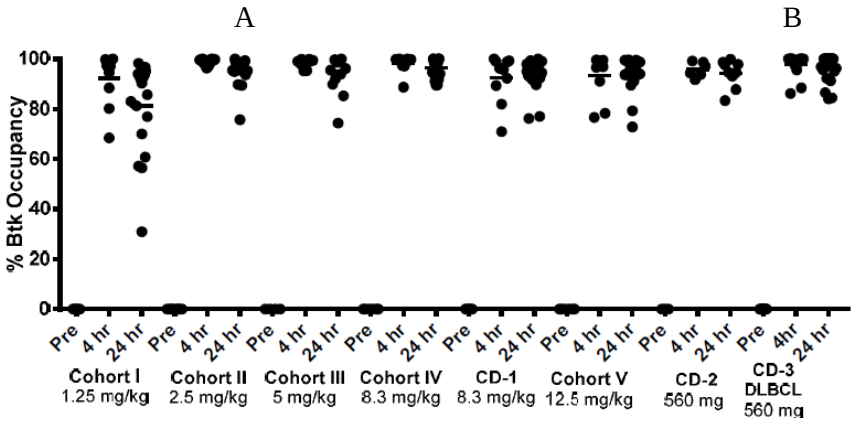
1.1.1 Is there dose/exposure-response relationship for PD marker and effectiveness endpoint?

There is no evidence of an exposure-response for overall response rate (ORR) in the range of exposures observed following ibrutinib dose of 560 mg in mantle cell lymphoma (MCL) in pivotal phase 2 trial (Figure 3). Dose-response relationship for BTK (Bruton's tyrosine kinase) occupancy and clinical response in phase 1 study showed that maximum BTK occupancy and maximum response was achieves at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg) (Figures 1 and 2).

Dose selection for the pivotal phase 2 studies was based on a phase 1 dose escalation study that evaluated ibrutinib doses of 1.25 mg/kg to 12.5 mg/kg where, actual doses administered to patients ranged from 80 to 1400 mg. It is important to note that the sponsor initially administered ibrutinib on 35-day treatment cycle where the drug was administered for 28 days followed by a 7 day treatment free period. The sponsor then evaluated the 8.3 mg/kg dose and 560 mg doses on continues dose schedules.

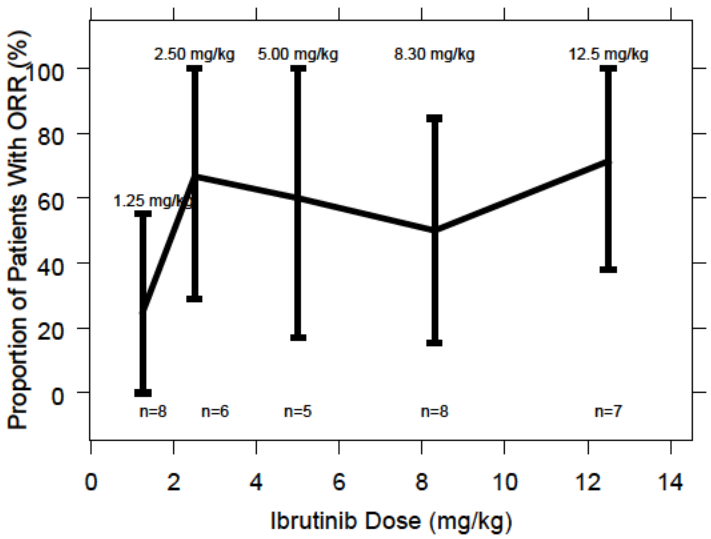
The phase 1 study used PD marker (BTK occupancy) and clinical response for dose selection. As shown in **Figure 1** below, maximum BTK occupancy was achieved for dose 2.5 mg/kg and greater. Similarly, maximum clinical response was achieves at doses ≥ 2.5 mg/kg. BTK occupancy and clinical response rates were similar for continuous dosing (CD) and 35-day treatment cycle schedules (**Figure 1)**, except in patients with diffuse large B-cell lymphoma (DLBCL), where response rate was 30%.

Figure 2. Maximal clinical response BTK occupancy achieved at doses > 2.5 mg/kg*.



Cohorts 1 through 6 received treatment in a 35-day treatment cycle , cohorts CD-1,CD-2, CD-3= received treatment as continuous dosing

Figure 3. Maximal clinical response (ORR) achieved at doses > 2.5 mg/kg*.



*ORR for the CD-1,CD-2, CD-3 cohorts were, 67%, 66.7, and 30%, respectively

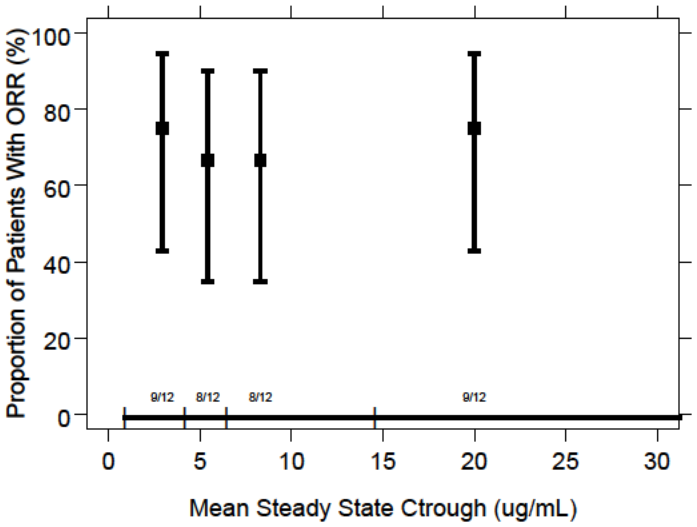
Efficacy data were available from the in 111 mantle cell lymphoma (MCL) patients that were enrolled in the pivotal phase 2 study. The MCL patients were treated with either 560 mg ibrutinib once daily as detailed in **Table 1** below.

Table 1. Summary of phase 2 study design

Study Number	Study Description	Treatment Groups	Primary Study Endpoint
PCYC-1104-CA	Phase 2, open label, nonrandomized study in relapsed or refractory MCL (N=111)	Ibrutinib 560 mg/day	ORR

There is no evidence of an exposure-response for overall response rate (ORR) in the range of exposures observed following treatment ibrutinib dose of 560 mg in MCL patients. Steady state trough plasma concentrations were available from a total of 48 patients. Trough concentrations were obtained on days 1, 8, 15, and 22. Trough concentrations obtained on days 8 or later were used to calculate mean steady state trough concentrations. Figure 3 shows that increasing concentrations of ibrutinib does not influence the proportion of patients with ORR.

Figure 4. Proportion of objective response rate (ORR) is not influenced by increasing steady trough concentrations in MCL patients.

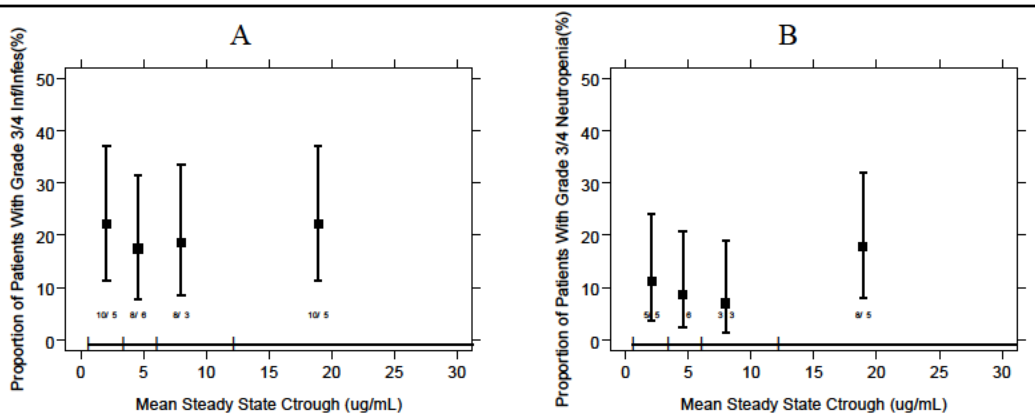


1.1.2 Is there exposure-response relationship for adverse events?

There is no evidence for exposure-response relationship for Grade 3 or 4 infection and infestation and Grade 3 or 4 neutropenia within the range of exposures achieved in phase 2 trials.

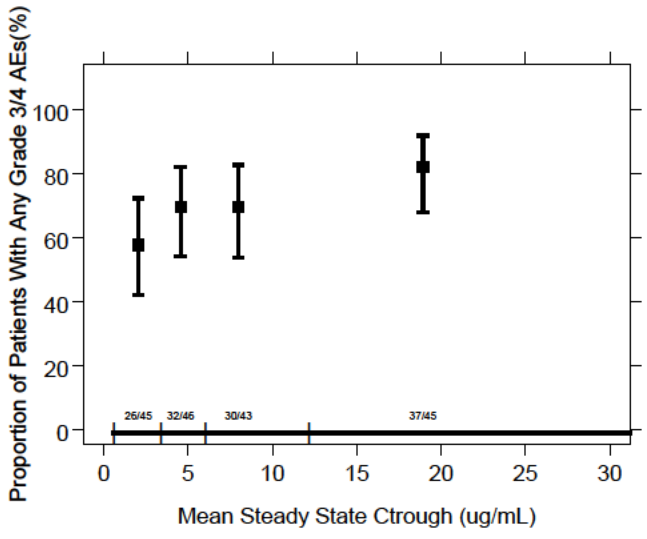
Exposure safety analyses for ibrutinib were conducted using data from the 179 patients who were enrolled in the two phase 2 trials with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). The most frequent and important Grade 3 or higher (Grade 3+) adverse events were infections and infestations and neutropenia. Pharmacokinetic data were available from 125 patients from the phase 2 trials. As shown in the figure below, the proportion of patients with Grade 3+ infections and infestations does not increase with increasing ibrutinib concentrations (**Figure 4**). Similarly Grade 3+ neutropenia did not increase with increasing ibrutinib concentration.

Figure 5. Proportions of patients with Grade 3+ infections and infestations (A) and Grade 3+ neutropenia (B) do not increase with increasing mean steady state concentrations.



While an exposure response relationship for individual toxicities could not be identified (Grade 3+ neutropenia and Grade 3+ infections and infestations),there was a slight increase in the proportion of patients with any Grade 3+ adverse events with increasing mean steady state trough concentrations (**Figure 5**).

Figure 6. Proportion of patients with Grade 3+ adverse events do not increase with increasing trough concentrations.



1.1.3 Is the proposed dose of 560 mg QD in MCL patients appropriate?

The proposed dose of 560 mg QD in MCL patients appears acceptable based on reasonable safety profile and a response rate of 67.6% that was achieved in the phase 2 trial. Additionally no meaningful exposure-response relationship is identified for Grade 3 or 4 neutropenia and Grade 3 or 4 infections and infestations. Thus based on available effectiveness and safety data, the proposed dose appears acceptable. However, the proposed dose is 3-fold higher than the lowest dose that resulted in maximum BTK occupancy and maximum clinical response. Dose-response relationship for ORR and BTK occupancy from Phase 1 study suggested that maximum ORR and maximum occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg). The sponsor should thus consider exploring lower doses in future development programs.

1.1.4 Do age, creatinine clearance, and gender affect the pharmacokinetics of ibrutinib?

The effect of age (< 65 years old vs. > 65 years old), creatinine clearance (categorized as normal, mild, moderate, and severe) and gender was explored on the mean steady state trough concentrations of the drug. **Figure 6** shows that age and creatinine clearance do not influence the exposure of ibrutinib. Similarly, exposure of ibrutinib is not influenced by gender (**Figure 7**). These findings are consistent with findings of sponsor's population PK analysis.

Figure 7. Mean steady state ibrutinib concentrations stratified by age (A) and status of renal function (B).

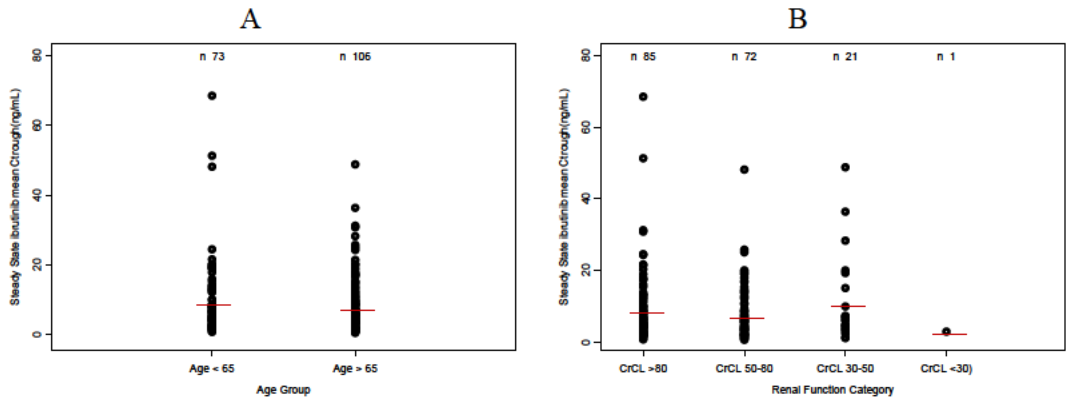
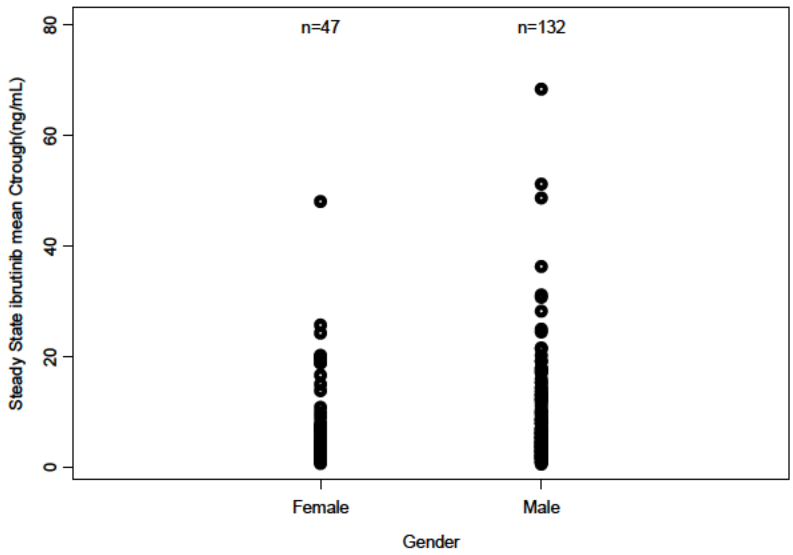


Figure 8. Mean steady state ibrutinib concentrations stratified by gender



Recommendations

Division of Pharmacometrics finds the NDA 205552 acceptable from a clinical pharmacology perspective.

Labeling Statements

See section12.3 of the draft labeling.

RESULTS OF SPONSOR'S ANALYSIS

Population PK Model

Using plasma concentration data from 245 subjects from one phase 1 and two phase 2 trials, the sponsor conducted a population PK analyses to determine the influence of patient covariates on the disposition of ibrutinib. Below are key finding of the population PK analysis results.

- The PK of ibrutinib was described using a standard linear two-compartment model with sequential zero-first order model and a lag time. **Table 2** summarizes the final PK parameter estimates.
- Patient covariates such as age (range: 37-84 years), weight (range: 40.6 – 146.2 kg), creatinine clearance (range: 24.6-212 mL/min), and gender do not have meaningful influence on the clearance of ibrutinib.
- Weight had influence on volume of distribution. This doesn't seem to have any meaningful impact on the exposure to ibrutinib.

- Extrinsic factors such as food and antacids were evaluated. It appeared that food increased the duration of absorption to 3.29 hours while antacids delayed absorption to 1.61 hours. Since this is a chronic treatment, delayed absorption is not expected to influence overall exposure or response to treatment.

Table 2. Summary of Ibrutinib Population PK Parameter Estimates

Parameter	Population Mean Estimate	% SEM	BSV (%CV)	% SEM
CL/F (L/h)	1060	4.32	21.9	51.3
V2/F (L)	246	10.4	153	17.7
Q/F (L/h)	865	5.79	60.7	22.1
V3/F (L)	9620	5.64	47.3	22.5
k_a (h^{-1})	0.463	4.15	0 FIX	-
ALAG1 (h)	0.283	7.67	27.8	30.0
D1 fast/mod fast (h)	1.10	4.62	20.9	45.2
D1 fed (h)	3.29	9.00	20.9	45.2
F1 mod fast/fed (fixed)	1 FIX	-	62.8	11.4
F1 fast	0.666	15.8	62.8	11.4
Power on volumes (allometric coefficient) for body weight	0.641	35.6		
Antacids on D1 (factor)	1.61	3.95		
RUV (CV%)	72.7	5.85		

CL/F = apparent (oral) drug clearance; V2/F = apparent central volume of distribution; Q/F = apparent inter-compartmental flow; V3/F = apparent peripheral volume of distribution; k_a = first-order absorption rate constant; ALAG1=temporal delay (lag time) before absorption process is started; D1 = duration of zero order input; F1 = relative bioavailability; the allometric correction for describing the effect of weight on volumes was implemented as $(WT/median\ weight)^{power}$.
RUV: residual unexplained variability (percent square root of the SIGMA-COV matrix, see Appendix 6); SEM: relative standard error of the mean parameter; BSV: between-subject variability (per cent square root of the OMEGA-COV matrix, see Appendix 6); %CV: percent coefficient of variation

Source: Table 11 from sponsor's population PK report

Goodness of fit plot for the final model

Figure 9. Observation versus population (left plot) and individual predictions (right plot).

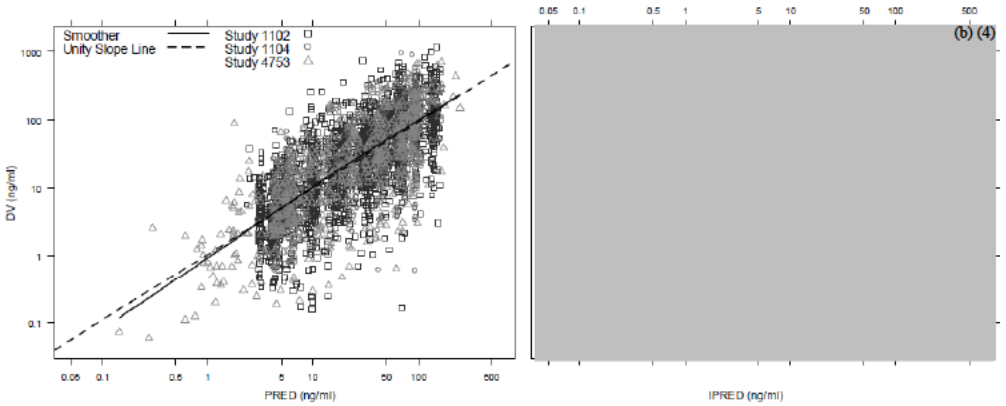
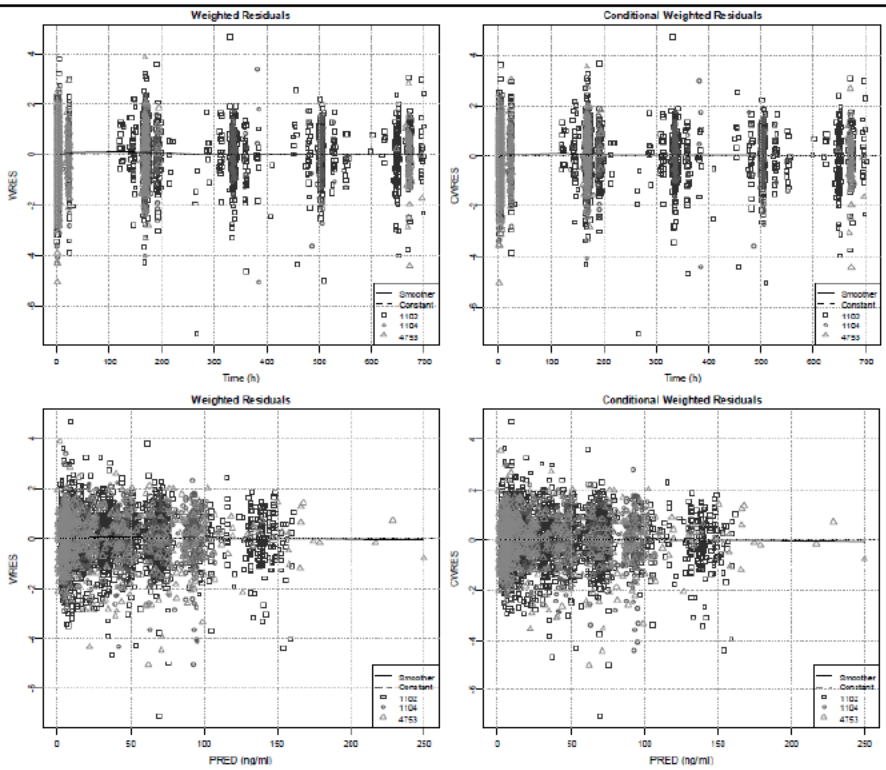


Figure 10. Population residuals (WRES) and conditional weighted residuals (CWRES) versus time and population predictions.



Reviewer's comments:
The sponsor's current model shows high unexplained residual variability (CV=72.7%), high (>35%) shrinkage on several parameters including CL/F and high inter-individual variability on

volume parameters. The sponsor should update the current population PK model with data from current ongoing/future trials.

Exposure-Response Analyses

The sponsor did not conduct exposure-response analysis.

REVIEWER'S ANALYSIS

Objectives

Exposure-response analyses were performed to determine if there is exposure-response relationship for safety and efficacy endpoints. The efficacy endpoint was ORR and the safety endpoints were Grade 3+ infections and infestations and Grade 3+ neutropenia.

Methods

Efficacy, safety, trough concentrations, and dosing data were available from two pivotal phase 2 studies (see section 1 above for details).

Data Sets

Data sets used are summarized in **Table 1** below.

Table 3: Analysis Data Sets.

Name (description)	**(description)**	**Link to EDR**
ibrutinib-nmpk-fv2a-csv.xpt	Pop PK	\\Cdsesub1\evsprod\NDA205552\0005\m5\datasets\pop-pk\analysis\legacy\datasets
adae.xpt (safety)	Safety MCL & CLL patients	\\Cdsesub1\evsprod\NDA205552\0005\m5\datasets\iss-mcl\analysis\adam\datasets \\Cdsesub1\evsprod\NDA205552\0005\m5\datasets\iss-cll\analysis\adam\datasets
adrs.xpt	Efficacy MCL patients	\\Cdsesub1\evsprod\NDA205552\0005\m5\datasets\ise-mcl\analysis\adam\datasets \\Cdsesub1\evsprod\NDA205552\0005\m5\datasets\ise-cll\analysis\adam\datasets

Software

S-PLUS was used for the reviewer's analyses.

Results

See section 1.1

3.2 PBPK REVIEW

Physiological-based Pharmacokinetic Modeling Review Memo

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 205552
Drug Name	ibrutinib (PCI-32765, JNJ-54179060)
Proposed Indication	For the treatment of patients with Mantle cell lymphoma (MCL) with at least 1 prior therapy, (b) (4)
Clinical Division	DHP
PBPK Consult request	Elimika Pfuma, Pharm.D Ph.D.
Primary PBPK Reviewer	Yuzhuo Pan, Ph.D.
Secondary PBPK Reviewer	Ping Zhao, Ph.D
Sponsor	Pharmacyclics, Inc.(Pharmacyclics) and Janssen Research & Development, LLC (Janssen R&D)

1. *Objectives*

The main purposes of this review memo are to (a) review sponsor's physiologically-based pharmacokinetic (PBPK) report entitled "Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-5417960 (PCI-32765 or Ibrutinib) and Strong, Moderate and Mild Inhibitors and Inducers of CYP3A in Human Subjects" [1] in NDA205552; and (b) to conduct further simulations to support ibrutinib dose regimen in patients taking different CYP3A inhibitors/inducers.

2. *Background*

2.1. Regulatory history on PBPK submission

Ibrutinib (PCI-32765, JNJ-54179060) is a first-in-class, orally administered, covalent inhibitor of Bruton's tyrosine kinase (BTK) being developed for the treatment of B lymphocyte (B-cell) malignancies, including Mantle cell lymphoma (MCL) (b) (4) Sponsor proposed dose regimen is oral dose of 560 mg once daily (q.d.) in MCL (b) (4)
A PBPK model was developed by the sponsor (b) (4) After initial review of the report, an information request was sent to the sponsor on July 18, 2013 (07182013IR, Appendix 1). On August 2, 2013, sponsor submitted additional information to address issues raised in IR [2].

2.2. Highlight of drug absorption and disposition

Table 4. Summary of ibrutinib's absorption, distribution, metabolism and excretion (ADME) [3]

Absorption	Complete absorption. Low absolute bioavailability due to extensive first pass metabolism with high inter-subject variability
Distribution	Rapid and extensive distribution to peripheral tissues and/or binding to macromolecules in the circulation (Vdss/F=10,000 L), highly bound to plasma proteins (97.3%)
Metabolism	Extensive metabolism by CYP3A; near hepatic blood flow clearance
Excretion	Negligible urinary excretion

The submitted PBPK modeling report [1] and additional information requested by the Office of Clinical Pharmacology [2] addressed the key questions on whether PBPK model predicts ibrutinib exposure change when the drug is co-administered with CYP3A inhibitors or inducers. The sponsor also used PBPK model of ibrutinib to explain potential food effect and to predict drug exposure in subjects with hepatic impairment.

3. Methods

Simcyp® (V12, Sheffield, UK) [4-5] was used by the sponsor to construct and verify PBPK model. Software's "Healthy volunteer" population, a modified "Oncology" population [6], and cirrhosis populations (Child-Pugh A, B, or C) [7] were tested. Final model parameters and their sources are summarized in **Appendix Tables A1 and A2**. PBPK modeling of ibrutinib followed three steps.

3.1. Model building

Results of in vitro ADME experiments and physicochemical properties, and in vivo PK studies were used.

3.2. Model verification

Clinical drug-drug interaction (DDI) studies with strong CYP3A inhibitor and inducer (ketoconazole 400mg q.d. combined with single dose ibrutinib, study PCI-32765CLL1002, and rifampin 600mg q.d. combined with single dose ibrutinib, study PCI-32765CLL1010) were used to verify ibrutinib PBPK model.

3.3. Model applications

The sponsor conducted simulations to predict the effect of moderate CYP3A inhibitors (diltiazem, erythromycin), weak CYP3A inhibitor fluvoxamine, and moderate CYP3A inducer efavirenz on ibrutinib exposure. Inhibitor PBPK models were verified via simulations using probe substrates based on literature findings. Sponsor also explored the effect of food and hepatic impairment on ibrutinib exposure.

Using sponsor's models, reviewer conducted additional simulations to (a) predict the effect of dose staggering (for example, administering ibrutinib 2 hours before the administration of an inhibitor) or a 3- to 4-fold dose reduction on ibrutinib exposure following concurrent use with strong or moderate CYP3A inhibitors, and (b) to predict the effect of dose doubling or no dose adjustment on ibrutinib exposure following concurrent use with a strong or a moderate CYP3A inducer, respectively. For inhibitors, two scenarios were compared to evaluate dose staggering and dose reduction:

Inhibitor Dosing Scenario 1. Ibrutinib, washout, ibrutinib 2 hours before inhibitor

Inhibitor Dosing Scenario 2. Ibrutinib, washout, ibrutinib + inhibitor at the same time

Besides inhibitors and inducers used by the sponsor, FDA reviewer also simulated the effect of another strong CYP3A inhibitor ritonavir, and another moderate CYP3A inhibitor fluconazole. The same ritonavir drug model applied to another NDA submission by the same sponsor was used in this analysis. Fluconazole model in the software's drug library was directly used.

Reviewer also evaluated simulation output with regard to predicted ibrutinib exposure in different segments of the gastrointestinal tract to determine the potential for ibrutinib to inhibit P-glycoprotein (P-gp).

4. Results

4.1. Can PBPK model predict ibrutinib exposure change when the drug is co-administered with CYP3A inhibitors or inducers?

The constructed PBPK model of ibrutinib reasonably captured the observed PK profiles of ibrutinib. The model was further verified using clinical DDI data when the drug was co-administered with a strong CYP3A inhibitor ketoconazole, or a strong CYP3A inducer rifampin. As shown in **Figure 1**, the effects of strong inhibitor and inducer were well predicted using the PBPK model. The predicted and observed mean AUC ratios (AUCR, with/without an interacting drug) by ketoconazole were 27 and 30, respectively. The predicted and observed mean AUC ratios by a rifampin were 0.08 and 0.08, respectively. Cmax ratios (CmaxR) were also reasonably predicted by the PBPK models.

Using the established ibrutinib PBPK model, the sponsor predicted the effects of several moderate and weak inhibitors and a moderate inducer of CYP3A, and the results are shown in **Figure 1**. The model simulated mean AUCRs were 8.6, 5.5, 2.0, and 0.4 for the effect of a moderate inhibitor erythromycin, a moderate inhibitor diltiazem, a weak inhibitor fluvoxamine, and a moderate inducer efavirenz, respectively.

4.2. Can PBPK model provide dose optimization strategy for combined use of ibrutinib with specific CYP3A inhibitors or inducers?

Based on the available efficacy and safety data (See Clinical Pharmacology Question Based Review), exposures associated with a 4-fold dose reduction (140 mg) and an approximately 2-fold dose increase (840 mg) from the proposed ibrutinib dose (b) (4) 560 mg) can be used to set the lower and upper bounds for assessing the effects by CYP3A modulators. Dose reduction of ibrutinib and/or dose staggering in the presence of a CYP3A inhibitor, or doubling or keeping the proposed dose of ibrutinib in the presence of a CYP3A inducer, may achieve an ibrutinib exposure that can fall in between the exposure boundaries. The FDA reviewer used sponsor's models to simulate (a) the effect of dose staggering or a 3- to 4-fold dose reduction on ibrutinib exposure following concurrent use with strong or moderate CYP3A inhibitors, and (b) the effect of dose doubling or no dose adjustment on ibrutinib exposure following concurrent use with a strong or a moderate CYP3A inducer, respectively. The simulation results for inhibitors and inducers are summarized in Appendix Tables A3-A5 and Tables A6-A7, respectively. Consequently, a dose optimization strategy for individual CYP3A inhibitors and inducers for their abilities to achieve ibrutinib exposure within the range described above is proposed in **Table 1**. For a strong reversible inhibitor that does not significantly accumulate, such as ketoconazole given 400 mg q.d., a reduced dose of ibrutinib (140 mg) should be given more than 2 hours prior to inhibitor; for a strong time-dependent CYP3A inhibitor such as ritonavir given 100 mg given twice daily, dose-staggering, dose reduction of ibrutinib, or the combination of both staggering and dose reduction, cannot achieve ibrutinib exposure within the exposure range defined above; for moderate inhibitors, a reduced ibrutinib dose to 140 mg can be used; for strong inducer such as rifampin, doubling ibrutinib to 1120 mg cannot achieve ibrutinib exposure within the exposure range defined above; and for moderate inducer such as efavirenz, the proposed dose (560 mg) can be used and should not be further reduced.

4.3. Predicting ibrutinib PK in specific populations

In clinical trials, exposure of ibrutinib in oncology subjects appears to be approximately 2-fold higher than that in healthy volunteers. Sponsor ascribed this difference to the type and timing of food with respect to drug administration in their response document to the information request (Appendix 1 and Appendix Figure A1) [2]. For drugs that are efficiently eliminated by intestinal and liver CYP3A with a clearance that is blood flow limited (such as ibrutinib), the effect of food on blood flows in the liver and in the intestine may lead to significant increase in drug exposure [7]. Sponsor conducted further simulations to support this mechanism [1].

In addition, the sponsor simulated exposure increase in subjects with varying degrees of hepatic impairment (Child-Pugh A, B, and C). Interim PK data of ibrutinib in limited number of subjects showed an approximately 6-fold increase in plasma AUC in subjects with moderate hepatic impairment (study PCI-32765CLL1006 described in reference [2]). PBPK model significantly over-predicted exposure change (mean simulated exposure changes were 4.7-, 14, and 21-fold in mild, moderate, and severe hepatic impaired patients, respectively). The over-prediction is consistent with sponsor's in-house experiences with other investigational drugs [2].

4.4. Predicted ibrutinib exposure in gastrointestinal tract during oral absorption

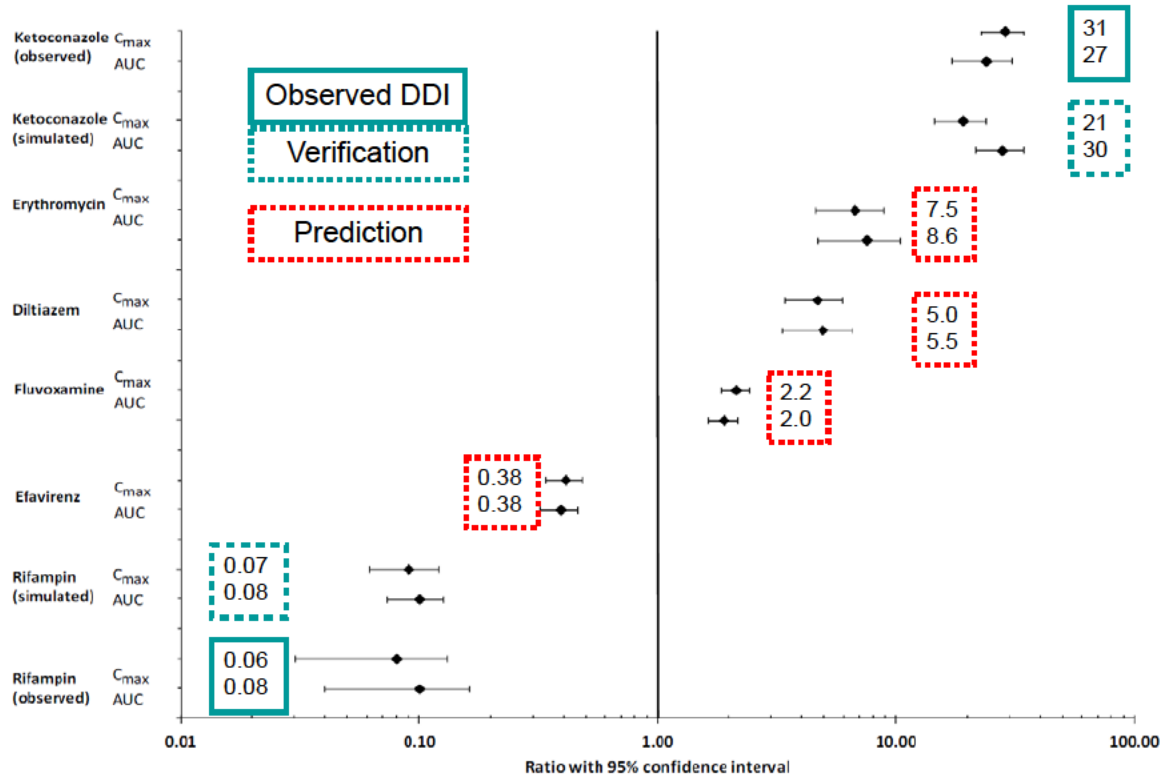
In vitro, ibrutinib was an inhibitor of P-gp, with an IC50 of 4.88 μM (2.15 μg/mL) [3].

According to the current FDA draft drug interaction guidance [9], ibrutinib is likely to inhibit P-gp in the gut. The calculated mean gut luminal inhibitor concentration at proposed dose of 560 mg over IC50, assuming the drug is taken with 250 mL water, was greater than 10. Further analysis was conducted by the FDA reviewer on the simulation output from the PBPK model. The PBPK software provides simulated drug absorption kinetics and luminal drug concentration-time profiles for each segment of the GI tract. Generally, ibrutinib is predicted to be quickly absorbed at different segments (Tmax ranges from 1 to 2 hours), and absorption is generally completed in 2.5 hours. Therefore, assuming ibrutinib can inhibit P-gp along the GI tract in vivo, the inhibitory effect on substrates that have narrow therapeutic index (such as digoxin) can be minimized if the substrate is not administered during the absorption phase of ibrutinib.

5. Conclusion

The sponsor's PBPK model reasonably predicted the observed effect of strong CYP3A inhibitor and inducer. The PK difference between cancer and healthy populations appears to be explained mainly by food effect. The simulations of PBPK model provided a dose optimization strategy for combined use of ibrutinib with specific CYP3A inhibitors or inducers.

Figure 1. Simulated and observed ibrutinib Cmax ratios[¶] and AUC ratios[¶] with 95% confidence intervals of weak, moderate, and strong inhibitors and moderate and strong inducers of CYP3A (Modified from Figure 14 of reference [1]).



[¶]ratios expressing the mean fold changes and calculated as follows: parameter with inhibitor or inducer/parameter without inhibitor or inducer

Table 1. PBPK driven dose optimization following concurrent use of ibrutinib with various CYP3A modulators.

CYP3A modulators	Goal	CYP3A interaction mechanisms of co-medications	Ibrutinib dosing
Inhibitors	Simulated ibrutinib exposure vs. that of 560 mg without inhibitor should be <2 fold	Strong, reversible, minimal accumulation (e.g. ketoconazole)	Reduce to 140 mg and give 2 hours before inhibitor
		Strong, time-dependent (e.g. ritonavir)	Do not use
		Moderate	Reduce to140 mg
Inducers	Simulated ibrutinib exposure vs. that of 140 mg without inducer should be >1	Moderate	No dose adjustment
		Strong	Do not use

6. Appendices

Abbreviations: ADAM: Advanced dissolution, absorption, and metabolism model; ADME, absorption, distribution, metabolism, and excretion; b.i.d., twice daily dosing; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; B/P, blood to plasma ratio; BTK: Bruton's tyrosine kinase; CLL: Chronic lymphocytic leukemia; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; Clint, intrinsic clearance; DDI: drug-drug interaction; ER, extended release formulation; F, bioavailability; Fa, fraction absorbed; FASSIF: fasted in combination with enhanced solubility in biorelevant media; Fg, fraction that escapes intestinal metabolism; fmj fraction of total clearance mediated by j CYP isoform or renal elimination; fp, fraction unbound in plasma; fu,mic, fraction unbound in microsomes; fu,gut, apparent unbound fraction in enterocytes; GI: gastrointestinal; IR, immediate release formulation; ka, first order absorption rate constant; Ki, reversible inhibition constant; LogP, logarithm of the octanol-water partition coefficient; MCL: Mantle cell lymphoma; NA, not applicable; ND, not determined; NDA: new drug application; P_{eff}, passive permeability; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; q.d., once daily dosing; Q_{gut}, a hypothetical flow term for the intestine absorption model; TDI, time-dependent enzyme inhibition; Tmax: time at maximal concentration in plasma; V_{ss}, volume of distribution.

Appendix 1. Information Request-Clinical Pharmacology July 18, 2013 (07182013IR)

Please address the following information request regarding PBPK Modeling:

We noticed that you used PBPK modeling to predict drug-drug interactions for Ibrutinib.

•You should further investigate the potential PK differences between healthy subjects and oncology subjects (for example under fasted condition) with respect to formulation differences, age differences and/or other factors using your PBPK models.

•Subsequently, the effect of CYP3A inhibitors/inducers on ibrutinib PK in the prototype oncology population should be predicted.

•You should also simulate ibrutinib PK in subjects with mild/moderate/severe hepatic impairment.

Please submit model files used to generate the final PBPK simulations (compound and population files, such as .cmp, .lbr, and .wks). The model files should be executable using Simcyp software Version 12.2. These files may be submitted via CD.

Appendix 2. PBPK Modeling Building and Simulations

Appendix Table A1. Physicochemical parameters of Ibrutinib for PBPK model

Input parameter	Value	Unit	Comment
MW	440.5	g/mol	
LogP	3.97		at pH=7, PS-CHAR Result 12-308 JNJ54179060[1]
Compound Type	Basic – HCl salt		
pKa1	3.78		
Dosage form	Immediate release capsules of 40 mg (120 mg; 3*40 mg) or 5 mg/ml HP-β-CD solution (140 mg)		

Appendix Table A2. Input parameters of Ibrutinib for PBPK model using Simcyp (V12)

Parameter	Value	Unit	Comment
Absorption			
Absorption Model	ADAM		Study Report [1]
Solubility in (b) (4)	15.8 (pH 7.0)	µg/mL	In vitro results of solubility in (b) (4) as input parameter in the model did not predict a complete absorption of ibrutinib (fa=1) as was observed in the human mass balance study (PCI-32765 CLL1004)[3] PS-CHAR Result 12-378 [1]
Caco-2 permeability Ibrutinib 10 µM pH7.4/7.4	32.6	10^{-6} cm/s	Study report FK10429 [3]
Caco-2 permeability Atenolol pH7.4/7.4	0.34	10^{-6} cm/s	Study report FK10429 [3]
Distribution			
B/P (blood to plasma ratio)	0.827	Simcyp predicted Ratio	Predicted value was in line with measured values during blood stability testing (0.78-0.89)
fu plasma	0.027	fraction	Evaluated in ex vivo plasma in healthy volunteers in studies (PCI-32765 CLL1002 and CLL1004) [1]
V_{ss} based on Kp values	11	L/kg	Summary of clinical pharmacology [3], prediction method according to references [10,11]
Metabolism/Excretion			
Human liver microsomes $CL_{int, in vitro}$	8676	µL/min/mg	Study report FK10269 and FK10269: human liver microsomes $Cl_{int, in vitro}$ of 8676 ul/min/mg protein calculated from in human hepatocytes results.
$F_{u,gut}$	0.11		Fitted parameter according to sensitivity analysis
human liver microsomes CL_{int} CYP3A	8312	µL/min/mg	95.8% of human liver microsomes Clint could be inhibited with 1 µM ketoconazole
human liver microsomes Other CL_{int}	364.4	µL/min/mg	4.2% of human liver microsomes other CLint not inhibited with 1µM ketoconazole
CL_{renal}	0.00365	L/h	Summary of clinical pharmacology [3]

Appendix Table A3. Dose staggering simulations with inhibitors (560 mg full dose). All simulations were conducted using population representative feature (n=1 healthy volunteer)

CYP3A inhibitor and dosing regimen	Inhibition mechanism	Ibrutinib dosing in relation to inhibitor dosing*				Does dose staggering have effect?
		Scenario 1 2 hrs. before inhibitor		Scenario 2 Co-administration		
		Ibrutinib exposure ratio (with/without inhibitor)				
		AUC	Cmax	AUC	Cmax	
Ketoconazole 400 mg QD	Strong, reversible	5.1	3.1	29	21	Yes
Ritonavir 100 mg BID	Strong, TDI**	39	23	40	24	No
Diltiazem, 120 mg BID	Moderate, TDI**	4.0	3.9	4.2	4.1	No
Erythromycin, 500 mg TID	Moderate, TDI**	6.9	6.6	7.0	6.4	No
Fluconazole, 200 mg QD	Moderate, reversible	4.3	3.9	5.5	5.3	slightly

**: Another scenario when ibrutinib is given 2 hr after inhibitor showed no difference compared to scenario 2 for all inhibitors*

***: TDI: time dependent inhibitor*

Appendix Table A4. Dose staggering simulations with inhibitors (140 mg reduced dose). All simulations were conducted using population representative feature (n=1 healthy volunteer)

CYP3A inhibitor and dosing regimen	Inhibition mechanism	Ibrutinib dosing in relation to inhibitor dosing*				Does dose staggering have effect?
		Scenario 1 2 hrs. before inhibitor		Scenario 2 Co-administration		
		Ibrutinib exposure ratio (with/without inhibitor)				
		AUC	Cmax	AUC	Cmax	
Ketoconazole 400 mg QD	Strong, reversible	6.5	3.7	29	21	Yes
Ritonavir 100 mg BID	Strong, TDI**	39	23	40	24	No
Diltiazem, 120 mg BID	Moderate, TDI**	4.0	3.9	4.3	4.1	No
Erythromycin, 500 mg TID	Moderate, TDI**	6.9	6.6	7.0	6.5	No

Fluconazole, 200 mg QD	Moderate, reversible	4.3	3.9	5.5	5.3	slightly

**: Another scenario when ibrutinib is given 2 hr after inhibitor showed no difference compared to scenario 2 for all inhibitors*

***: TDI: time dependent inhibitor*

Appendix Table A5. Dose reduction with staggering simulations (inhibition). All simulations were conducted using population representative feature (n=1 healthyvolunteer)

CYP3A inhibitor	Inhibition mechanism	Ibrutinib exposure ratio 140 mg with inhibitor*/560 mg no inhibitor		Exposure ratio <2-fold?
		AUC	Cmax	
ketoconazole	Strong, competitive	1.8	1.0	Yes
Ritonavir	Strong TDI**	11	6.3	**No**
diltiazem	Moderate TDI**	1.1	1.1	Yes
erythromycin	Moderate TDI**	1.9	1.8	Yes
Fluconazole	Moderate, competitive	1.2	1.1	Yes

**With dose staggering - ibrutinib given 2 hours before inhibitor. This staggering has minimal or no effect on strong TDI such as ritonavir, or moderate inhibitors*

***: TDI: time dependent inhibitor*

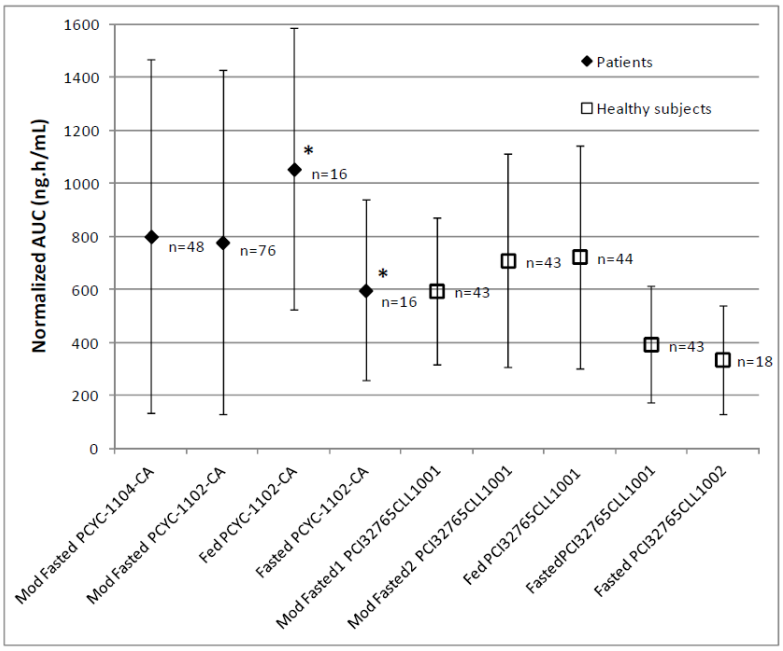
Appendix Table A6. Dose doubling simulations with inducers (1120 mg ibrutinib). All simulations were conducted using population representative feature (n=1 healthy volunteer)

Interacting Drug	Mechanism	Ibrutinib exposure ratio (with inducer vs. 140 mg no inducer)		Exposure ratio vs. 140 mg above 1?
		AUC	Cmax	
Rifampin	Strong	0.6	0.5	No
Efavirenz	Moderate	3.2	3.2	Yes

Appendix Table A7. Proposed dose simulations with inducers (560 mg ibrutinib). All simulations were conducted using population representative feature (n=1 healthy volunteer)

Interacting Drug	Mechanism	Ibrutinib exposure ratio (with inducer vs. 140 mg no inducer)		Exposure ratio vs. 140 mg above 1?
		AUC	Cmax	
Rifampin	Strong	0.3	0.3	No
Efavirenz	Moderate	1.6	1.6	Yes

Appendix Figure A1. Sponsor's cross study comparison of dose-normalized ibrutinib $AUC_{0\text{-}24hr}$ or AUC_{last} in two patient studies and two healthy volunteers studies in fasted, modified fasted[1], and fed dosing conditions after a single dose[2] administration of 560, 420, or 120 mg dosed as capsules [ref 7]



[1]."Mod fasted" in patients: drug intake 0.5 hr before or 2 hr after high fat breakfast; "Mod Fasted1" in healthy subjects: drug intake 0.5 hr before high fat breakfast; "Mod Fasted2" in healthy subjects: drug intake 2 hr after high fat breakfast.

[2]. Patient food effect data (marked with * in plots) were obtained after repeated dosing, implying that an accumulation of approximately 1.5-2-fold has to be taken into account.

References

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[redacted] (b) (4) Who have Received at Least 1 Prior Therapy. June 4 2013.

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/s/

ELIMIKA PFUMA
11/01/2013

YUZHUO PAN
11/01/2013

BAHRU A HABTEMARIAM
11/01/2013

PING ZHAO
11/01/2013

ANSHU MARATHE
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MICHAEL A PACANOWSKI
11/01/2013
Signing on behalf of Rosane Charlab Orbach

JULIE M BULLOCK
11/01/2013

NAM ATIQUR RAHMAN
11/01/2013

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**205-552**
Submission Date:	6/28/2013, 8/9/2013
Drug Name:	Ibrutinib (PCI-32765, JNJ 54179060)
Formulation:	Hard gelatin capsules
Strength:	140 mg
Applicant:	Pharmacyclics, Inc
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA 505(b)(1)

SYNOPSIS

Background: Ibrutinib (NDA 205-552, also named as PCI-32765 and JNJ 54179060) is a first-in-class, potent, orally administered, covalent inhibitor of Bruton's tyrosine kinase (BTK) indicated for the treatment of patients with mantle cell lymphoma (MCL) (b) (4)

Submission: Two dissolution methods were submitted in the NDA, one with SLS as surfactant and another with Tween 20.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion.

COMMENTS

1. Both (b) (4) formulation and (b) (4) formulation were used in the pivotal clinical trials. The two formulations are significantly different (SUPAC Composition and Component Level 3). Since 85% or more of patients used the to-be-marketed formulation in the pivotal clinical trials, the to-be-marketed formulation is considered the major contributor for the efficacy and safety demonstrated. Therefore, demonstration of the bioequivalence between the two formulations is not necessary.

2. Evaluation of the overall dissolution data showed that the Tween 20 dissolution method QCM-168 is superior to the SLS dissolution method QCM-164. However, currently limited GMP QC data are available for the drug product tested with the Tween 20 method and virtually no GMP QC-stability testing data have been obtained with the Tween 20 method. Therefore, a Postmarketing Commitment (PMC) was agreed upon with the Applicant for the collection of additional dissolution profile data (n=12) using the Tween 20 GMP QC method.

   To fulfill the PMC, the Applicant will collect complete dissolution profile data using the Tween 20 method from QC release testing of at least ten drug product batches, as well as from the stability-registration/primary batches through 12 months of storage

at the long-term condition. The dissolution method will be changed from QCM-164 (SLS) to QCM-168 (Tween 20), once sufficient QC GMP release and stability data have been gathered to support the implementation of the Tween 20 method.

As part of the PMC, the Applicant will use the overall dissolution data that have been collected from the drug product's release and stability batches using Tween 20 method to set the final dissolution acceptance criterion. The Applicant will submit the final report with the complete dissolution information/data and a proposal for the dissolution acceptance criterion under a supplement to the NDA within 15 months from action date.

RECOMMENDATION

ONDQA-Biopharmaceutics had reviewed the information provided in NDA 205-552 for Ibrutinib (PCI-32765, JNJ 54179060) 140 mg hard gelatin capsules. The proposed SLS dissolution method QCM-164 and acceptance criterion of Q = (b) (4) at 30 minutes are acceptable on an interim basis. The final dissolution method and acceptance criterion for Ibrutinib capsules will be implemented after the dissolution information/data to be collected under the PMC is evaluated and approved.

From the Biopharmaceutics perspective this NDA is recommended for approval with a Post Marketing Commitment (*for details refer to the PMC in page 21 of this review*).

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
Team Leader
ONDQA Biopharmaceutics

cc: NDA 205-552 *DARRTS, RLostritto*

BIOPHARMACEUTICS EVALUATION

1. Introduction

Ibrutinib (PCI-32765) is a first-in-class, potent, orally administered, covalent inhibitor of Bruton's tyrosine kinase (BTK) indicated for the treatment of patients with mantle cell lymphoma (MCL) [redacted] (b) (4)

The NDA obtained Fast Track and Breakthrough Therapy Designation and is under priority review based on its favorable benefit risk profile as an oral agent in the treatment of patients with relapsed/refractory MCL [redacted] (b) (4)

2. Physiological properties of the drug substance

The drug substance has [redacted] (b) (4) The pKa was determined using a spectrophotometric method.

The logP value was 3.97 at pH=7.0, and the logD values were 2.14 (pH=2.0) and 3.65 (pH=4.0) using a shake-flask method with 1-octanol and buffered solutions (pH 2 to pH 12).

The screening studies identified [redacted] (b) (4)

[redacted] (b) (4) the Biopharmaceutics Classification System (BCS) class, the solubility of the drug substance has been studied in various aqueous buffer systems across the pH range 1.0-7.5 as shown in the following table.

Solvent	Solubility in mg/mL Solution	pH of Solution	USP Definition
Purified Water	0.003	~5.5	Practically insoluble
0.1 N HCl	2	1.2	Slightly soluble
60:40 Water: Acetonitrile (H_2O:CH_3CN)	7	NA	Slightly soluble
0.5% DMSO in 60:40 H_2O:CH_3CN	6	NA	Slightly soluble
0.2% Formic Acid	0.06	3	Practically insoluble
0.1% Trifluoroacetic acid	0.25	1.9	Very slightly soluble
10 mM Ammonium acetate	0.003	4.5	Practically insoluble
10 mM Ammonium acetate	0.003	6	Practically insoluble
100 mM Ammonium acetate	0.003	8	Practically insoluble
0.3% Sodium lauryl sulphate	1.1	6.8	Slightly soluble

NA = Not applicable

The extent of absorption in humans for ibrutinib was determined to be ≥90%, demonstrating high permeability.

(b) (4)

Reviewer's Comments: *The solubility of the drug substance is low while the absorption is complete. Therefore, to mimic the in vivo performance, a surfactant may be needed in the in vitro dissolution medium.*

3. The Pharmacokinetics of Ibrutinib

Absolute bioavailability of ibrutinib has not formally been determined. Current data indicate absolute bioavailability is low and displays high inter-subject variability (60% CV). Ibrutinib absorption from the gastrointestinal tract (GI) is practically complete as observed in the human mass balance study. Following oral administration of 420 to 840 mg ibrutinib, the median Tmax is approximately 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after overnight fasting. The median time to Tmax was delayed from 2 to 4 hours.

Dose-normalized systemic exposure in healthy subjects, who received ibrutinib in fasted conditions, was up to 4 times less as compared to subjects with B-cell malignancies taking ibrutinib in fasting conditions.

Relative bioavailability of an oral solution and a solid dose, as assessed by AUC in healthy subjects, was very similar. Dosing with the oral solution did however result in an earlier peak with median Tmax shifting from 2 to 0.5 hours (first PK time point) and 2 to 3 times the Cmax as compared to the capsule formulation.

The plasma protein binding of ibrutinib and PCI-45227 in human plasma is 97.3% and 91.0%, respectively. The apparent steady-state volume of distribution (Vdss/F) was approximately 10,000 L, suggesting extensive distribution to peripheral tissues and/or binding to macromolecules in the circulation. The blood-to-plasma concentration ratio around Tmax is approximately 0.7.

Ibrutinib is extensively metabolized, predominantly by cytochrome P450 (CYP) 3A4-mediated metabolic pathways.

Excretion of radioactivity was predominantly via the feces with approximately 80% recovered mostly within 2 days, whereas ~8% was excreted in urine. Approximately 1% of the excreted radioactivity was recovered as unchanged drug, all in feces. The mean terminal half-life of ibrutinib, as determined by non-compartmental analysis, ranged from 4 to 9 hours and appeared independent of population, dose, and dosing regimen (single or multiple dose). The apparent clearance in subjects with B-cell malignancies is high, in the order of 1000 L/h as determined through non-compartmental and population PK analysis. Minimal accumulation (<2-fold) was observed for both parent compound and metabolite PCI-45227 on repeated daily dosing of ibrutinib.

Reviewer's Comments: *Although the bioavailability of an oral solution and a solid dosage, as assessed by AUC in healthy subjects, was very similar, the oral solution did result in an earlier peak with Tmax shifting from 2 to 0.5 hours and 2 to 3 times the Cmax as compared to the capsule formulation. Therefore, dissolution may play a role in the absorption.*

4. The composition and the formulation development

The composition of the Ibrutinib Capsules used in clinical studies is shown in the following table.

Component	Quality Reference	Function	Quantity/Unit Dose (mg/capsule)
Ibrutinib	In house specification	Active pharmaceutical agent	140 [a]
Microcrystalline cellulose	NF, Ph. Eur., JP	(b) (4)	
Croscarmellose sodium	NF, Ph. Eur., JP		
Sodium lauryl sulfate	NF, Ph. Eur., JP		
Magnesium stearate[b]	NF, Ph. Eur., JP		
Size 0, white, opaque, hard gelatin capsule with black "ibr 140 mg" print [c]	In house specification	Capsule shell	1 capsule
		Total	330.0
(b) (4)			

Development of the formulation for ibrutinib capsule 140 mg, was initiated at (b) (4) The (b) (4) drug product batches were used in Phase 1 and 2 clinical trials as well as early stability studies. The manufacturing was then transferred to the proposed commercial manufacturing site, (b) (4) for the products of Phase 1, 2 and 3 clinical supplies. The supportive, primary and registration stability batches as well as process scale up to the commercial size scale batches were also manufactured at (b) (4)

Three drug product batches (L0401341, L0401343, and L0401352) are identified as the registration stability batches. These batches were manufactured according to the intended commercial process and formulation. The capsule fill content of the registration batches is identical to the (b) (4) clinical, primary and supportive stability batches. (b) (4)

Table 3: Ibrutinib Capsule Formulations used in Phase 1 and Phase 2 Clinical Studies

(b) (4)

Formulation	Dosage Strength					
	40 mg[a]		140 mg[b]		200 mg[c]	
	Amount					
Component	mg/capsule	w/w %	mg/capsule	w/w %	mg/capsule	w/w %
Ibrutinib[d]						(b) (4)
Microcrystalline cellulose						
Croscarmellose sodium						
Sodium lauryl sulfate						
Total						

(b) (4)

Table 4: Ibrutinib Capsule, 140 mg Formulation Used in Phase 1, 2 and 3 Clinical Studies

(b) (4)

	140 mg[b]	
Component	mg/capsule	w/w %
Ibrutinib[a]	140.0	(b) (4)
Microcrystalline cellulose	(b) (4)	
Croscarmellose sodium		
Sodium lauryl sulfate		
Magnesium stearate		
Total	330	100.0

(b) (4)

The formulations used in pivotal clinical trails PCYC-1102 and PCYC-1104 are shown in the following table.

Batch	Manufacturing Site	Manufacturing Process	Date	Theoretical Batch Size		Pivotal Clinical Study
				capsules	Blend (kg)	
10-0119	(b) (4)	A	December 2010		(b) (4)	PCYC-1102 PCYC-1104
10-0109		A	November 2010			PCYC-1102
10-0062		A	September 2010			PCYC-1102
10-0033		A	May 2010			PCYC-1102
10-0023		A	March 2010			PCYC-1102
L0304110		B	December 2010			PCYC-1102 PCYC-1104
L0305448		C	April 2011			PCYC-1102 PCYC-1104
L0305985		C	July 2011			PCYC-1102 PCYC-1104
L0307025		C	October 2011			PCYC-1102 PCYC-1104
L0307693		C	January 2012			PCYC-1102 PCYC-1104
L0304897		C	March 2012			PCYC-1102 PCYC-1104
L0308265		C	March 2012			PCYC-1104
L0308266		C	May 2012			PCYC-1104

Reviewer's Comments: *All the formulations manufactured at different sites with different excipients and processes were used in the pivotal clinical trials. The formulations manufactured at* (b) (4) *and at* (b) (4) *are quite different and can be classified as SUPAC Level 3 component and composition change. However, considering that both formulations were used in pivotal clinical trials, the following information request was sent to the Applicant on 8/1/2013.*

> ***Both*** (b) (4) ***and*** (b) (4) ***formulations with three different processes (A, B and C) were used in the pivotal clinical trials*** (b) (4) ***PCYC 1104. Provide a table listing the patient ID and the corresponding formulation (process) used for each specific patient in these two trials.***

On 8/9/2013, the Applicant provided the response listing the lot number, manufacturing site and manufacturing process for each patient in trials (b) (4) PCYC1104. A representative page as an example is shown below.

Subject ID	Lot Number	Manufacturing Site	Manufacturing Process
032-101	10-0023	(b) (4)	A
	10-0033		A
	10-0062		A
	10-0109		A
	10-0119		A
	L0304110		B
	L0304897		C
	L0305448		C
	L0305985		C
	L0307025		C
	L0307693		C
032-102	10-0033		A
032-103	10-0033		A
	10-0062		A
	10-0109		A
	10-0119		A
	L0304110		B
	L0304897		C
	L0305448		C
	L0305985		C
	L0307025		C
	L0307693		C
032-104	10-0033		A
	10-0062		A
	10-0109		A
	L0304110		B

Reviewer's Comments: *Based on the data provided, it is apparent that many of the patients used both formulations* (b) (4) *with three processes (A, B and C), such as patient 032-101 shown in the above table. Since we are concerned with the significant difference between* (b) (4) *(with process A) and* (b) (4) *(with processes*

B and C) formulations, the percent of patients who used [redacted] *formulation only (such as the patient 32-102 shown in the above table) should be taken into consideration for the overall data analysis. If high percent of patients used* [redacted] *formulation only, a sub-group analysis will be necessary to differentiate the potential differences for efficacy and safety between the two formulations; otherwise, the efficacy and safety can be attributed to the dominating effect of* [redacted] *formulation (the to-be-marketed). The following table lists the number and percent of patients who used* [redacted] *formulation only.*

Trial number	[redacted]	*PCYC 1104-CA*
Total # of patients		*112*
# of patients who used [redacted] *formulation only*		*12*
% of patients who used [redacted] *formulation only*		*11%*

The results indicate that >85% patients used the to-be-marketed formulation, suggesting that the to-be-marketed formulation is the major contributor for the efficacy and safety demonstrated.

5. Dissolution method development

1. Proposed dissolution method and acceptance criterion

The proposed dissolution method and acceptance criterion are shown below.

Apparatus:	USP 2 (paddle). [redacted]
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm
Volume:	900 mL
Medium:	0.3% SLS in Purified water
Sampling volume:	1.8 mL (automated sampling); 5 mL (manual sampling)
Detection:	HPLC
Acceptance criterion:	Q = [redacted] in 30 minutes

In addition, another dissolution method using different surfactant (Tween 20) has also been developed as shown below.

Apparatus:	USP 2 (paddle). [redacted]
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm
Volume:	900 mL
Medium:	3.0% *w/v* Tween 20 in phosphate buffer pH 6.8, 50 mM
Sampling volume:	1.8 mL (automated sampling); 5 mL (manual sampling)
Detection:	HPLC

13 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX. Biopharmaceutics Post Marketing Commitment (PMC)

PMR/PMC Development Template-C

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

PMC Description:

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

The Applicant will use the overall dissolution data that were collected from the drug product's release and stability batches to set the final dissolution acceptance criteria.

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

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

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

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)

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

/s/

JOHN Z DUAN
09/25/2013

ANGELICA DORANTES
09/26/2013

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA # 205-552

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**205-552** (IND# 102688 & (b) (4)	**Proposed Brand Name**	**Imbruvica®**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Ibrutinib**
Medical Division	**Oncology**	**Drug Class**	**Bruton's tyrosine kinase (BTK) inhibitor**
OCP and Genomics Reviewer	Elimika Pfuma, Pharm.D. /Ph.D.	**Proposed Indication**	The treatment of mantle cell lymphoma (MCL) (b) (4) who have received at least one prior therapy
OCP Team Leader	Julie Bullock, Pharm.D.	**Dosage Form**	140 mg hard gelatin capsules
Genomics Team Leader	Rosane Charlab Orbach, PhD	**Dosing Regimen**	**Proposed:** 560 mg once daily in MCL (b) (4)
Pharmacometrics Reviewers	Bahru Habtemariam, PharmD and Yuzhuo Pan, PhD		
Pharmacometrics Team Leader	Anshu Marathe, PhD and Ping Zhao, PhD		
Date of Submission	**28-June-2013**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**27-September-2013**	**Sponsor**	**Pharmacyclics**
Medical Division Due Date		**Priority Classification**	**Priority Review**
PDUFA Due Date	**31-October-2013**		

Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted (*numbers in smaller font were already counted in another section*)	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**7**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**PCI-32765CLL1004**
Isozyme characterization:				
Blood/plasma ratio:	**X**	**1**		
Plasma protein binding:	**X**	**6**		

Pharmacokinetics -	**X**	**5**		**Single dose – 2 studies in healthy volunteers.** **Multiple dose – Dose-escalation trial and 2 pivotal trials**
Healthy Volunteers-				
single dose:	**X**	**2**		**PCI-2765CLL1002** **PCI-32765CLL1004**
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**3**		**PCYC-04753** **PCYC-1102-CA** **PCYC-1104-CA**
Dose proportionality -				
fasting / **non-fasting single dose**:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**1**		**Effect of strong CYP3A4 inhibitor: PCI-2765CLL1002**
In-vivo effects of primary drug:				
In-vitro:	**X**	**16**		**P-gp substrate/inhibitor, CYP substrate/inhibitor/induction**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD - QT Study:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	**1**		**Population PK model**
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		**Sub-study in PCYC-1102-CA**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	**X**	**1**		**PBPK Model**
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**37**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		X		
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Applicant is applying for waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			No exposure–response information is in the proposed

					label
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Elimika Pfuma, Pharm.D. / Ph.D.	07-August-13
Clinical Pharmacology and Genomics Reviewer	Date
Julie Bullock, Pharm.D.	07-August-13
Clinical Pharmacology Team Leader	Date
Rosane Charlab Orbach, PhD	07-August-13
Genomics Team Leader	Date
Bahru Habtemariam, PharmD and Yuzhuo Pan, PhD	07-August-13
Pharmacometrics Reviewers	Date
Anshu Marathe, PhD and Ping Zhao, PhD	07-August-13
Pharmacometrics Team Leaders	Date

Clinical Pharmacology – What is in the NDA?

NDA (NME): 205-552 **Associated IND#:** 102688 (b) (4)
Compound: Ibrutinib 140 mg hard gelatin capsules
Sponsor: Pharmacyclics
Filing: August 7th, 2013
Midcycle: August 14th, 2013
Reviewers: Elimika Pfuma, PharmD, PhD, Bahru Habtemariam, PharmD and Yuzhuo Pan, PhD
Team Leaders: Julie Bullock, PharmD, Rosane Charlab Orbach, PhD and Anshu Marathe, PhD and Ping Zhao, PhD

Mechanism of Action and Proposed Indication

Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor proposed for the treatment of patients with mantle cell lymphoma (MCL) (b) (4) who have received at least one prior therapy. BTK, is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in several B-cell malignancies, including MCL (b) (4).

Sponsor's Phase 3 Dose Selection Rationale

The proposed dosing regimens are 560 mg once daily in MCL (b) (4) The MTD was not reached in the phase 1 trial (#04753) with doses of up to 12.5 mg/kg/day evaluated. Sponsor determined that full and sustained (> 90% at 24 hours) occupancy of the BTK active site is reached at ibrutinib doses ≥2.5 mg/kg/day (≥175 mg/day for average weight of 70 kg).

(b) (4) A high-fat meal increased AUC 1.7 fold and Cmax 2.2 fold in a sub-study performed as part of Trial # 1102. The proposed instructions reflect the pivotal trials' dosing instructions.

Pivotal Efficacy Trials

Table 1

Study Number	Study Description	Treatment Groups	Primary Study Endpoint
(b) (4)			
PCYC-1104-CA	Phase 2, open label, nonrandomized study in relapsed or refractory MCL (N=111)	Ibrutinib 560 mg/day	ORR

(b) (4) In Trial PCYC-1104-CA (MCL), the ORR was 67.6% (95% CI: 58.0, 76.1).

Most common Grade 3/4 AEs (≥ 5%) are neutropenia, thrombocytopenia, anemia, pneumonia, diarrhea, abdominal pain, hypertension, dehydration, sinusitis and atrial fibrillation. Warnings and precautions proposed for lymphocytosis, infections and bleeding related events.

Clinical Pharmacology Studies

PK data is submitted for the two pivotal trials (intensive and sparse sampling) and three additional trials (intensive sampling). The three additional trials (**Table 2**) are a phase 1 dose-escalation trial, a mass balance trial and a DDI trial. Trial PCYC-1102-CA included a cohort for the evaluation of food effect. In addition, several *in vitro* study reports have been submitted for P-gp substrate/inhibitor (3 studies), protein binding (6), CYP substrate/inhibitor/induction (15) and S-ibrutinib racemic exposure (1) and bioanalytical methods (9).

Table 2

Study Number	Study Description	Treatment Regimen	PK Sampling (Population)
PCYC-04753	Phase 1, dose-escalation trial to determine MTD, PK and PD in patients with recurrent B-cell lymphoma (N=66)	**Body Weight Based Cohorts:** 1.25, 2.5, 5, 8.3 and 12.5 mg/kg/day for 28 days **Continuous Dosing Cohorts:** 8.3 mg/kg/day and 560 mg/day	Intensive (Patients)
PCI-2765CLL1002	Phase 1 DDI trial evaluating the effect of ketoconazole on the PK of Ibrutinib (N=18+3)	**DDI Cohort:** • Ibrutinib 120 mg on Day 1 and 40 mg on Day 7 • Ketoconazole 400 mg on Days 4 to 9 **Exploratory Cohort:** Ibrutinib 70 mg solution on Day 1	Intensive (male HV)
PCI-32765CLL1004	Phase 1 mass-balance ADME trial (N=6). Trial used to support claim of no effect in CYP2D6 PM	140 mg of ^{14}C-ibrutinib solution	Intensive (male HV)

Population PK, PBPK and Exposure Response Analyses

The sponsor submitted a population PK model and a PBPK model, but did not submit any exposure response analyses.

- The sponsor submitted a population PK model for patients with cancer including data from the two pivotal trials and the phase 1 trial PCYC-04753 (3477 concentrations from 245 patients). The model included the effect of the fasted/fed conditions and body weight. Covariate analysis was performed for age, gender, patient pretreatment, co-administered drugs, clinical chemistry data [eg, transaminases, creatinine clearance, LDH] and drug product characteristics. Model is used to support mild and moderate renal impairment labeling. In addition, 2 formulations used in the trials without relative BA trials are evaluated in this model (87% of cycles in 1104-CA (b) (4)).
- PBPK model used to predict CYP3A4 mediated DDIs – mild and moderate inhibitors and moderate inducers.

Potential PMRs

1. Submit final study report for hepatic impairment trial (mild, moderate and severe)
2. Submit final study report for strong CYP3A4 inducer (rifampin) trial

3. Submit final study report for TQT

(b) (4)

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/s/

ELIMIKA PFUMA
08/09/2013

JULIE M BULLOCK
08/15/2013

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

NDA Number	205-552
Submission Date	June 28, 2013
Product name, generic name of the active	Ibrutinib (PCI-32765, JNJ 54179060)
Dosage form and strength	Hard gelatin capsules, 140 mg
Applicant	Pharmacyclics, Inc
Clinical Division	Division of Hematology Drug Products
Type of Submission	Original NDA 505(b)1
Biopharmaceutics Primary Reviewer	John Duan, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

BIOPHARMACEUTICS INITIAL ASSESSMENT

Biopharmaceutics Summary

Ibrutinib (PCI-32765) is a first-in-class, potent, orally administered, covalent inhibitor of Bruton's tyrosine kinase (BTK).

The present New Drug Application (NDA) 205552 concerns ibrutinib 140 mg hard gelatin capsules as a single-agent oral therapy to treat patients with mantle cell lymphoma (MCL) (b) (4) The recommended dose for the treatment of MCL is 560 mg of ibrutinib administered once daily. (b) (4)

The NDA is under priority review due to Fast Track and Breakthrough Therapy Designation based on the its favorable benefit risk profile as an oral agent in the treatment of patients with relapsed/refractory MCL (b) (4)

1. Formulation development

The capsule formulations developed and used in the Phase 1 and 2 clinical studies (b) (4) are summarized in the following table.

	Dosage Strength					
Formulation	40 mg[a]		140 mg[b]		200 mg[c]	
	Amount					
Component	mg/capsule	w/w %	mg/capsule	w/w %	mg/capsule	w/w %
Ibrutinib[d]	(b) (4)					
Microcrystalline cellulose						
Croscarmellose sodium						
Sodium lauryl sulfate						
Total						

The scale-up and process development activities at (b) (4) focused on the 140 mg strength. The

composition of the formulation is shown in the following table.

Component	140 mg[b] mg/capsule	w/w %
Ibrutinib[a]	140.0	(b) (4)
(b) (4)	(b) (4)	
Total	330	100.0

[a] The ibrutinib quantity per capsule is adjusted based on its purity (b) (4) with a corresponding adjustment to the microcrystalline cellulose

[b] Hard gelatin capsule, Size 0, gray, opaque

The above two formulations are significantly different (SUPAC Level 3 Composition Change). However, both formulations were used in both of the pivotal clinical trails PCYC-1102 and PCYC-1104 as shown in the following table. Whether these formulations have similar clinical performance is of concern. Therefore, information is requested from the Applicant regarding the formulation (process) for each specific patient in the two pivotal clinical trials.

Batch	Manufacturing Site	Manufacturing Process	Date	Theoretical Batch Size		Pivotal Clinical Study
				capsules	Blend (kg)	
10-0119	(b) (4)	A	December 2010	(b) (4)		PCYC-1102 PCYC-1104
10-0109		A	November 2010			PCYC-1102
10-0062		A	September 2010			PCYC-1102
10-0033		A	May 2010			PCYC-1102
10-0023		A	March 2010			PCYC-1102
L0304110		B	December 2010			PCYC-1102 PCYC-1104
L0305448		C	April 2011			PCYC-1102 PCYC-1104
L0305985		C	July 2011			PCYC-1102 PCYC-1104
L0307025		C	October 2011			PCYC-1102 PCYC-1104
L0307693		C	January 2012			PCYC-1102 PCYC-1104
L0304897		C	March 2012			PCYC-1102 PCYC-1104
L0308265		C	March 2012			PCYC-1104
L0308266		C	May 2012			PCYC-1104

2. **Dissolution**

Two dissolution methods were developed: SLS method and Tween 20 method. Although the provided information showed that Tween 20 method is a better dissolution method, the Applicant requested during the pre-NDA meeting the use of the SLS method as the regulatory method for dissolution testing in the NDA and post-approval plans for the Tween 20 method. Considering the designation of breakthrough therapy, the request was accepted. The dissolution testing conditions for

the SLS method are shown below.

Apparatus:	USP 2 (paddle). [redacted]
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm
Volume:	900 mL
Medium:	0.3% SLS in Purified water
Sampling volume:	1.8 mL (automated sampling); 5 mL (manual sampling)
Detection:	HPLC

The proposed acceptance criterion is Q = [redacted] in 30 minutes. However, based on the provided data for batch release, it seems that an acceptance criterion of Q = [redacted] is appropriate for this product. Since the stability data only included the dissolution values at 45 minutes, the dissolution values at other time points will be requested.

Critical Review Issues

Critical review issues identified during filing are as follows.

- Suitability of the proposed dissolution method and acceptance criterion.
- Bridging of the two different formulations used in the Pivotal clinical trials.

Comments for Day 74-Letter

The following comments should be conveyed to the Applicant:

- Both [redacted] and [redacted] formulations with three different processes (A, B and C) were used in the pivotal clinical trials PCYC-1102 and PCYC-1104. Provide a table listing the patient ID and the corresponding formulation (process) used for each specific patient in these two trails.
- It is noted that the dissolution values in the batch analysis (3.2.P.5.4) are for the time point at 45 minutes only. Provide the dissolution data at other time points (5, 10, 15, and 30 minutes) and the dissolution method used (QCM-140 or QCM-164).
- There is a set of dissolution values (mean, min and max) provided in the stability data section (3.2.P.8.3). Clarify what dissolution method was used (QCM-140 or QCM-164) and at what time point the data were collected. Provide the dissolution data at other time points (including 5, 10, 15, 20 and 30 minutes).

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
1.	Does the application contain dissolution data?	X		
2.	Is the dissolution test part of the DP specifications?	X		
3.	Does the application contain the dissolution method development report?	X		
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application include a biowaiver request?		X	
6.	Does the application include an IVIVC model?		X	
7.	Is information such as BCS classification mentioned, and supportive data provided?		X	
8.	Is information on mixing the product with foods or liquids included?		X	
9.	Is there any in *vivo* BA or BE information in the submission?	X		In vivo PK data will be reviewed by the Office of Clinical Pharmacology.
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?		X	Not applicable

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		Please convey to the Applicant in the 74-Day letter the Biopharmaceutics comments listed in pages 3 of this filing review.

Administrative Block: *{See appended electronic signature page}*

John Duan, Ph.D.
Biopharmaceutics Primary Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc RLostritto

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

/s/

JOHN Z DUAN
07/30/2013

ANGELICA DORANTES
07/30/2013