# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203469Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# OFFICE OF CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **NDA:** 203469 | **Submission Date(s):**7/30/12 (SDN 1), 9/11/12 (SDN 7&8), 9/14/12 (SDN 9 &10), 9/17/12 (SDN11), 10/04/12 (SDN 22), 10/16/12 (SDN 26), 10/19/12 (SDN 27), and 10/24/12 (SDN 28) |
| **Brand Name** | Iclusig® |
| **Generic Name** | Ponatinib tablets |
| **CP Reviewer(s)** | Joseph Grillo, Pharm. D. (Primary) & Rachelle M. Lubin, Pharm. D. |
| **CP TL** | Julie Bullock, Pharm. D. |
| **Pharmacometrics Reviewer(s)** | Li Zhang, Ph.D. & Hongshan Li, Ph.D. |
| **Pharmacometrics Reviewer TL (Acting)** | Nitin Mehrotra, Ph.D. |
| **PBPK Review Secondary** | Ping Zhao, Ph.D. |
| **OCP Division** | OTS/OCP/DCP5 |
| **ORM division** | OND/OHOP/DHP |
| **Sponsor** | ARIAD Pharmaceuticals, Inc. (ARIAD) |
| **Relevant IND(s)** | 78,375 |
| **Submission Type; Code** | NME NDA ("Breakthrough" 3 month timeline) |
| **Formulation; Strength(s)** | 15 mg and 45 mg immediate release tablets |
| **Indication** | The treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy |

## Table of Contents

# 1 EXECUTIVE SUMMARY

Iclusig (ponatinib) is an orally administered tyrosine kinase inhibitor (TKI) that primarily targets BCR-ABL (including the BCR-ABL T315I mutant). The proposed indication is for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior TKI therapy. The recommended dose and schedule for Iclusig is 45 mg administered orally once daily with or without food.

The safety and efficacy of Iclusig in CML and Ph+ALL patients who were resistant or intolerant to prior TKI therapy were evaluated in an ongoing single-arm, open-label, international, multicenter trial. The primary endpoint for CP-CML was major cytogenetic response (MCyR). The primary endpoint for AP-CML, BP-CML or Ph+ ALL was major hematologic response (MaHR). Overall 54% of the CP-CML patients studied achieved a MCyR, 52% of the AP-CML patients achieved a MaHR, and 34% of the BP-CML/Ph+ALL patients achieved a MaHR. The most common non-hematologic adverse reactions were rash, abdominal pain, headache, dry skin, constipation, fatigue, pyrexia, arthralgia, and nausea. Thrombotic, cardiac, gastrointestinal, hepatic, and myelosuppressive safety issues were also observed with the use of ponatinib. Pharmacokinetic sampling was not done.

An FDA dose intensity-response analysis showed there is a significant relationship between dose intensity and probability of MCyR in CP-CML. In addition, the dose intensity-safety relationship indicates significant increases in adverse events (i.e., thrombocytopenia, neutropenia, rash, ALT elevation, AST elevation, pancreatitis, and lipase elevation) with an increase in dose intensity. The reviewer finds that the proposed 45 mg daily dose is not supported by dose intensity-response relationship for efficacy and safety. A lower dose, especially for CP-CML patients, may offer a better benefit-risk profile.

Peak concentrations of ponatinib are observed within 6 hours after oral administration. Drugs that elevate the gastric pH may reduce the bioavailability of ponatinib. The geometric mean terminal elimination half-life of ponatinib was approximately 24 hours with a 90% median accumulation observed with repeat dosing.

Ponatinib is greater than 99% bound to plasma proteins in vitro and the potential for displacement related drug interactions is unknown. CYP3A4 and to a lesser extent CYP2C8, CYP2D6 and CYP3A5 are involved in the phase I metabolism of ponatinib in vitro. Ponatinib is mainly eliminated via feces. Iclusig has not been studied in patients with renal or hepatic impairment. As hepatic elimination is a major route of excretion for ponatinib, hepatic impairment may result in increased plasma ponatinib concentrations.

Coadministration of a single 15 mg oral dose of ponatinib in the presence of a strong CYP3A inhibitor, increased ponatinib $AUC_{0-\infty}$ and $C_{max}$ by 78% and 47%, respectively, compared to administration of ponatinib alone. Based on these findings, the starting dose should be reduced to 30 mg once daily. The effect of CYP3A4 enzyme induction on the metabolism of ponatinib was not evaluated in vivo by the applicant; however FDA generated mechanistic modeling simulations suggest that concurrent use of ponatinib with strong inducers of CYP3A has the potential to lower ponatinib exposure by as much as 71%. In vitro, ponatinib is an inhibitor of the transporter systems P-gp, BCRP, and BSEP. Additional safety monitoring is recommended for substrates of P-gp and BCRP when used concurrently with Iclusig.

## 1.1 Recommendation

From a clinical pharmacology perspective, this NDA application is acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the applicant commits to the following post marketing

requirements and commitments addressing clinical pharmacology related safety concerns with ponatinib treatment.

### 1.2 Post Marketing Requirements

1.2.1 Conduct a dedicated drug interaction trial in humans to determine the effect of coadministration of the strong CYP3A4 inducer rifampin on the pharmacokinetics of ponatinib in healthy subjects.

1.2.2 Conduct a dedicated hepatic impairment trial in humans to determine the effect of hepatic impairment (i.e., Child-Pugh classes A, B, and C) on the pharmacokinetics of ponatinib when compared to healthy subjects.

1.2.3 Conduct a dedicated clinical trial in humans to determine the effect of multiple doses of lansoprazole on the pharmacokinetics of ponatinib in healthy subjects.

1.2.4 Collect sparse PK in the ongoing trial AP24534-12-301 from all patients. Exposure-response analysis should be conducted for both efficacy and safety endpoints. Based on the results of these analyses, a trial to evaluate lower dose or an alternate dosing regimen of ponatinib may be required.

### 1.3 Post Marketing Commitments

1.3.1 Evaluate the in vitro potential for the displacement of ponatinib from its protein binding sites in human plasma following addition of frequently used, highly protein-bound co-medications (e.g., warfarin, salicylic acid, ibuprofen, propranolol, glibenclamide, digitoxin, phenytoin, and nifedipine) at therapeutic or at supratherapeutic concentrations. Positive findings from this in vitro study may require additional trials in vivo.

### 1.4 Comments to the Applicant

1.4.1 Assess the relative bioavailability (BA) between the capsule formulation and the to-be-marketed tablet formulation used in study AP24534-07-101 to enrich the PK dataset and provide more information on dose proportionality.

1.4.2 Evaluate the relative bioavailability of one 45 mg Iclusig tablet relative to concomitant administration of three 15 mg Iclusig tablets to address the issue of inconsistency in administration of the 45 mg dose in the dose escalation/PK trial AP24534-07-101 (ie., administered as three 15 mg tablets) and the pivotal trial AP24534-10-201 (i.e., administered as a single 45 mg tablet).

### 1.5 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Iclusig (ponatinib) is an orally administered TKI. In vitro, ponatinib inhibited the activity of multiple kinases (including the BCR-ABL T315I mutant). The proposed indication is for the treatment of adult patients with CP, AP, or BP CML or Ph+ALL resistant or intolerant to prior TKI therapy. The recommended dose and schedule for Iclusig is 45 mg administered orally once daily (QD) with or without food. The applicant is proposing safety related dose modifications for myelosuppression, pancreatic adverse reactions and other severe non-hematologic adverse events. Iclusig will be marketed as 15 mg and 45 mg round, white, film-coated tablets.

The safety and efficacy of Iclusig were evaluated in an ongoing single-arm, open-label, international, multicenter trial. All patients were administered 45 mg of Iclusig once daily with the possibility of dose modifications for toxicities. Patients were assigned to one of six cohorts based on disease phase (CP-CML, AP-CML, or BP-CML/Ph+ ALL), resistance or intolerance (R/I)

to prior TKI therapy, and the presence of the T315I mutation. The primary endpoint for CP-CML was major cytogenetic response (MCyR). The primary endpoint for AP-CM, BP-CML or Ph+ ALL was major hematologic response (MaHR). Pharmacokinetic sampling was not done.

Overall 54% of the 267 CP-CML patients studied achieved a MCyR and 52% of the 83 AP-CML patients and 34% of the 94 BP-CML/Ph+ ALL patients studied achieved a MaHR. The most common non-hematologic adverse reactions (≥20%) were rash, abdominal pain, headache, dry skin, constipation, fatigue, pyrexia, arthralgia, and nausea. Other important safety issues observed with the use of ponatinib include: arterial thromboembolic events, hypertension, gastrointestinal perforation, hepatotoxicity, pancreatitis, elevated lipase, CNS or GI hemorrhage, cardiac failure, pericardial effusion, pleural effusion, ascites, thrombocytopenia, neutropenia, and anemia.

The proposed 45 mg QD dose is not supported by the dose intensity-response relationship for efficacy and safety. A lower dose, for CP-CML patients may offer a better benefit-risk profile. The 45 mg QD dose is adequate for AP/BP CML patients. This dosing concern is strengthened by the fact that 75% of patients had their dose reduced in the pivotal trial due to adverse events. Forty-nine percent of patients required dose reduction to 30 mg while 25% of patients required dose reduction to 15 mg. A PMR for collection of additional PK sampling in the ongoing phase 3 trial AP24534-12-301 will provide the needed information to support future exploration of an optimal dose.

The dose intensity-response analysis showed there is a statistically significant relationship between dose intensity and probability of MCyR in CP-CML, but not with MaHR in AP-CML/BP-CML/Ph+ ALL. In addition, the dose intensity-safety relationship indicates significant increases in adverse events (i.e., thrombocytopenia, neutropenia, rash, ALT elevation, AST elevation, pancreatitis, and lipase elevation) with increasing dose intensity. Additional analyses suggest dose intensity-safety relationships for the hypertension and ischemia risk associated with ponatinib use.

The absolute BA of ponatinib is unknown. Peak concentrations of ponatinib are observed within 6 hours after Iclusig oral administration. Following ingestion of either a high-fat or low-fat meal, plasma ponatinib exposures (AUC and $C_{max}$) were not different when compared to fasting conditions. The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility. Drugs that elevate the gastric pH may reduce its bioavailability and will be evaluated as a PMR.

Ponatinib is greater than 99% bound to plasma proteins in vitro. The potential for displacement related drug interactions is unknown and will be evaluated in vitro as a PMC. The geometric mean (CV%) apparent steady state volume of distribution is 1223 L (102%) following Iclusig 45 mg oral administration once daily for 28 days. Ponatinib is a weak substrate for both p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in vitro. Ponatinib is not a substrate for organic anion transporting polypeptides (OATP1B1, OATP1B3) and organic cation transporter 1 (OCT 1) in vitro.

At least 64% of a ponatinib dose undergoes phase I and phase II metabolism. CYP3A4 and to a lesser extent CYP2C8, CYP2D6 and CYP3A5 are involved in the phase I metabolism of ponatinib in vitro. Ponatinib is mainly eliminated via feces. Following a single oral dose of [14C]-labeled ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine.

The geometric mean (CV%) terminal elimination half-life of ponatinib was approximately 24 (55.1) hours following Iclusig 45 mg oral administration once daily for 28 days. A 90% median accumulation (range: 20% to 440%) of ponatinib exposure was also reported between the first dose and presumed steady state conditions.

Iclusig has not been studied in patients with hepatic impairment. As hepatic elimination is a major route of excretion for ponatinib, hepatic impairment may result in increased plasma ponatinib concentrations. The effect of varying degrees of hepatic impairment on ponatinib exposure in humans will be evaluated as a PMR. Iclusig has not been studied in patients with renal impairment as this is not a major route of ponatinib elimination. The effect of other intrinsic factors such as age, body weight, gender, and race is unknown due to limitations of the applicants proposed population based pharmacokinetic model.

Coadministration of a single 15 mg oral dose of ponatinib in the presence of ketoconazole (400 mg daily), a strong CYP3A inhibitor, increased ponatinib $AUC_{0-\infty}$ and $C_{max}$ by 78% and 47%, respectively, compared to administration of ponatinib alone. Based on these findings, the ponatinib dose should be reduced to 30 mg once daily. An in vivo with a CYP3A4 inducer was not conducted; however FDA generated mechanistic modeling simulations suggest that concurrent use of ponatinib with strong inducers of CYP3A has the potential to lower ponatinib exposure by as much as 71%. The effect of strong CYP3A4 inducers on ponatinib exposure in humans will be evaluated as a PMR. In addition, ponatinib does not inhibit the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, or CYP2D6 or induce the metabolism of substrates for CYP1A2, CYP2B6, or CYP3A in vitro.

In vitro, ponatinib is an inhibitor of the transporter systems P-gp, BCRP, and BSEP. In vitro, ponatinib does not inhibit the human organic anion transporting polypeptides OATP1B1 or OATP1B3, or organic cation transporters OCT1, OCT2, OAT1, and OAT3.

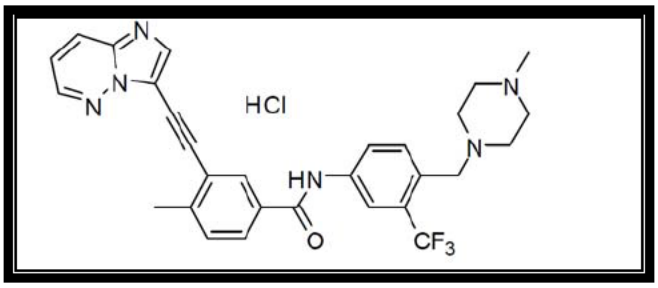
**Signatures**

| | |
|---|---|
| Joseph Grillo, Pharm.D.<br>Clinical Pharmacology Reviewer<br>Division of Clinical Pharmacology 5 | Rachelle M. Lubin, Pharm.D.<br>Clinical Pharmacology Reviewer<br>Division of Clinical Pharmacology 5 |
| Li Zhang, Ph.D.<br>Pharmacometrics Reviewer<br>Division of Clinical Pharmacology 5 | Hongshan Li, Ph.D.<br>Pharmacometrics Team Reviewer<br>Division of Clinical Pharmacology 5 |
| Nitin Mehrotra, Ph.D.<br>Pharmacometrics Team Leader (Acting)<br>Division of Clinical Pharmacology 5 | Ping Zhao, Ph.D.<br>PBPK Secondary Reviewer<br>OCP Immediate Office |
| Julie Bullock, Pharm.D.<br>Clinical Pharmacology Team Leader<br>Division of Clinical Pharmacology 5 | Nam Atiqur Rahman, Ph.D.<br>Division Director<br>Division of Clinical Pharmacology 5 |

# 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 clinical pharmacology and biopharmaceutics review?




| | |
|---|---|
| **Established name:** | Ponatinib Hydrochloride |
| **Molecular Weight:** | 569.02 g/mol (532.56 g/mol (free base)) |
| **Molecular Formula:** | $C_{29}H_{28}ClF_3N_6O$ (HCl salt); ($C_{29}H_{27}F_3N_6O$ (free base)) |
| **Chemical Name:** | 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide hydrochloride |
| **Description:** | Off-white to yellow powder which may contain some agglomerates |
| **Polymorphism** | The preferred form of ponatinib HCl is the (b) (4) |
| **Chirality:** | There are no chiral centers present in ponatinib. |
| **Solubility:** | The solubility of ponatinib in aqueous solutions decreases with increasing pH [>71,000 mg/mL (pH 1.2) to 0.16 mg/mL (pH 7.5). Soluble in the following organic solvents: 2,2,2-trifluoroethanol, Dimethyl sulfoxide, and N,N-dimethylacetamide |
| **Log P** | 5.14 (± 0.42) |
| **pKa-Values:** | 2.77 (± 0.09) and 7.8 (± 0.2) within a pH range of 2.5-10.5 |

Iclusig 15 mg and 45 mg immediate release tablets are white, round, film-coated tablets containing ponatinib (as ponatinib HCl), with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type B), colloidal silicon dioxide and magnesium stearate. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

### 2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Ponatinib is a TKI primarily targeting BCR-ABL, an abnormal tyrosine kinase that is often found in CML and Ph+ ALL patients. Ponatinib inhibited the activity of multiple kinases (including the BCR-ABL T315I mutant) when tested in vitro. Investigation of a panel of >100 kinases using a radiometric phosphor-transfer method demonstrated ponatinib inhibited 40% of those tested with $IC_{50}$ concentrations below 20 nM, including: native and mutant forms of BCR-ABL; VEGFR, FGFR, PDGFR and EPH family members; RET, KIT, SRC, RAF, and FLT3. Ponatinib inhibited the in

vitro viability of cells expressing native or mutant forms of BCR-ABL also with $IC_{50}$ concentrations below 20 nM. Ponatinib elicited anti-tumor activity in mice bearing tumors expressing native or T315I mutant BCR-ABL. The proposed indication for Iclusig is for the treatment of adult patients with CP, AP, or BP CML or Ph+ALL resistant or intolerant to prior tyrosine kinase inhibitor therapy.

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

The recommended dose and schedule for Iclusig is 45 mg administered orally once daily as long as the patient does not show evidence of disease progression or unacceptable toxicity. The applicant is proposing safety related dose modifications for myelosuppression, pancreatic adverse reactions and other severe non-hematologic adverse events. Depending on predetermined severity indices this may include discontinuation or withholding therapy and restarting based on predetermined clinical criteria at the 45 mg, 30 mg, or 15 mg once daily dosing level.

## 2.2 General Clinical Pharmacology

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

The applicant submitted five open label clinical trials in support of dosing and other clinical pharmacology related claims in this application (Table 1). Four of these were phase 1 trials (3 healthy volunteer and one in cancer patients) related to clinical pharmacology and one was a phase 2 trial efficacy and safety trial in the target population.

**Table 1:** Clinical trials in support of dosing and other clinical pharmacology related claims in this application.

| Type | N | Ponatinib Dose (formulation) | Population |
|---|---|---|---|
| Phase 1<br>Food Effect<br>[Trial AP24534-11-102] | 24 | 45 mg po single dose (SD) [Tablet] | Healthy subjects |
| Phase 1<br>ADME<br>[Trial AP24534-11-104] | 6 | 45 mg [$^{14}$C]ponatinib po SD [Capsule] | Healthy subjects |
| Phase 1<br>Drug Interaction<br>[Trial AP24534-11-103] | 23 | 15 mg po SD [Tablet] alone then again following 5 days of 400 mg ketoconazole qd | Healthy subjects |
| Phase 1<br>Dose Escalation<br>[Trial AP24534-07-101] | 81 | Once daily oral administration of ponatinib for four 28 day cycles.<br>Dose levels were:<br>• Capsule: 2 mg, 4 mg, 8 mg, 15mg, 30 mg, 45 mg, and 60 mg<br>• Tablet: 45 mg and 60 mg | Adult patients with (b) (4) advanced CML and other hematologic malignancies |
| Phase 2*<br>Efficacy and Safety<br>[Trial AP24534-10-201] | 449 | 45 mg po once daily [Tablet] | Adult patients with CML in chronic phase (CP), accelerated phase (AP) or blast phase (BP) or with Ph+ acute lymphoblastic leukemia (ALL) who either are resistant or intolerant to either dasatinib or nilotinib or have the T315I mutation |

*PK data not collected
*Source: Reviewer generated*

### 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 studies?

The primary objective for the phase 2 pivotal trial (trial AP24534-10-201) was efficacy. The primary endpoint for patients with CP-CML was MCyR. The MCyR rate was defined as the proportion of patients who achieved a complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR) after the initiation of study treatment. Patients entering the trial already in PCyR had to achieve CCyR in order to be considered a success for MCyR. The primary endpoint for patients with AP-CML or BP-CML or patients with Ph+ ALL in was MaHR. The MaHR rate is defined

as the proportion of patients who achieved a complete hematologic response (CHR) or no evidence of leukemia (NEL) response after the initiation of study treatment, with 1 additional assessment, at least 28 days after the first assessment of response, at which CHR or NEL criteria were met.

FDA stated that these surrogate endpoints could be considered clinically meaningful depending upon the sample size, response rate, and associated toxicities in its 5/14/10 end of phase 2 (EOP2) meeting with the applicant. These endpoints are generally acceptable from a clinical pharmacology perspective, but we defer to the clinical reviewer regarding whether or not the specific criteria cited during the 2010 EOP2 meeting were met.

The applicant also assessed BCR-ABL T315I mutation at screening and post-treatment by direct sequencing in trial 201. A 5/17/10 OCP review by the genomics group deemed this biomarker endpoint acceptable.

Pharmacodynamic (PD) assessments in the dose escalation trial AP24534-07-101 were performed by measuring relative levels of phosphorylated CRKL (pCRKL) protein relative to total CRKL in peripheral blood mononuclear cells (PBMCs), at baseline and multiple time points throughout the first cycle of ponatinib treatment. CRKL is a well known surrogate substrate of BCR-ABL kinase in chronic myeloid leukemia and acute lymphoblastic leukemia, and intensive studies of CRKL in Philadelphia chromosome-positive leukemia have been performed.[1 2 3] PD assessments were performed on peripheral blood mononuclear cells (PBMCs) using an immunoblot assay. While this PD biomarker endpoint is deemed acceptable these findings from trial AP24534-07-101 are not deemed reliable by the reviewer due to concerns regarding validation of the pCRKL assay (see Section 2.6.2).

### 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?

No. The assay report for the gel electrophoresis and immunoblotting were used to measure the PD endpoint CRKL was not deemed reliable by the reviewer due to concerns regarding validation (see Section 2.6.2).

### 2.2.4 Exposure-response

#### 2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

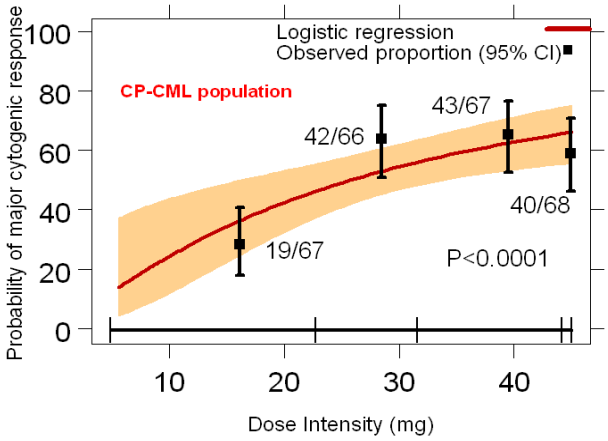
There was significant dose intensity-response relationship for efficacy identified for patients with CP-CML. However, there dose not appear to be an association between dose intensity and efficacy for AP-CML, BP-CML or Ph+ CML population.

Since pharmacokinetic data was not available for study AP24534-10-201, we investigated dose intensity-efficacy relationship in CP-CML patients (n=267), and AP-CML/BP-CML/Ph+ ALL patients (n=177). Dose intensity is defined as the average daily dose (total dose divided by the number of days the subject is on the study) and ranges from 0.34 to 45.2 mg in CP-CML patients and 1.41 mg to 45 mg AP-CML/BP-CML/Ph+ ALL patients. The two primary efficacy endpoints were used

---

[1] Birge RB, Kalodimos C, Inagaki F, Tanaka S. Crk and CrkL adaptor proteins: networks for physiological and pathological signaling. *Cell Commun Signal.* 2009;7-13.
[2] Sattler M, Salgia R. Role of the adapter protein CRKL in signal transduction of normal hematopoietic and BCR/ABL-transformed cells. *Leukemia.* 1998;12:637–644.
[3] ten Hoeve J, Arlinghaus RB, Guo JQ, Heisterkamp N, Groffen J. Tyrosine phosphorylation of CRKL in Philadelphia + leukemia. *Blood.* 1994;84:1731–1736.

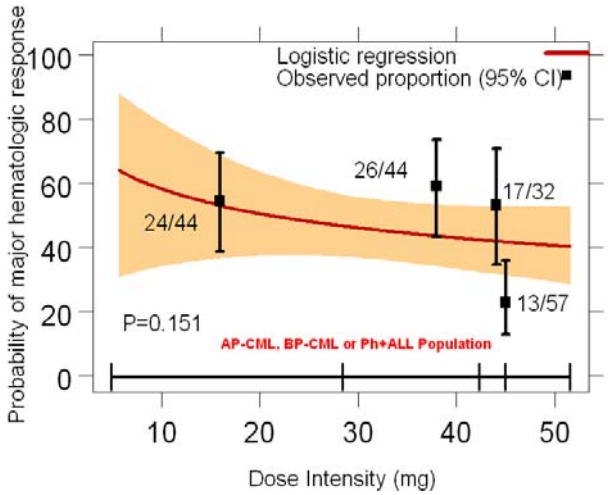
in the dose intensity response analysis: major cytogenetic responses for CP-CML patients and major hematologic response for AP-CML/BP-CML/Ph+ ALL patients. Figure 1 shows there is a statistically significant relationship between dose intensity and probability of major cytogenetic responses in CP-CML patients (p<0.0001). The observed data also shows the major cytogenetic response increases with higher dose intensity and appears to reach a plateau at higher doses (30 mg). It is important to note that this is univariate analysis which may be confounded by patient disease status and other risk factors since these are second line patients who had already failed prior TKIs. Multivariate analysis accounting for various risk factors was also explored for CP-CML and it was observed that dose intensity was a significantly related to response after accounting for other risk factors although the relationship became shallow.




*Source: FDA reviewer's analysis*

**Figure 1:** Relationship of dose intensity and probability of MCyR. The 4 fraction numbers in the plot are the observed response rates of the 4 quartiles with the numerator as number of responders and the denominator as total number of patients in each quartile. With every unit of log dose increases, the odd of having a response is 1.32 fold.

Figure 2 shows dose intensity does not appear to be related with major hematological response in AP-CML/BP-CML/Ph+ ALL patients (p=0.151).



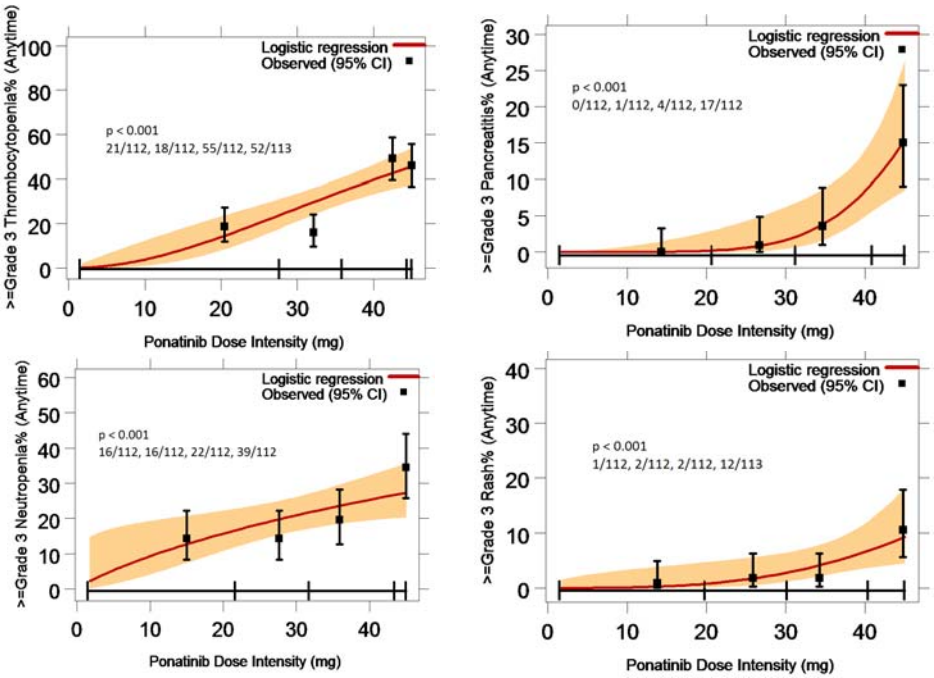

*Source: FDA reviewer's analysis*

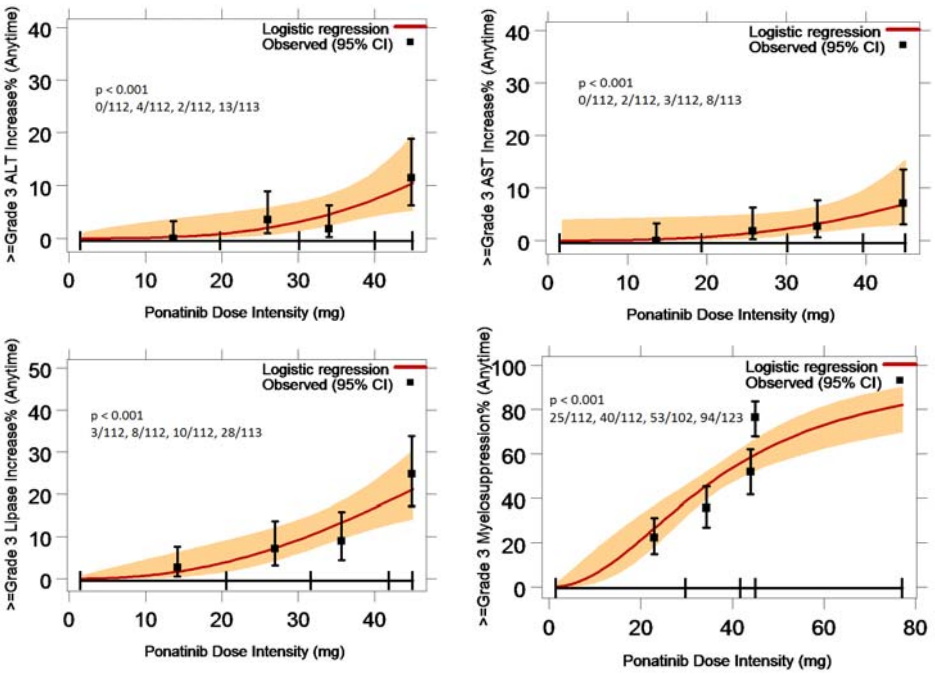
**Figure 2:** Relationship of dose intensity and probability of MaHR. The 4 fraction numbers in the plot are the observed response rates of the 4 quartiles with the numerator as number of responders and the denominator as total number of patients in each quartile.

In addition, one of the secondary objectives of the ponatinib phase 1 trial (AP24534-07-101) was to examine the pharmacodynamic activity of ponatinib in CML and Ph+ ALL patients, including patients with T315I mutant BCR-ABL (Report no. ARP288). Pharmacodynamic assessments were performed on 64 of 65 CML and Ph+ ALL patients enrolled in the study by measuring relative levels of phosphorylation of the BCR-ABL substrate CRKL (pCRKL), relative to total CRKL, in peripheral blood mononuclear cells (PBMCs), at baseline and multiple time points throughout the first cycle of ponatinib treatment. A ≥50% reduction of pCRKL levels relative to baseline was considered to represent substantial inhibition of BCR-ABL activity as this level of inhibition by imatinib has been associated with improved clinical response. The applicant reported that maximal activity, including patients with T315I mutant BCR, was seen at dose levels of 15 mg and above. These findings are not deemed reliable by the reviewer due to concerns regarding validation of the pCRKL assay (see Section 2.6.2).

#### 2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

The dose intensity-safety relationship indicated that there is significant increase in grade ≥ 3 safety events with increase in dose. Dose intensity-safety analyses of relevant adverse events were conducted for trial AP24534-10-201. Based on univariate logistic regression analyses, significant dose intensity-safety relationship was observed for variety Grade 3 & 4 adverse events (Figure 3). It is worth noting that these are univariate analysis which may be confounded by patient disease status and other risk factors since these are second line patients who had already failed prior TKIs.






*Source: FDA reviewer's analysis*

**Figure 3:** Dose intensity versus response relationships for some ≥Grade 3 safety endpoints of Trial AP24534-10-201. The four fraction numbers against the p value represents the observed adverse event rates in the four quartiles with the numerator as number of responders and the denominator as total number of patients in each quartile.

The dose reduction strategy proposed by the sponsor to manage adverse events appears reasonable. Based on the logistic regression model, the risk of having these adverse events decreases if dose is decreased from 45 to 30 to 15 mg QD (Table 2). For example, reducing dose from 45 mg QD to 30 mg QD will reduce severe pancreatitis rate by 9-fold.

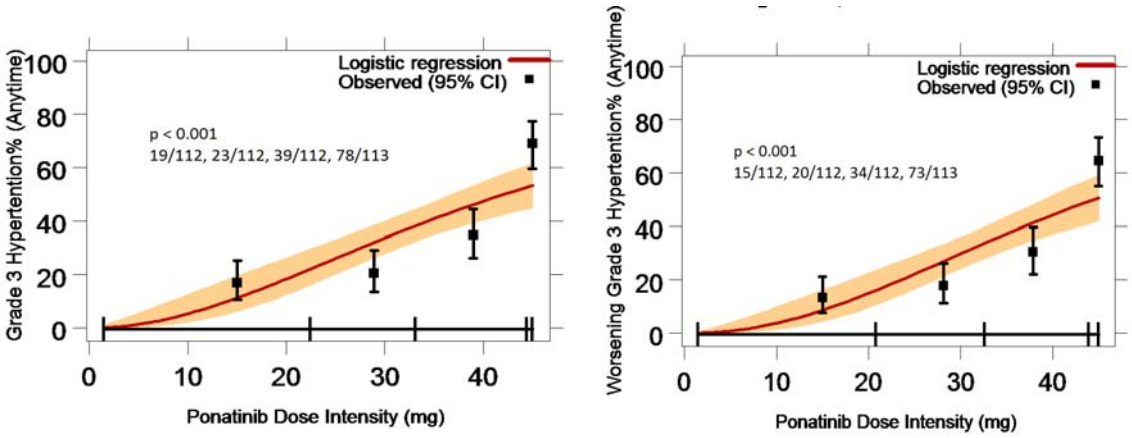
**Table 2:** Predicted probability (%) of Grade ≥ 3 adverse events at 45, 30 and 15 mg QD dose in Trial AP24534-10-201

| Grade ≥ 3 Adverse Event | Probability at 15 mg QD | Probability at 30 mg QD | Probability at 45 mg QD |
|---|---|---|---|
| Thrombocytopenia | 8.4 | 26.9 | 45.5 |
| Pancreatitis | 0.0 | 1.7 | 15.4 |
| Neutropenia | 12.7 | 20.9 | 27.3 |
| Rash | 0.3 | 2.7 | 9.3 |
| ALT increase | 0.3 | 3.1 | 10.5 |
| AST increase | 0.3 | 2.2 | 7.0 |
| Lipase increase | 0.3 | 2.2 | 7.0 |
| Myelosuppression | 12.9 | 38.7 | 59.7 |

*Source: FDA reviewer s analysis*

In addition, there is significant dose intensity-response relationship for hypertension in the patient population (Figure 4, left). Grade 3 or higher hypertension is defined as patient meeting criteria for grade 3 or higher hypertension (systolic BP > 160 or diastolic BP > 100) at any time, regardless of baseline values. Reducing dose from 45 mg QD to 30 mg QD will reduce the probability of having Grade ≥ 3 hypertension from 53% to 34%.

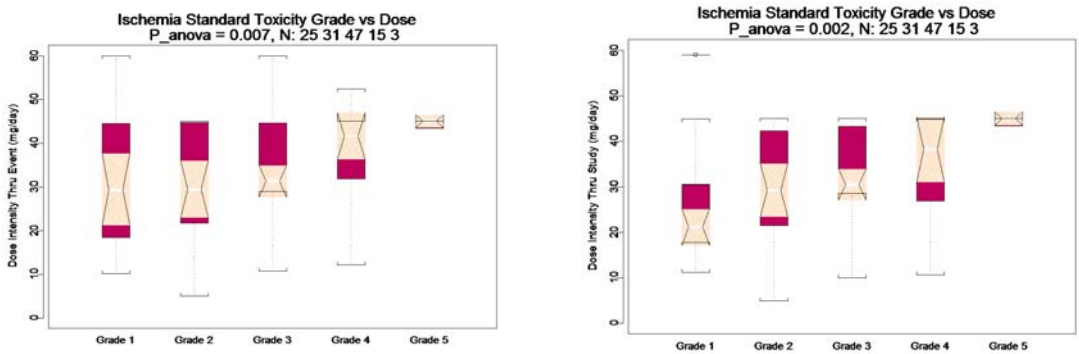
Dose intensity was also related to worsening grade of hypertension as evident from the figure below (Figure 4, right). Worsening of grade 3 or higher hypertension is defined as 'treatment emergent hypertension' i.e. patient meeting criteria for grade 3 or higher hypertension worsening from baseline ((systolic BP > 160 and baseline systolic BP =< 160) or (diastolic BP > 100 and baseline diastolic BP =< 100)) at any time.




*Source: FDA reviewer's analysis*

**Figure 4:** Effect of Ponatinib on hypertension in Trial AP24534-10-201

Further, the relationship between risk of ischemia and ponatinib dose intensity is likely. Higher ponatinib dose resulted in higher grade of ischemia ($p < 0.01$) as shown in Figure 5 where the data of 70 ischemia patients from Trials AP24534-07-101 and AP24534-10-201 are presented and multiple events might have occurred for a specific patient. It is important to note that this analysis may be confounded by patient disease status since some of these patients may be predisposed to this risk because of their prior medical history. However, no trend was found when all 449 patients were analyzed using logistic regression with severe ischemia event as the categorical variable.




*Note: Lower and upper hinges of the red box are the 25th and 75th percentiles of the dose intensities; the band near the middle of the box is the 50th percentile, and whiskers are drawn to the nearest value not beyond a standard span from the hinges. The standard span is 1.5×(upper hinge - lower hinge). Points beyond the end of the whiskers (outliers) are drawn individually. The slanted shaded orange area represents 95% confidence of the median.*
*Source: FDA reviewer's analysis*

**Figure 5:** Effect of Ponatinib on Ischemia Grade of Patients in Trial AP24534-10-201

#### 2.2.4.3 Does this drug prolong the QT or QTc interval?

The applicant submitted an evaluation of ponatinib's potential to influence the QTc interval in patients with advanced/refractory hematologic malignancies as a secondary objective of trial AP24534-07-101. The FDA Interdisciplinary Review Team (IRT) for QT Studies reviewed the results of these trial data to address the applicants request to waive the requirement for a dedicated QTc study. In its 2/10/2012 response the IRT stated that "the information provided in the study AP24534-07-101 appears reasonable to conclude that an additional dedicated QTc study may not be necessary. However, sponsor has not provided the ECGs and adverse event data and intends to submit it as part of the NDA submission. Thus, the final decision on whether to waive a separate dedicated QT study will be made once all the data are available. Also, whether or not

60 mg QD covers the high exposure clinical scenario will depend on the results of the studies evaluating the effect of food, organ impairment or administration of CYP3A4 inhibitors on ponatinib PK."

On 11/30/2012 QT-IRT provided a review of the additional safety and ECG data from study AP24534-07-101. From this data, IRT concluded that no large changes (i.e., >20 ms) were observed in this study and no apparent relationship between concentration and QT was identified. Based on these observations, IRT believes an additional QT study is not recommended. However, as mentioned in its previous review, IRT states that there were unknown factors which had potential to increase exposure of ponatinib (i.e., food, hepatic impairment and administration of CYP3A4 inhibitors) and the potential for ponatinib to prolong the QT interval should ultimately take into account these factors as well as adverse event and ECG data from Study AP24534-10-201 that was not reviewed this subsequent data. IRT has also proposed labeling language related to its analysis of trial AP24534-07-101.

The Clinical reviewer has expressed additional concern regarding QTcF outliers observed between the AP24534-07-101 and AP24534-10-201 (Table 3) and has proposed a PMR for the evaluation of QTc prolongation in the ongoing Phase 3 RCT in patients with newly-diagnosed CML and inclusion of the QTcF outlier information into the labeling. The clinical pharmacology reviewer does not object to the clinical reviewer's proposal.

**Table 3:** QTcF outliers observed between the AP24534-07-101 and AP24534-10-201

| Treatment-emergent | Phase 1 Trial (N=39) | Phase 2 Trial (N=449) |
|---|---|---|
| QTcF >450 ms | not reported | 27 (6%) |
| QTcF>480 ms | 2 (5%) | 6 (1.3%) |
| QTcF>500 ms | 1 (3%) | 3 (0.6%) |
| QTcF prolongation >30ms | 4 (10%) | 45 (10%) |
| QTcF prolongation >60 ms | 1 (3%) | 11 (2%) |

*Source: FDA clinical reviewer's analysis*

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

No, the proposed 45 mg daily dose is not supported by the dose intensity-response relationship for efficacy and safety. A lower dose, especially for CP-CML patients, may offer a better benefit-risk profile. We agree that a 45 mg QD dose is adequate for AP/BP CML patients in order to provide maximum chance of efficacy since these patients are in the advanced phase of the disease and have lower survival rate than CP-CML patients.

- Based on the dose intensity-efficacy relationship for CP-CML patients, it appears that you may not compromise substantially on efficacy if dose is decreased from 45 to 30 mg QD (Figure 1). The efficacy rate reached maximum at the 2nd quartile of dose intensity (corresponding to ~30 mg QD) for major cytogenetic responses (Figure 1).

- In AP-CML/BP-CML/Ph+ ALL patients, the dose intensity does not appear to be related with major hematological response. Due to the limited survival time, it is more appropriate to give patients the maximum tolerated dose to increase their survival opportunity (Figure 2).

- Furthermore, there is a significant relationship between dose intensity and safety endpoints (≥ Grade 3 including thrombocytopenia, ischemia, rash, hypertension, myelosuppression, pancreatitis, lipase elevation, ALT/AST elevation) indicating that the rate of these adverse events are 2 to 9 fold at 45 mg QD compared to 30 mg QD (Figure 3). The rates of adverse events in the 4th quartile of dose intensity were 2 to 10-fold the

rates of ≥ Grade 3 AE in the 2nd or 3rd quartiles of dose intensities (Figure 3). This indicates that a lower dose will likely reduce the risk of these adverse events.

- Moreover, about 75% of patients had their dose reduced during the trial due to adverse events. Forty nine percent patients required dose reduction to 30 mg while 25% patients required dose reduction to 15 mg. The median time to the first dose reduction was 68 days. The median time to dose reduction to 30 mg was 71 days and the median time to dose reduction to 15 mg was 134 days.

Based on the dose intensity-response relationships for efficacy and safety, the reviewer recommends a PMR to collect sparse PK in the ongoing trial (AP24534-12-301) from all patients. These data be used to conduct exposure-response analysis for both efficacy and safety endpoints. The findings from these analyses may require an additional trial to evaluate a lower dose or an alternate dosing regimen of ponatinib.

### 2.2.5 What are the PK characteristics of the drug and its major metabolite?

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

The single dose and multiple dose pharmacokinetics of ponatinib and its primary metabolites AP24567 (active) and AP24600 (inactive) were evaluated in patients with advanced hematologic malignancies. In trial AP24534-07-101, 81 patients were treated continuously with once-daily doses of ponatinib, ranging from 2 to 60 mg under fasted conditions. Trial treatment was divided into 28-day cycles. The pharmacokinetic profiles of parent ponatinib and metabolites were characterized on the first day of trial treatment, Cycle 1 Day 1 (C1D1), and on Day 1 of Cycle 2 (C2D1). No trial drug was given on C2D2, and plasma sampling extended to 48 h post dose under presumed steady-state conditions. In addition, pre-dose trough concentrations were measured on Day 8, 15, 22 and 29 during C1 at dose levels of 30 mg and higher. All patients in the 2, 4, 8, 15 and 30 mg cohorts received the ponatinib capsule formulation. However, approximately half of the patients enrolled in the 45 mg and 60 mg cohorts received the to-be-marketed tablet formulation instead of the capsule. In these cases either three (45 mg) or four (60 mg) 15 mg to-be-marketed tablets were administered to achieve the required dose.

The applicant did not provide sufficient information to support a conclusion of relative BA between the capsule and the to-be-marketed tablet formulation used in this trial. While it is ultimately the applicants responsibility to prove relative BA between investigational formulations used in the development of ponatinib, the reviewer attempted assess whether relative BA between the capsule and tablet formulation could be reasonably assumed by conducting an exploratory analysis of the ratio and 90% confidence interval ($CI_{90}$) for the $C_{max}$ and $AUC_{0-\tau}$. Based on this analysis, the reviewer could not reasonably rule out the possibility of a relative BA effect between the capsule and tablet formulations because the $CI_{90}$'s were outside of the 0.80-1.25 equivalence range (Table 4). This analysis was limited by its post hoc nature, high variability, and small sample size. Therefore, PK data from the capsule and tablet formulation are evaluated separately in this review rather than combined as proposed by the applicant. These data should be reevaluated if relative BA is demonstrated between the tablet and capsule at a later point (see Section 2.5.9).

**Table 4:** Comparison of relative ponatinib exposure of capsule to the tablet formulation in at the 45 mg or 60 mg dose once daily (fasted) for 28 days in patients with advanced hematologic malignancies

| Ponatinib Dose | Parameter | Capsule $Mean_{geo}$ (CV%) [n] | Tablet $Mean_{geo}$ ($CV_{geo}$%) [n] | Ratio T/C | $CI_{90}$ | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| 45 mg | $C_{max}$ | 82.5 (55) [10] | 73.03 (74.3) [11] | 0.89 | 0.6 | 1.3 |
| 45 mg | $AUC_{0-\tau}$ | 1351 (56.9) [9] | 1253.3 (73.1) [11] | 0.93 | 0.62 | 1.4 |
| 60 mg | $C_{max}$ | 109.4 (54.7) [6] | 77.41 (5.8) [3] | 0.71 | 0.48 | 0.95 |
| 60 mg | $AUC_{0-\tau}$ | 1751.8 (75.5) [6] | 1147.65 (17.8) [3] | 0.66 | 0.39 | 1.11 |

*Source: Applicant's datasets nca534c2.xpt*

In conclusion, PK data from the capsule and tablet formulation are evaluated separately in this review rather than combined as proposed by the applicant. These data should be reevaluated if relative BA is demonstrated between the tablet and capsule at a later point (see Section 2.5.9).

The pharmacokinetic parameters for ponatinib and its metabolites AP24567 and AP24600 following single dose (Cycle 1) and multiple dose (Cycle 2 [presumed steady state]) Iclusig tablet administration can be found in Table 5 and Table 6 below. On a molar basis, the $C_{max}$ /$AUC_{0-\tau}$ of the metabolites AP24567 (0.003/0.059 μM) and AP24600 (0.061/0.606 μM) were approximately 2.5%/2.6% and 47%/27% of ponatinib (0.137/2.35 μM) following multiple ponatinib doses at the 45 mg daily dosing level (Cycle 2, Day 1), respectively.[4]

Overall these parameter estimates in patients with advanced hematologic malignancies were highly variable with coefficients of variation often greater than 50%. Variability was similar following multiple dose capsule and tablet administration at the same dose level and slightly lower following single dose capsule administration. Due to the small sample size, parameters for the 60 mg tablet dose level following multiple dosing should be considered exploratory. Despite these limitations these estimates are deemed acceptable given the challenges in conducting trials in an advanced cancer population, but not ideal.

**Table 5:** Summary of Pharmacokinetic Parameters for Ponatinib and its primary metabolites AP24567 and AP24600 in patients with advanced hematologic malignancies at Cycle 1 Day 1 (Trial AP24534-07-101)

| Substance | Dose | Statistic | Cmax (ng/mL) | Tmax (h) | $AUC_{ALL}$ (h•ng/mL) | $AUC_{0-\tau}$ (h•ng/mL) |
|---|---|---|---|---|---|---|
| Ponatinib | 45 mg | N | 18 | 18 | 18 | 15 |
| | | Mean (SD) [CV%] | 56.3 (35.6) [63.3] | | 712.6 (393.4) [55.2] | 776.2 (388.3) [50 ] |
| | | $Mean_{geo}$ (CV%) | 48 (72.3) | | 605.8 (90.5) | 705.9 (51.7) |
| | | Median (Range) | 41.2 (19.7-141) | 6 (4-30.3) | 597.4 (72.7-1650) | 656.3 (373.5-1650) |
| | 60 mg | N | 6 | 6 | 6 | 5 |
| | | Mean (SD) [CV%] | 102.5 (32.4) [31.6] | | 1358 (764) [56.3] | 1532 (709.1) [46.3] |
| | | $Mean_{geo}$ (CV%) | 98.8 (30.1) | | 1189 (69.3) | 1420 (45.9) |
| | | Median (Range) | 87.4 (75.3-159) | 4 (2-8) | 1178 (488.3-2693) | 1328 (941.3-2693) |
| AP24567 | 45 mg | N | 18 | 18 | 18 | 15 |
| | | Mean(SD) [CV%] | 1.9 (3) [158.4] | | 23.4 (34.1) [145.7] | 27 (36.5) [135.1] |
| | | $Mean_{geo}$ (CV%) | 1 (201.8) | | 11.3 (299.3) | 15.9 (165.3) |
| | | Median (Range) | 1 (0.2-13.1) | 6 (4-30.3) | 14.1 (0.2-147.2) | 15.8 (3.1-147.2) |

[4] Assumes molecular weights of 532.56, 518.20, & 277.09 g/mol for ponatinib, AP24567, & AP24600, respectively

**Table 5:** Summary of Pharmacokinetic Parameters for Ponatinib and its primary metabolites AP24567 and AP24600 in patients with advanced hematologic malignancies at Cycle 1 Day 1 (Trial AP24534-07-101)

| | | | | | | |
|---|---|---|---|---|---|---|
| | 60 mg | N | 6 | 6 | 6 | 5 |
| | | Mean(SD) [CV%] | 3.5 (2.7) [76.3%] | | 48.1 (40.5) [84.1%] | 54.4 (41.9) [77%] |
| | | Geomean (CV%) | 2.7 (121.5) | | 33.1 (156.4) | 37.9 (147.7) |
| | | Median (Range) | 2.9 (0.7-8.2) | 4 (4-8) | 36.5 (6.8-112.4) | 43.1 (6.8-112.4) |
| AP24600 | 45 mg | N | 6 | 6 | | 6 |
| | | Mean(SD) [CV%] | 19.7 (13.5) [68.5] | | | 187.7 (99.5) [53] |
| | | Geomean (CV%) | 17 (64.5) | | | 167.9 (60) |
| | | Median (Range) | 15.6 (9.1-46.4) | 2 (2) | | 175.7 (93.8-361.3) |

*$AUC_{\tau}$ = includes patients with 1 or more missing data points*
*Source: Applicant's datasets nca534c1.xpt, nca567c1.xpt, & adpk101.xpt*

**Table 6:** Summary of Pharmacokinetic Parameters for Ponatinib and its primary metabolites AP24567 and AP24600 AP24600 in patients with advanced hematologic malignancies at Cycle 2 Day 1 (Trial AP24534-07-101)

| Substance | Dose | Statistic | $C_{MAX}$ (ng/mL) | $T_{MAX}$ (h) | $C_{24}$ | $AUC_{0-\tau}$ (h•ng/mL) | $CL_{ss}$ /F (L/h) | $V_z$ /F (L) | $T_{1/2}$ | Accum. |
|---|---|---|---|---|---|---|---|---|---|---|
| Ponatinib | 45 mg | N | 11 | 10 | 11 | 11 | 11 | 11 | 11 | 8 |
| | | Mean (SD) [CV%] | 85.7 (52.3) [61] | | 39.8 (21.1) [53] | 1458.3 (843.9) [57.9] | 41.3 (21.2) [51.3] | 1609.7 (1511.4) [93.9] | 26.3 (14.8) [56.3] | 2.7 (1.7) [63] |
| | | $Mean_{geo}$ (CV%) | 73 (74.3) | | 34.4 (75.6) | 1253.3 (73.1) | 35.9 (73.1) | 1222.5 (102.2) | 23.6 (55.1) | 2.3 (67.3) |
| | | Median (Min - Max) | 57.6 (36.3-179) | 5.4 (4-8.2) | 34.1 (11.7-73.2) | 1015.4 (598.1-2898) | 44.3 (15.5-75.2) | 1155.5 (390.2-5850.3) | 22.8 (11.8-66.5) | 1.9 (1.2-5.4) |
| | 60 mg | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 |
| | | Mean (SD) [CV%] | 77.5 (5.4) [6.9%] | | 28.7 (10.7) [37.2%] | 1163 (236) [20.3%] | 53 (10.4) [19.6%] | 1487 (212.1) [14.3%] | 19.7 (2.9) [14.9%] | 1.3 (0.1) [10.5%] |
| | | $Mean_{geo}$ (CV%) | 77.4 (5.8) | | 27.3 (39) | 1148 (17.8) | 52.3 (17.8) | 1477 (12.5) | 19.6 (13.5) | 1.3 (7.5) |
| | | Median (Min - Max) | 77.7 (72.1-82.8) | 4.05 (4-6) | 29.6 (17.6-38.9) | 1122 (950.5-1417) | 53.5 (42.3-63.1) | 1495 (1271-1695) | 20.8 (16.4-22) | 1.3 (1.2-1.4) |
| AP24567 | 45 mg | N | 13 | 13 | 13 | 13 | | | | |
| | | Mean(SD) [CV%] | 2.1 (1.7) [81.4] | | 1.5 (1.6) [104.1] | 41.1 (36.7) [89.3] | | | | |
| | | $Mean_{geo}$ (CV%) | 1.7 (74.5) | | 1 (91.9) | 30.6 (83.7) | | | | |
| | | Median (Min-Max) | 1.9 (0.6-6.9) | 6 (0.5-23.5) | 0.9 (0.2-6.1) | 29.7 (9.7-143.5) | | | | |
| | 60 mg | N | 3 | 3 | 3 | 3 | | | | |
| | | Mean(SD) [CV%] | 1.2 (0.4) [31.8] | | 0.5 (0.1) [19.2] | 20.1 (4.2) [21] | | | | |
| | | $Mean_{geo}$ (CV%) | 1.2 (30) | | 0.5 (16.2) | 19.7 (20.2) | | | | |
| | | Median (Min-Max) | 1.2 (0.8-1.6) | 4.1 (4-6) | 0.5 (0.5-0.6) | 21.7 (15.3-23.2) | | | | |
| AP24600 | 45 mg | N | 6 | 6 | | 6 | | | | |
| | | Mean(SD) [CV%] | 19.7 (13.5) [68.5] | | | 187.7 (99.5) [53] | | | | |
| | | $Mean_{geo}$ (CV%) | 17 (81.7) | | | 167.9 (57.3) | | | | |
| | | Median (Min-Max) | 15.6 (9.1-46.4) | 2 (2) | | 175.7 (93.8-361.3) | | | | |

*Source: Applicant's datasets nca534c2.xpt, nca567c2.xpt, & adpk101.xpt*

#### 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 full pharmacokinetic profile of ponatinib was only reported following multiple dose administration in patients with advanced hematologic malignancies. Since all of the healthy volunteer trials (i.e., AP24534-11-102 and AP24534-11-103) were single dose trials a formal direct comparison is not possible. A visual comparison of the pharmacokinetic profile for ponatinib following 45 mg once daily tablet administration (fasted) for 28 days in patients with advanced

hematologic malignancies (Table 6) [trial AP24534-07-101] and the "fasted" cohort from the food effect trial AP24534-11-102, where a 45 mg single dose of ponatinib was administered to healthy volunteers (see Section 2.5.3), does not suggest a substantial difference in the PK parameters beyond what would be expected from accumulation. This would need to be confirmed scientifically before this anecdotal observation could be considered for inclusion in labeling.

#### 2.2.5.3 What are the characteristics of drug absorption?

Absolute oral bioavailability of Iclusig tablets has not been determined in humans. The relative bioavailability of the ponatinib capsule formulation was estimated from the mass balance trial (AP24534-11-104) by the reviewer. Based on total urinary excretion (~4.5% of the total dose) and biotransformation products eliminated in feces (~60.1% of the total dose), the oral absorption of drug-related material following administration of a single radiolabeled 45 mg oral capsule ponatinib dose is estimated to be at least 65%. This estimate is based on the applicants Report No. ARP257.0 which states that radioactivity excreted cumulatively in feces during the 0 to 144 hr collection period was 78.8% of the administered dose. Radioactivity excreted cumulatively in urine during the 0 to 72 hr collection period was 4.5% of the total dose.

Maximum ponatinib blood concentrations in healthy subjects (Trials AP24534-11-102 and AP24534-11-103) and patients with advanced hematologic malignancies (Trial AP24534-07-101) occurred approximately 6 hours following oral tablet administration of ponatinib. In 22 healthy subjects, ponatinib absorption was not affected by concurrent ingestion of either a high- or low-fat meal (see Section 2.5.3).

In vitro data suggest that the aqueous solubility of ponatinib is dependent on pH, with solubility decreasing as pH increases (see Section 2.1.1). Ponatinib HCl is insoluble at pH greater than 3.7. Therefore, the reviewer agrees with the applicants concern that coadministration of drugs that raise gastric pH (proton pump inhibitors (PPI), histamine $H_2$ antagonists, and antacids) may alter the pharmacokinetics of orally administered ponatinib by reducing solubility in the gastrointestinal tract. The applicant submitted a proposed clinical trial protocol on 6/8/2012 to evaluate the effect of a multiple doses of lansoprazole, a potent suppressor of gastric acid secretion, on the single dose PK of ponatinib in healthy subjects. FDA found the proposed protocol generally acceptable and did not provide any additional comments (see the 06/29/2012 clinical pharmacology review for IND 78,375). Completion of this trial is a post marketing requirement.

#### 2.2.5.4 What are the characteristics of drug distribution?

Estimated Geometric mean [$mean_{geo}$] (CV%)for the apparent volume of distribution ($V_z/F$) of ponatinib at the 45 mg tablet dose once daily (fasted) for 28 days in patients with advanced hematologic malignancies (Table 6) [trial AP24534-07-101] is 1222 L (102%), suggesting extensive tissue distribution. Despite the high variability, this estimate is deemed acceptable given it is similar to that reported (with a lower variability) in the healthy volunteer food effect trial (AP24534-11-102) following administration of a single 45 mg dose (tablet) of ponatinib in the fasted cohort ($V_z/F$ = 1242 L (28.5%)).

The mean in vitro binding of ponatinib (100 to 3000 ng/mL) in human plasma is 99.92% (range: 99.91% to 99.94%) using an equilibrium dialysis method. The primary binding protein was not determined. The blood to plasma partition ratio of ponatinib was 0.96 respectively, in human blood. Ponatinib distribution into RBCs was 46.8%. AP24600, the major metabolite in human plasma (see Section 2.2.5.6), was also highly bound to plasma proteins (94.7%). These estimates are deemed acceptable. Ponatinib's greater than 99% protein binding estimate should be communicated in the labeling.

Results of in vitro studies indicate that ponatinib is a weak substrate of P-gp and BCRP but not a substrate of OCT-1, OATP1B1 and OATP1B3 (see Sections 2.4.2.4 and 2.4.2.5).

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

Fecal elimination is the major excretion pathway for ponatinib. In the mass balance trial AP24534-11-104 (Report No. ARP257.0), fecal excretion accounted for 86.6% of the radioactive ponatinib dose (capsule) following a 336 hour total sampling period. Characterization of fecal metabolites from the pre-planned 0-144 hour recovery period reported the following 23.7% ponatinib, 65.2% metabolites and 11.1% unknown (Table 7).

**Table 7: Percent distribution of [14C]ponatinib and metabolites in human feces sample**

| Metabolite ID | Feces (hrs)[a] | | | | |
|---|---|---|---|---|---|
| | 0 to 24 | 24 to 48 | 48 to 72 | 72 to 144 | 0 to 144 |
| M23 Cluster[b] | 7.2 | 9.8 | 16.4 | 21.8 | 17.2 |
| M31 | 6.2 | 15.2 | 23.1 | 29.4 | 20.4 |
| M32-M35Cluster[c] | | 4.0 | 1.5 | 1.6 | 2.1 |
| M36/M38 | | 1.7 | 4.1 | 1.8 | 3.2 |
| M39/M41 | | 4 | 3.3 | 2.2 | 3.0 |
| M42(AP24567)/M43 | 10.4 | 11.5/0.1 | 12.1 | 6.1 | 9.6/3.4 |
| Ponatinib/M46 & M47 | 51.1 | 40.1/1.2 | 24.8 | 16.7 | 23.7/3.2 |
| M49 | | 4.4 | 3.4 | 4 | 3.1 |

a Only peaks containing >1.5 % of the total radioactivity in each matrix were included.
b M23 (despiperazine acid) Cluster (33.0 to 37.6 min). Several metabolites include M23, M24, M25, M26, M27 and other co-eluting unknown metabolites individually account for approximately 0.1-3% of the fecal radioactivity.
c M32-M35 Cluster- Several metabolites include M32, M33, M35 and other co-eluting unknown metabolites individually account for approximately 0.1-1.0% of the fecal radioactivity.
Source: Report No. ARP257.0

The amount of ponatinib and metabolites eliminated through urine was approximately 5% of the dose with less than 1% as parent compound and the remainder as metabolites (Table 8). These estimates of fecal and urinary elimination are deemed acceptable.

**Table 8:** Percent distribution of [$^{14}$C]ponatinib and metabolites in human urine sample

| Metabolite ID | Urine (hr)[a] | | | |
|---|---|---|---|---|
| | 0 to 24 | 24 to 48 | 48 to 72 | 0-72 |
| M11 | - | 4.6 | - | - |
| M14(AP24600) | 12.5 | 33 | 3.7 | 5.6 |
| M15 | 31.6 | 7.1 | 18.4 | 28.1 |
| M16 | 14.6 | 8.4 | 7.8 | 19.8 |
| M24 | 2.8 | 12.5 | 9.8 | 5.1 |
| M25-M41Cluster[b] | 17.8% | 18.1% | 19.2% | 14.0% |
| Ponatinib | <1.0% | 1.4 | 3 | <1.0% |

a: Only peaks containing >1.5 % of the total radioactivity in each matrix were included.
b: M25-M41 Cluster (35-41min) Several metabolites include M25, M29, M30, M31, M32, M33, M34, M35, M36,M38, M39, M41and other co-eluting unknown metabolites individually account for approximately 0.1-3% of the urine radioactivity.
Source: Report No. ARP257.0

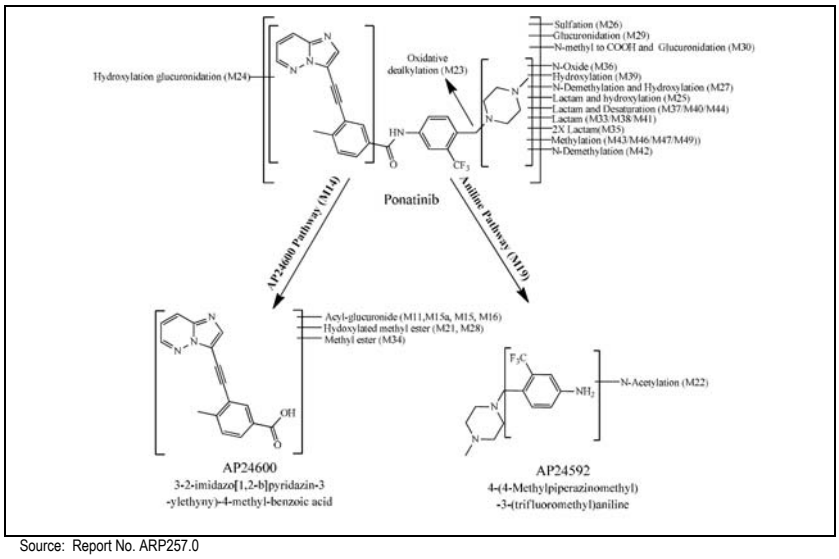
### 2.2.5.6 What are the characteristics of drug metabolism?

In vitro, ponatinib was incubated with 20 pmol/mL of individual recombinant human CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP3A4/5, and CYP2C9) at an initial substrate concentration of 5 to 10 µM. Ponatinib was stable in these incubations with all enzymes tested, except CYP3A4, CYP2C8, CYP2D6, and CYP3A5. Fifty-two percent, 28.4%, 9%, and 2.6% of ponatinib was metabolized by CYP3A4, CYP2C8, CYP2D6, and CYP3A5 to AP24567 at 60 minutes. Selectively inhibiting ponatinib metabolism with CYP-specific inhibitors and monoclonal antibodies also suggested that ponatinib was metabolized primarily by CYP3A4 and to a lesser extent by CYP2C8, CYP2D6, and CYP3A5. These in vitro findings are acceptable. The

discrepancy that the formation of the metabolite AP24734 was inhibited by the 2C9 and 2C19 inhibitor yet rhCYP2C9 and rhCYP2C19 did not metabolize ponatinib in vitro is likely the result of overlapping inhibition of P450 isoforms.[5]

Assuming 87% hepatic elimination with approximately 76% of this fraction from metabolism, the expected contribution of the CYP3A4 and CYP2C8 pathways to the elimination of ponatinib is approximately 34% and 19% of the administered dose, respectively. Based on the current FDA draft drug interaction guidance, an in vivo trial with a specific strong inhibitor of the CYP3A4 pathways is required because this pathway contributes to > 25% of ponatinib's metabolic elimination.[6] The applicant has studied the effect of ponatinib co-administered with the strong CYP3A4/5 inhibitor ketoconazole (see Section 2.4.2.2). Additional in vivo trials with strong inhibitors of CYP2C8 and CYP2D6 are not required at this time.

The excretion and biotransformation of [$^{14}$C]ponatinib following a single target oral dose of 45 mg/100 µCi (capsule) to 6 healthy subjects was investigated in trial AP24534-11-104. This trial reports that ponatinib undergoes extensive phase 1 & II metabolism (Table 9 and Figure 6). The applicant has identified several ponatinib structural moieties that make it susceptible for metabolism (Figure 7). In addition to phase I metabolism demonstrated by the cytochrome P450 superfamily in vitro, the applicant also believes esterases, amidases or proteases are involved in the in vivo enzymatic hydrolysis of ponatinib. Given the reported ponatinib storage stability in plasma, from the applicants assay validation reports (Section 2.6.1), it appears unlikely that plasma enzymes are involved in the enzymatic hydrolysis of ponatinib.

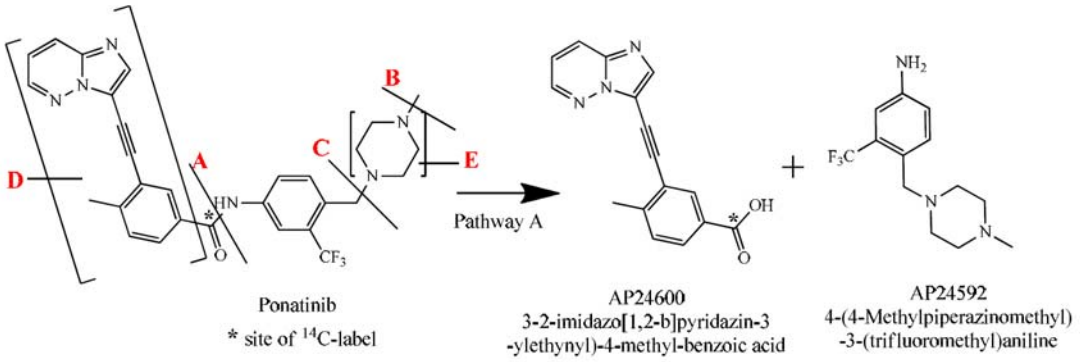



Source: Report No. ARP257.0

**Figure 6:** Proposed In Vivo Metabolic Pathways of Ponatinib

[5] Sai Y, Dai R, Yang TJ, Krausz KW, Gonzalez FJ, Gelboin HV, Shou M. Assessment of specificity of eight chemical inhibitors using cDNA-expressed cytochromes P450. *Xenobiotica.* 2000 30(4):327-43.

[6] Draft Guidance for Industry Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (02/17/12) [http://1.usa.gov/yaOuKn]




Source: Report No. ARP257.0

**Figure 7:** Metabolically Active Sites in Ponatinib

Elimination of ponatinb's metabolites occurs in the urine and feces as outline in (Table 9). The primary components circulating in whole plasma up to 24 hours were ponatinib (25.5%) in addition to the metabolites AP24600 [M14] (14.9%), AP24600 glucuronide [M15] (3.4%), AP24534 despiperazinyl acid [M23] (7.0%), and ponatinib glucuronide [M29] (6.0%). The metabolite profile in urine was dominated by AP24600 [M14] (5.6% and its glucuronides, M15 (28.1%) and M16 (19.8%). Ponatinib was the primary fecal component (23.7%) in addition to the metabolites hydroxyl ponatinib [M31](20.4%), M36 (3.2%), M47 (3.2%), and M49 (3.1%). The reviewer finds the applicant's results and conclusions regarding the metabolism of ponatinib, based on trial AP24534-11-104, acceptable. The OCP reviewer defers to the pharmacology/toxicology reviewer regarding the acceptability of the applicant's claims that the AP24600 metabolite is inactive and the metabolite, AP24567, is approximately 4-fold less potent than ponatinib in vitro.

**Table 9:** Ponatinib Human Biotransformation Pathways

| Biotransformation Pathway | | Metabolites ID | Site Observed |
|---|---|---|---|
| Ponatinib Phase I | Hydroxylation | M31 | U, **F** |
| | | M32 | U, F |
| | | M39 | U, F |
| | N-Oxidation (AP24734) | M36 | P, U, F |
| | Oxidation and lactam formation | M25 | U |
| | Lactam formation or N-oxidation with | M33 | U, F |
| | | M38 | U, F |
| | | M41 | F |
| | Double oxidation with lactam formation | M35 | U, F |
| | N-Demethylation ( AP24567) | M42 | P, F |
| | N-Demethylation and hydroxylation | M27 | F |
| | Despiperazinyl acid | M23 | P, F |
| | Amide hydrolysis (AP24600, AP24592) | M14 | **P**, U |
| | | M19 | Unobserved intermediate |
| Ponatinib Phase II | Methylation | M43 | F |
| | | M46 | F |
| | | M47 | F |
| | | M49 | F |
| | Glucuronide conjugation | M29 | U |
| | Sulfate conjugation | M26 | F |
| | Hydroxylation and glucuronidation | M24 | P, U, F |
| | Methylpiperazine to COOH-and glucuronide | M30 | U |
| AP24600 (M14) Metabolism pathway | AP24600 Methylester (AP25407) | M34 | U |
| | AP24600 Glucuronide | M11, , | U |
| | | M15 | P, **U** |
| | | M16 | U |
| AP24592 (M19)[a] Aniline Metabolism Pathway | Aniline Acetylation | M22 | U, F |
| P=plasma, U= urine, F= feces; a: non-radioactive - determined only by mass spectrometry.<br>Note : -O is monooxygenation, =O is monooxygenation leading to hydroxylation and then oxidation to a ketone (or aldehyde) | | | |

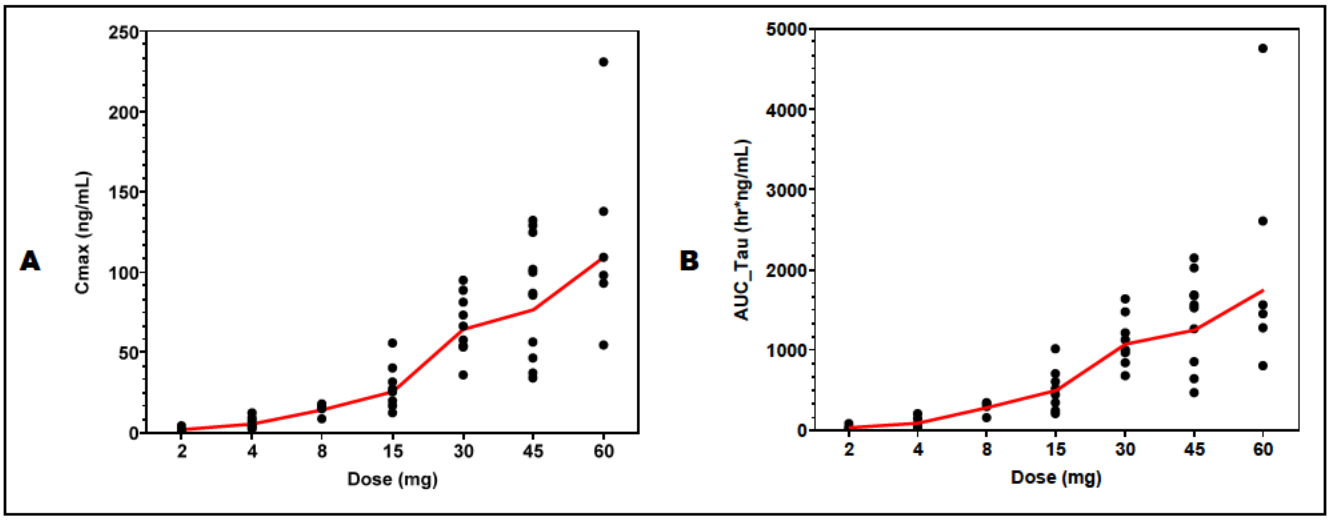
Source: Report No. ARP257.0

#### 2.2.5.7 What are the characteristics of drug excretion?

The estimated $mean_{geo}$ (CV%) for the apparent clearance (CL/F) of ponatinib at the 45 mg tablet dose once daily (fasted) for 28 days in patients with advanced hematologic malignancies (Table 6) [trial AP24534-07-101] is 35.9 L/Hr (73.1%). The $mean_{geo}$ (CV%) terminal elimination half-life of ponatinib at steady state at a daily dose of 45 mg was 23.6 (55.1%) hours, resulting in a 90% median accumulation [range: 20% - 440%] of exposures at presumed steady-state. Despite the high variability of the CL/F and half-life, these estimates is deemed acceptable given it is similar to that reported, with a lower variability, in the healthy volunteer food effect trial AP24534-11-102 following administration of a single 45 mg dose (tablet) of ponatinib in the fasted cohort (CL/F = 35.4 L/Hr (32%)). Half-life and accumulation estimates are also acceptable.

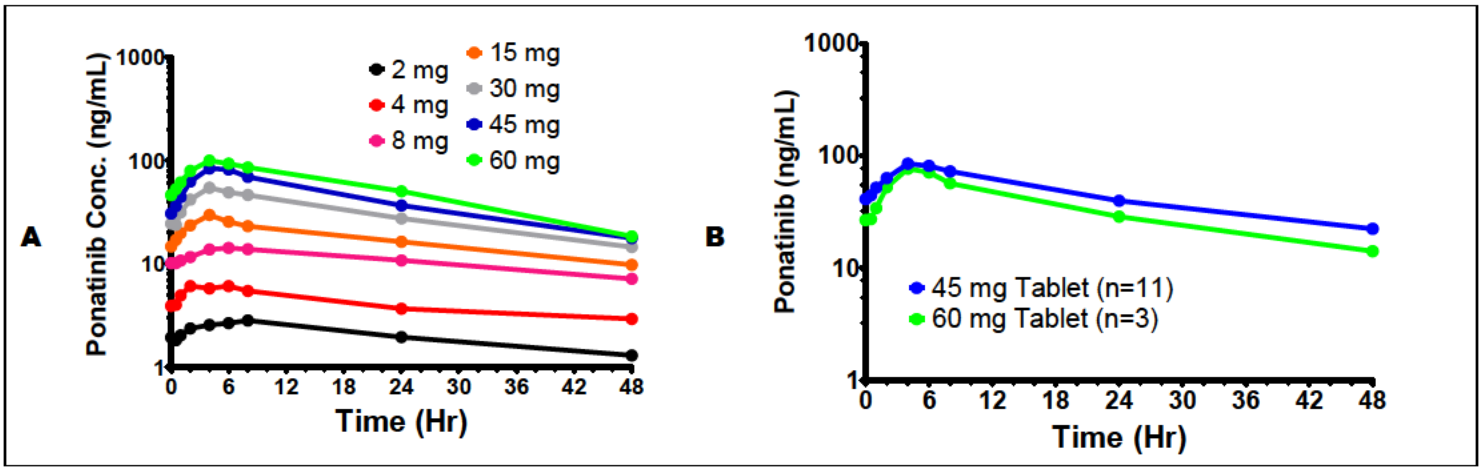
#### 2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Conclusions regarding dose proportionality following dose once daily (fasted) for 28 days in patients with advanced hematologic malignancies [trial AP24534-07-101] could not be firmly drawn for the tablet formulation due to the limited dosing levels and small sample sizes. Despite high variability, ponatinib exhibited an approximately dose proportional increase in $C_{max}$ and $AUC_{0-\tau}$ following single and multiple dosing with the capsule formulation at the proposed clinical dosing and modified dosing levels (i.e., 15 mg to 45 mg) based on a visual inspection (Figure 8). Elimination appeared linear based on a visual inspection for both the capsule and tablet formulations (Figure 9) at these dosing levels. The apparent lower exposure at the 60 mg tablet level relative to the 45 mg tablet is likely the result of the limitations noted above. These findings are acceptable, but not ideal due to the limitations noted above and lack of relative bioavailability between the capsule and tablet formulations (see Section 2.5.9).




Red line through the geometic mean
*Source: Reviewer generated*

**Figure 8:** Plasma Ponatinib Exposures ($C_{max}$ [A] & $AUC_{0-\tau}$ [B]) Versus Dose (once daily capsule administration [fasted] for 28 days) in patients with advanced hematologic malignancies [trial AP24534-07-101]

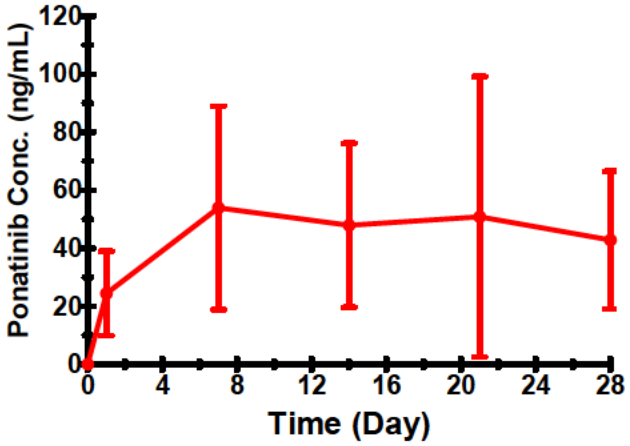



*Source: Reviewer generated*

**Figure 9:** Plasma ponatinib plasma concentrations vs. time by dose (once daily capsule [A] or tablet [B] administration [fasted] for 28 days) in patients with advanced hematologic malignancies [trial AP24534-07-101]

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

Ponatinib concentrations were likely at steady-state by day 7 following 45 mg once daily tablet administration (Figure 10) in patients with advanced hematologic malignancies (trial AP24534-07-101) based on a visual inspection. This is consistent with the reported half-life of approximately 24 hrs in this population (Table 6). The applicant did not conduct a formal analysis to confirm steady state. A 70% median accumulation [range: 40% - 440%] of exposures was reported at presumed steady-state at the 45 mg tablet dose once daily (fasted) for 28 days in patients with advanced hematologic malignancies (Table 6) [trial AP24534-07-101]. Time-dependence was not observed; however, it is unknown whether PK parameters of ponatinib change with treatment cycles. The reviewer deems these findings acceptable, but not ideal due to the high variability observed.




*Source: Reviewer generated from the applicant's dataset pkload.xpt*

**Figure 10:** Mean±SD ponatinib trough concentrations overtime following 45 mg once daily tablet dosing (Trial AP24534-07-101)

#### 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?

Inter-subject PK parameter variability (CV% of the $mean_{geo}$) was approximately 30% in the healthy volunteer food effect trial AP24534-11-102 following administration of a single 45 mg dose (tablet) of ponatinib in the fasted cohort. High inter-patient variability, approximately 70%, was observed in patients with advanced hematologic malignancies (trial AP24534-07-101) following 45 mg tablet dosed once daily (fasted) for 28 days. The higher variability in patients was likely the result of the small sample size and disease related comorbidities.

## 2.3 Intrinsic Factors

### 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, 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 will likely influence ponatinib exposure although the impact is unknown at this time (see Sections 2.2.5.5 and 2.3.2.7).

### 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 (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dose adjustments are recommended in patients with hepatic impairment, but careful patient selection and increased safety monitoring is recommended at this time (see Section 2.3.2.7). This should be reevaluated when the dedicated hepatic impairment trial results are available.

#### 2.3.2.1 Elderly

A population based PK analysis conducted by the applicant reported declining ponatinib clearance with age. Compared to the applicant's estimated clearance 37.2 L/h for a person of 48 years (median age), a person of age 70 is predicted to have a clearance of 30.5 L/h, (18.1% decrease) whereas a person of age 20 is predicted to have 58.9% higher clearance. The inclusion of covariates in the final model did not decrease the between subject variability on clearance which indicates age is probably not a significant covariate on clearance (see Section 2.2.4.4). The reviewer agrees no dose modification is warranted at this time based on this magnitude of change.

#### 2.3.2.2 Pediatric patients

No studies have been performed to evaluate ponatinib pharmacokinetics in pediatric populations. Although as an orphan drug ponatinib is exempt from the pediatric study requirements in 21 CFR 314.55, the applicant submitted a proposed pediatric study request (PPSR) outlining proposed studies for ponatinib in the pediatric population on 8/3/12.

#### 2.3.2.3 Body weight

A population based PK analysis conducted by the applicant did not indicate that body mass index (BMI) was an important covariate to explain ponatinib pharmacokinetic intersubject variability. A ±14% change in volume of distribution was reported at the $90^{th}$ and $10^{th}$ percentiles for BMI. The reviewer agrees no dose modification is warranted at this time.

#### 2.3.2.4 Gender

As part of the integrated population pharmacokinetic analysis completed by the applicant, the effect of gender on ponatinib pharmacokinetics was evaluated. Gender was not found to be an important covariate to explain ponatinib pharmacokinetic intersubject variability. The reviewer finds these results acceptable.

#### 2.3.2.5 Race

As part of the integrated population pharmacokinetic analysis completed by the applicant, the effect of race on ponatinib pharmacokinetics was evaluated. Race was not found to be an important covariate to explain ponatinib pharmacokinetic intersubject variability. This analysis was limited by relatively small numbers of subjects in select groups. Despite this limitation, the reviewer finds these results acceptable.

#### 2.3.2.6 Renal impairment

The effect of varying degrees of renal impairment on ponatinib exposure has not been conclusively evaluated. Since renal excretion is not a major route of ponatinib elimination (see Sections 2.2.5.5) a dedicated renal trial is not warranted at this time. The potential for renal impairment to influence metabolism of ponatinib can not be ruled out. While this issue could have been further explored by the reviewer using a mechanistic approach (see Section 4.2), the truncated review timeline did not permit this to occur.[7]

#### 2.3.2.7 Hepatic impairment

The effect of varying degrees of hepatic impairment on ponatinib exposure has not been conclusively evaluated. Since hepatobiliary excretion is a major route of ponatinib elimination (see Sections 2.2.5.5) a dedicated hepatic impairment trial is warranted. The applicant submitted a proposed clinical trial protocol on 6/8/2012 to evaluation of pharmacokinetics and safety of ponatinib in patients with chronic hepatic impairment and matched healthy subjects. FDA found the proposed protocol generally acceptable and did not provide any additional comments (see the 06/29/2012 clinical pharmacology review for IND 78,375). Completion of this trial should be a post marketing requirement. In the interim labeling should state that Iclusig should be avoided in patients with moderate (Childs-Pugh B) to severe (Childs-Pugh C) unless the benefit outweighs the possible risk of ponatinib overexposure. Patients with any degree of hepatic impairment should also be closely monitored for exposure related adverse reactions (e.g., myelosupression, rash, increased lipase).

#### 2.3.2.8 What pharmacogenetics information is there in the application and is it important or not?

The pharmacogenomic information from trial AP24534-07-101 in this application was not deemed important by the genomics group following its review during the filing period.

#### 2.3.2.9 What pregnancy and lactation use information is there in the application?

No clinical information was provided.

#### 2.3.2.10 Other human factors that are important to understanding the drug's efficacy and safety

None.

[7] Zhao P, Vieira Mde L, Grillo JA, Song P, Wu TC, Zheng JH, et al. Evaluation of exposure change of nonrenally eliminated drugs in patients with chronic kidney disease using physiologically based pharmacokinetic modeling and simulation. *J Clin Pharmacol.* 2012; 52(1 Suppl):91S-108S.

## 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?

Drugs (see Sections 2.4.2.2, 2.4.2.4, 2.4.2.5, and 2.4.2.10)

#### 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.

The reviewer recommends a dose reduction to 30 mg daily if ponatinib is co-administered with a strong CYP3A4 inhibitor (see Section 2.4.2.2).

### 2.4.2 Drug-drug interactions

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

Yes. See Sections 2.4.2.2, 2.4.2.4, and 2.4.2.5 below

#### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Based on an in vitro study, ponatinib is primarily metabolized by CYP3A4 and to a lesser extent CYP2C8, CYP2D6, and CYP3A5 (see Section 2.2.5.6).

*CYP3A4 Inhibitors*

The applicant conducted an open-label, randomized, 2-period, 2-sequence crossover trial to evaluate the effects of concomitant multiple dose administration of ketoconazole, a strong CYP3A inhibitor on the PK profile of single-dose ponatinib administration in healthy subjects. Each subject received 2 single doses of 15 mg ponatinib, once given alone and once co-administered with daily doses of 400 mg of ketoconazole for 5 days. Plasma concentrations for ponatinib and the AP24567 metabolite were sampled over a 96 hour period. Trial periods were separated by a 14- to 21-day washout period. The reviewer finds the overall design acceptable. The 15 mg ponatinib dose is acceptable for this trial to allow an appropriate safety margin between potential plasma exposures resulting from CYP3A4 inhibition in this healthy population based on findings from the AP24534-07-101 patient trial.

Twenty four subjects were randomized to the treatment phase and 22 completed the trial completed the study following 2 subjects withdrawing consent. The trial population was composed primarily of Caucasian male healthy subjects 22-53 years old with an average (±SD) total body weight of 78±13 kg. Descriptive statistics for derived PK parameters for ponatinib and AP24567 are presented by treatment in Table 10. The estimated mean ratios of $AUC_{0-\infty}$ and of $C_{max}$ for ponatinib increased by 78% and 47%, respectively, while exposure to the metabolite AP24567 decreased by approximately 70% (Table 11). There were no deaths or other serious adverse events (SAEs) reported in this study, and no subjects discontinued due to an adverse event (AE). All AEs were mild in intensity.

**Table 10:** Ponatinib and AP24567 PK Parameters

| Treatment | Statistic | tmax (h) | $C_{max}$ (ng/mL) | $AUC_{0-t}$ (h*ng/mL) | $AUC_{0-\infty}$ (h*ng/mL) | $t1/2_Z$ (h) | CL/F (L/h) | $V_Z/F$ (L) |
|---|---|---|---|---|---|---|---|---|
| **Ponatinib PK Parameters** | | | | | | | | |
| Ponatinib alone (N=22) | n | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| | Mean (SD) [CV %] | | 17.5 (6.3) [36.0] | 442.9 (158.7) [35.8] | 508.1 (192.8) [38.0] | 35.3 (4.4) [12.4] | 34.5 (15.7) [45.6] | 1744 (888.9) [51.0] |
| | $Mean_{Geo}$ (CV %) | | 16.1 (48.5) | 413.5 (41.3) | 472.2 (42.0) | 35.3 (13.5) | 31.8 (42.0) | 1604 (40.4) |
| | Median [Range] | 6.00 [2.0-8.0] | 16.0 [3.5-28.6] | 434.0 [137-746] | 497.0 [171-922] | 34.7 [26.9-45.1] | 30.2 [16.3-87.9] | 1516 [944-5190] |
| ponatinib with ketoconazole (N=22) | n | 22 | 22 | 22 | 19[a] | 19[a] | 19[a] | 19[a] |
| | Mean (SD) [CV %] | | 24.7 (7.6) [30.7] | 740.3 (254.8) [34.4] | 831.1 (290.8) [35.0] | 36.7 (5.2) [14.3] | 20.2 (6.8) [33.9] | 1051 (351.5) [33.5] |
| | $Mean_{Geo}$ (CV %) | | 23.6 (31.6) | 700.7 (35.0) | 785.3 (35.6) | 36.3 (15.7) | 19.1 (35.6) | 1001 (32.5) |
| | Median [Range] | 6.0 [5.0-8.0] | 23.3 [11.3-42.9] | 678.5 [345-1290] | 748.4 [416-1420] | 37.3 [27.0-45.5] | 20.0 [10.5-36.1] | 978.3 [567-2110] |
| **AP24567 PK Parameters** | | | | | | | | |
| Ponatinib alone (N=22) | n | 22 | 22 | 22 | 2[a] | | | |
| | Mean (SD) [CV %] | | 0.6 (0.2) [40.8] | 15.4 (8.6) [55.6] | 25.6 (13.0) [50.8] | | | |
| | $Mean_{Geo}$ (CV %) | | 0.57 (53.3) | 12.2 (105.5) | 23.9 (57.1) | | | |
| | Median [Range] | 5.0 [4.0-12.0] | 0.6 [0.10-1.3] | 12.8 [0.6-28.8] | 25.6 [16.4-34.9] | | | |
| Ponatinib with ketoconazole (N=22) | n | 22 | 22 | 22 | | | | |
| | Mean (SD) [CV %] | | 0.2 (0.05) [27.1] | 5.3 (4.0) [76.0] | | | | |
| | $Mean_{Geo}$ (CV %) | | 0.2 (27.9) | 3.5 (141.9) | | | | |
| | Median [Range] | 6.0 [5.0-12.0] | 0.2 [0.1-0.3] | 5.1 [0.4-14.2] | | | | |

a=Subjects with an $AUC_{extrap}$ >20% were excluded from the summary statistics for this parameter
*Source: Trial AP24534-11-103 trial report and dataset adpkp.xpt*

**Table 11:** ANOVA Results for Ponatinib and AP24567 Test to Reference Outcomes

| Reference treatment (R) | Test treatment (T) | Ln-transformed parameter | Estimated mean ratio (T/R) [%] | 90% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower limit | Upper limit |
| **Ponatinib** | | | | | |
| Ponatinib alone | Ponatinib with ketoconazole | $AUC_{0-\infty}$ | 178.0 | 166.2 | 190.6 |
| | | $AUC_{0-t}$ | 170.1 | 159.4 | 181.4 |
| | | $C_{max}$ | 146.6 | 132.8 | 161.8 |
| **AP24567** | | | | | |
| Ponatinib alone | Ponatinib with ketoconazole | $AUC_{0-t}$ | 29.2 | 20.0 | 42.5 |
| | | $C_{max}$ | 32.2 | 27.8 | 37.2 |

*Source: Trial AP24534-11-103 trial report and dataset adpkp.xpt*

The reviewer agrees with the applicant's conclusion that the change in the AP24567 metabolite exposure will not substantially impact the effective exposure (ponatinib + active metabolites) because of the marginal exposure to the metabolite (see Section 2.2.5.6). However, the reviewer disagrees with the applicant's conclusion that a dose adjustment is not required and only "Caution should be exercised with concurrent use of ponatinib with strong CYP3A inhibitors." As stated above, an average 78% increase in ponatinib exposure would be expected if ponatinib were co-administered with a strong CYP3A4 inhibitor. Assuming a 45 mg daily dose and dose proportionality, the resulting ponatinib exposure is expected to be close to that seen following an 80 mg daily dose (45 * 1.78 = 80.1). As the applicant states in its clinical pharmacology summary, "cumulative phase 1 safety data were consistent with 60 mg exceeding the maximum tolerated dose (MTD)". Therefore, the reviewer recommends a dose reduction to 30 mg daily (30 * 1.78 = 53.4) if ponatinib is co-administered with a strong CYP3A4 inhibitor and close monitoring for signs (e.g., myelosuppression, rash, increased lipase, etc.) of possible increased drug related toxicity.

*CYP3A4 Inducers*

Based on the in vitro finding that CYP3A is involved in overall human clearance of ponatinib and the clinical finding regarding CYP inhibition above, it is anticipated inducers of CYP3A will theoretically increase the clearance of ponatinib; however, the magnitude is unknown. The effect of CYP3A4 enzyme induction on the metabolism of ponatinib was not specifically evaluated by the applicant in vitro or in vivo. The applicant has submitted a proposed clinical trial protocol on 6/8/2012 to evaluate the effect of rifampin (a strong CYP3A4 inducer) on the pharmacokinetics of ponatinib when administered concomitantly in healthy subjects. FDA found the proposed protocol generally acceptable and did not provide any additional comments (see the 06/29/2012 clinical pharmacology review for IND 78,375). Completion of this trial should be a post marketing requirement.

In the interim the reviewer used a mechanistic modeling approach to simulate the effect of a strong CYP3A4 inducer on the pharmacokinetics of ponatinib when administered concomitantly. Given the vulnerable population, the purpose of this analysis was to guide product labeling until additional clinical information was available. The details of the assumptions, model building, and calibration can be found in Section 4.2 of this review. The simulation from a physiologically based pharmacokinetic (PBPK) model, shown to reasonably predict ponatinib PK alone and following inhibition by a strong CYP3A4 inhibitor (see Section 4.2), suggests that a 52% reduction in ponatinib's $C_{max}$ and a 71% reduction in ponatinib's AUC may be expected following induction by a strong CYP3A4 inducer. Based on this information, the reviewer recommends the labeling communicate that coadministration of strong CYP3A4 inducers with ponatinib should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. This should be reevaluated once the results of the clinical trial are available.

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

*Inhibitor of CYP enzymes*

In vitro studies with ponatinib and AP24600 were conducted to assess the potential for ponatinib to inhibit CYP450 enzymes (Table 12). Ponatinib was evaluated for its ability to inhibit the CYP enzymes directly (reversible inhibition, RI) or in a NADPH-dependent manner (metabolism dependent inhibition, MDI) or in a time-dependent manner (time dependent inhibition, TDI). AP24600 was only evaluated for its ability to inhibit the human CYP enzymes directly (RI). The Km and Vmax for the marker substrates, and the reaction conditions were determined using the HLMs in order to select conditions for the ponatinib inhibition studies. Standard microsomal incubation conditions were used in these initial studies with marker substrates; times of incubation and protein concentrations were adjusted to limit the extent of metabolism of the marker substrates to less than 20%. This design is acceptable.

These studies demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A activities. The $IC_{50}$ values and $K_i$ values for all CYPs ranged from 5.2 – 13.6 uM and 2.6 – 6.8 uM for reversible inhibition, respectively. The steady state geometric mean $C_{max}$ of ponatinib was 73 ng/mL (0.137 uM) at a therapeutic dose of 45 mg using the to-be marketed tablet formulation in patients with advanced hematologic malignancies (see Section [2.2.5.1Trial AP24534-07-101]). The range of $C_{max}/K_i$ ratio was 0.020 – 0.053, which is less than 0.1. Out of all the CYPs, ponatinib inhibited CYP2C19 the strongest (Ki of 2.6 uM). The metabolite, AP24600 is a weak inhibitor of CYP450 enzymes ($IC_{50}$ > 100 uM for all CYPs), with a $C_{max}/K_i$ ratio of 0.001 assuming a steady state geometric mean $C_{max}$ of 17 ng/mL (0.061 uM) at a therapeutic dose of 45 mg using the to-be marketed tablet formulation in patients with advanced hematologic malignancies (see Section [2.2.5.1Trial AP24534-07-101]). Ponatinib was not found to be a metabolism dependent or time dependent inhibitor of CYP450 enzymes. The reviewer

finds these results and the applicant's conclusion acceptable. No additional in vivo trials are required at this time.

**Table 12:** Prediction of Ponatinib Clinical Impact of CYP450 Inhibition

| Enzyme | RI $IC_{50}$ | $K_i$ | $[I]/K_i$ [a,b] |
|---|---|---|---|
| 1A2 | 13.3 | 6.65 | 0.021 |
| 2B6 | 5.6 | 2.8 | 0.049 |
| 2C8 | 6.1 | 3.05 | 0.045 |
| 2C9 | 10.8 | 5.4 | 0.025 |
| 2C19 | 5.2 | 2.6 | 0.053 |
| 2D6 | 11.6 | 5.8 | 0.024 |
| 3A4/5 | 8.3 | 4.15 | 0.033 |
| 3A4/5 | 13.6 | 6.8 | 0.02 |

a[I] = Cmax= 0.137 µM at the therapeutic dose of 45 mg
b Ki= $IC_{50}/2$

*Inducer of CYP enzymes*

The potential of ponatinib (0.05 – 2 µM) to induce CYP1A2, 2B6 and 3A4 was investigated in vitro. Three preparations of cultured human hepatocytes from three separate livers were treated once daily for three consecutive days with dimethyl sulfoxide (DMSO, 0.1% v/v, vehicle control), one of four concentrations of AP24534 (0.05, 0.2, 0.6 or 2 µM) or one of three known human CYP inducers, namely, omeprazole (50 µM), phenobarbital (750 µM) and rifampin (10 µM). After treatment, the cells were harvested to isolate microsomes for the analysis of CYP activity and mRNA levels. This design is acceptable.

The study reports that at the concentration range studied, the percent increase in CYP1A2, CYP2B6 and CYP3A4/5 enzyme activity compared to positive control ranged from 0.609 – 10.8%, -0.918 – 4.47%, 10.1 – 25.6%, respectively. One reported culture showed that ponatinib (0.6 µM) was 46.0% as effective as rifampin at inducing CYP3A4/5 activity. Analysis also demonstrated that the increase in CYP1A2, CYP2B6 and CYP3A4/5 mRNA content when compared to positive control ranged from 0.129 – 5.67%, -0.547 – 9.14%, 3.28 – 10.5%, respectively. Ponatinib did not induce CYP1A2, 2B6 and 3A4 at concentrations expected when used clinically (up to 0.2 µM), but did induce CYP3A4/5 by 25.6% at 0.6 µM concentrations. The reviewer finds these results and the applicant's conclusion acceptable. No additional in vivo trials are required at this time.

#### 2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

In-vitro studies were conducted to determine the substrate and inhibitor potential of ponatinib for P-gp. Caco-2 cells and CPT-P1 cells (a proprietary cell line with reduced expression of human P-glycoprotein compared with parental Caco-2 cells) were used to determine the substrate/inhibition properties of ponatinib toward P-gp. Transport of the P-gp probe substrate digoxin (10 µM) across Caco-2 cell monolayers was used as an index of P-gp activity. Inhibition of P-gp activity was assessed in the presence of a range of ponatinib concentrations from 0.0165 to 12 µM. This design is acceptable.

The results of this in vitro study find that ponatinib is a weak substrate of P-gp (recovery of test compound was low). Ponatinib showed concentration dependent inhibition of P-gp with an $IC_{50}$ value of 0.49 µM. In addition, the $[I]1/IC_{50}$ and $[I]2/IC_{50}$ values were greater than 0.1 for P-gp ([I]1/IC50= 0.2/0.49 and [I]2/IC50= 338/0.49). The reviewer finds these results acceptable. The reviewer recommends that the labeling communicate these in vitro findings and the need for additional monitoring for possible exposure related adverse reactions from coadministered sensitive P-gp substrates. Additional in vivo exploration is not recommended at this time because it is unlikely that the results would impact the cautionary language that is recommended.

#### 2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Yes. Additional in vitro studies were conducted to determine the substrate and inhibitor potential of ponatinib for BCRP, OATP1B1, OATP1B3, OCT1, and inhibitor potential of ponatinib for BSEP, OAT1/OAT3 and OCT2.

*BCRP*

The effect of ponatinib on BCRP was evaluated using the same system as P-gp (see Section) except the transport of the BCRP probe substrate, cladribine (10 µM), across Caco-2 cell monolayers was used as an index of BCRP activity. This design is acceptable. The results of this in vitro study find that ponatinib is a weak substrate of BCRP (recovery of test compound was low). Ponatinib showed concentration dependent inhibition of BCRP with an $IC_{50}$ value of 0.013 µM. The $[I]1/IC_{50}$ and $[I]2/IC_{50}$ values was greater than 0.1 for BCRP ($[I]1/IC_{50}$= 0.2/0.0132 and $[I]2/IC_{50}$= 338/0.0132). The reviewer finds these results acceptable. The reviewer recommends that the labeling communicate these in vitro findings and the need for additional monitoring for possible exposure related adverse reactions from coadministered sensitive BCRP substrates. Additional in vivo exploration is not recommended at this time because it is unlikely that the results would impact the cautionary language that is recommended.

*Uptake Transporters OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2*

Uptake Transporters Human embryonic kidney epithelial cells (HEK293) transfected with individual uptake transporters (OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2) were used to assess the substrate and inhibition potential of ponatinib toward the corresponding transporter. The cells were incubated with ponatinib (0.5, 1, and 2 µM) for 5, 10 and 20 min in HBSSg buffer. Transporter-specific positive controls were run in parallel and treated identically. This design is acceptable.

This study reports that ponatinib is not a substrate of OATP1B1/OATP1B3 and OCT1. In addition, ponatinib was found not to be an inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, and OAT3 (inhibition did not exceed 50% for all 6 uptake transporters). The reviewer finds these results and the applicant's conclusion acceptable. No additional in vivo trials are required at this time.

*Bile Salt Export Pump (BSEP)*

BSEP vesicles were used to study inhibition of BSEP by ponatinib. The inhibition of BSEP by ponatinib (0.001 to 100 µM) was evaluated by measuring the uptake of the BSEP-specific probe substrate 1 µM [3H]-taurocholic acid (TCA) into inside-out vesicles from BSEP-expressing cells. This design is acceptable.

Ponatinib showed concentration dependent inhibition of BSEP with an $IC_{50}$ value of 32.0 µM. The reviewer finds these results and the applicant's conclusion acceptable. Currently there is no Agency criterion for BSEP in-vitro findings. Therefore we cannot predict the in-vivo consequences until further confirmatory guidance's have been established.

#### 2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No.

#### 2.4.2.7 What other co-medications are likely to be administered to the target patient population?

In the pivotal trial AP24534-10-201 the most frequently used individual concomitant medications overall were acetaminophen (50.1%), allopurinol (35.9%), furosemide (26.7%), lidocaine (22.5%), ibuprofen (18.0%), prednisone (15.4%), omeprazole (15.4%), and acetylsalicylic acid (15.1%). Of

these, omeprazole is of greatest concern given it effect on gastric pH. In addition, given the relatively high aspirin use, the potential for aspirin to displacement of ponatinib from its protein binding sites also requires further investigation (see Sections 2.2.5.4 and 2.4.2.10).

#### 2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes. See Section 2.4.2.2.

#### 2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No.

#### 2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Yes. Ponatinib is highly protein bound (see Section 2.2.5.4). However, the potential for displacement of ponatinib from its protein binding sites by other highly protein-bound comedications, thus increasing free (i.e., active) ponatinib exposure, is unknown. Assuming the proposed 45 mg daily dose, dose proportionality, and 99.92% plasma protein binding, then a decrease in the bound fraction from 99.92% to 99.89% would theoretically result in free drug exposures similar to that expected at the doses exceeding the MTD as defined by the applicant. Further, a reviewer initiated descriptive exploratory analysis of patients requiring dose modification versus aspirin use in the pivotal trial AP24534-10-201 suggest that approximately 70% of patients who received aspirin required a dose reduction compared to approximately 50% who did not received aspirin (Table 13). Given these theoretical safety concerns, the reviewer recommends a postmarketing commitment to evaluate the in vitro potential for the displacement of ponatinib from its protein binding sites following addition of frequently used highly protein-bound co-medications be communicated to the applicant. Additional in vivo trials may be needed depending on the results of this in vitro study.

**Table 13:** Reviewer analysis of Aspirin use versus Dose Modification in trail AP24534-10-201

| | | Dose Modification | | |
|---|---|---|---|---|
| | Count<br>Total %<br>Col %<br>Row % | Yes | No | Total |
| Aspirin Use | No | 192<br>42.8%<br>81.7%<br>49.6% | 195<br>43.4%<br>91.1%<br>50.4% | 387<br>86.2% |
| | Yes | 43<br>9.6%<br>18.3%<br>69.4% | 19<br>4.2%<br>8.9%<br>30.6% | 62<br>13.8% |
| | Total | 235<br>52.3% | 214<br>47.7% | 449 |

Statistic of interest in red

*Source: Reviewer generated based on applicant datasets ex.xpt & cm.xpt for trail AP24534-10-201*

### 2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Yes. See Section 2.2.4.4.

## 2.5 General Biopharmaceutics

### 2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The aqueous solubility of ponatinib HCl was evaluated in USP aqueous buffers ranging from pH 1.2 to 7.5. Ponatinib HCl is highly soluble in aqueous solution at pH values less than 1.7; slightly soluble at pH values between 1.7 and 2.7; and insoluble above pH 2.7. Therefore, the reviewer agrees with the applicant's conclusion that that Ponatinib HCl is considered a "low solubility" compound due to its insolubility in aqueous solution above pH 2. However, the reviewer disagrees with the applicants conclusion that the mean apparent permeability (Papp) value for the A-to-B transport was 4.4 x $10^{-6}$ cm/sec in Caco-2 cells and the efflux ratio ($P_{app}$B-to-A/$P_{app}$A-to-B) of <2.0 clearly suggests that ponatinib is a high permeability compound. The reviewer finds the reported permeability to be "moderate" and recommends a BCS classification of I (b) (4) rather than the Class II proposed by the applicant unless otherwise determined by the FDA BCS committee.

### 2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The to-be-marketed formulation was used in the pivotal trial AP24534-10-201.

#### 2.5.2.1 What data support or do not support a waiver of in vivo BE data?

This issue will be reviewed by ONDQA per memorandum of understanding with OCP.

#### 2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Ponatinib should be considered a narrow therapeutic index drug with regard to safety. BE studies that fail to meet the 90% CI, using equivalence limits of 80-125%, and resulting in higher than expected exposures will likely result in a considerable increase in risk. The proposed ponatinib dose of 45 mg daily is the MTD based on the dose escalation trial AP24534-10-101. Increasing the dose by 33% (i.e., 60 mg) in the same trial resulted in 4 dose limiting toxicities (DLT's) in 11 evaluable patients.

#### 2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

The to-be-marketed formulation was used in the pivotal trial AP24534-10-201.

### 2.5.3 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?

The applicant conducted a single-dose, randomized, open-label, 3-period, 6-sequence crossover, pivotal food effect trial. Ponatinib 45 mg was administered in the fasting state, after the completion of a standard high-fat meal[8], and after the completion of a low-fat meal.[9] Twenty-four healthy subjects were enrolled and 22 subjects were considered evaluable for all PK

[8] *Standardized high-fat meal:* 50% of total caloric content of the meal from fat with approximately 150, 250, and 500 to 600 calories derived from protein, carbohydrate, and fat, respectively (total of approximately 900 to 1000 calories).
[9] *Standardized low-fat meal:* ≤20% of total caloric content of the meal from fat with approximately 56, 428 and 63 calories derived from protein, carbohydrate, and fat, respectively (total of approximately 547 calories).

comparisons.[10] The trial population was composed primarily of Caucasian (63%) male (96%) healthy subjects 24-53 years old with an average (±SD) total body weight of 81±13 kg. The reviewer finds the design and trial population acceptable.

Descriptive statistics for derived PK parameters for ponatinib are presented by meal cohort in Table 14. All limits of the 90% CIs of the estimated mean ratios for all of the comparisons fell within the 80% to 125% margins (Table 15). In addition, outcomes of a paired Wilcoxon signed rank for $t_{max}$ did not show a significant difference between the fasted state and either the high fat or low fat meals. Therefore, the reviewer agrees with the applicant's conclusion that a food effect on BA is not established. This should be reflected in the product label.

**Table 14:** Ponatinib PK parameters for trial AP24534-11-102

| Group | Statistic | $T_{max}$ (h) | $C_{max}$ ng/mL) | $AUC_{0-t}$ h*ng/mL) | $AUC_{0-\infty}$ h*ng/mL) | $t_{1/2}$ (h) | CL/F (L/h) | $V_Z/F$ (L) |
|---|---|---|---|---|---|---|---|---|
| Fasted (N=22) | Mean (SD) [CV %] | | 56.7 (14.8) [26.1] | 1252 (336.6) [26.9] | 1329 (376.2) [28.3] | 24.6 (3.6) [14.7] | 37.2 (13) [35] | 1291 (387.9) [30] |
| | $Mean_{Geo}$ (CV %) | | 54.7 (29.3) | 1203 (30.5) | 1273 (32) | 24.6 (14.2) | 35.4 (32) | 1242 (28.5) |
| | Median [Range] | 6 [5-8] | 55.8 [25.1-80.2] | 1230 [592-1830] | 1312 [613-2040] | 24.2 [19.7-33.1] | 34.3 [22-73.4] | 1207 [814-2390] |
| High-fat (N=22) | Mean (SD) [CV %] | | 53.4 (14.1) [26.3] | 1369 (376.3) [27.5] | 1455 (422.6) [29.1] | 23.9 (3.8) [16.1] | 34 (11.6) [34.2] | 1145 (330) [28.8] |
| | $Mean_{Geo}$ (CV %) | | 51.5 (28.6) | 1315 (30.6) | 1392 (32.2) | 23.7 (15.6) | 32.3 (32.2) | 1104 (28) |
| | Median [Range] | 6 [4-12] | 51.3 [25.4-79.2] | 1384 [668-1980] | 1449 [695-2120] | 23.5 [19.3-36.4] | 31.1 [21.2-64.8] | 1081 [729-2040] |
| Low-fat (N=22) | Mean (SD) [CV %] | | 53.7 (14.6) [27.2] | 1230 (353.4) [28.7] | 1306 (388.3) [29.7] | 24.7 (3.7) [14.9] | 38.3 (14.8) [38.7] | 1349 (507.1) [37.6] |
| | $Mean_{Geo}$ (CV %) | | 51.6 (30.6) | 1175 (33.1) | 1244 (34.2) | 24.5 (15.4) | 36.2 (34.2) | 1278 (33.1) |
| | Median [Range] | 5 [5-8] | 51.1 [24.9-76.8] | 1202 [541-2000] | 1257 [567-2140] | 23.4 [19.6-31.4] | 35.8 [21-79.3] | 1200 [805-2910] |

*Source: Trial AP24534-11-102 trial report and dataset adpkp.xpt*

**Table 15:** Results for ponatinib test to reference outcomes for trial AP24534-11-102

| Reference Treatment (R) | Test treatment (T) | Ln-transformed parameter | Estimated mean ratio (T/R) in % | 90% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower limit | Upper limit |
| Fasted | High-fat meal | $AUC_{0-\infty}$ | 109.6 | 105.8 | 113.4 |
| | | $AUC_{0-t}$ | 109.5 | 105.8 | 113.3 |
| | | $C_{max}$ | 94.2 | 89.7 | 99 |
| Fasted | Low-fat meal | $AUC_{0-\infty}$ | 97.8 | 94.5 | 101.3 |
| | | $AUC_{0-t}$ | 97.7 | 94.5 | 101.1 |
| | | $C_{max}$ | 94.3 | 89.8 | 99.1 |

*Source: Trial AP24534-11-102 trial report*

### 2.5.4 When would a fed BE study be appropriate and was one conducted?

A fed BE study would not be appropriate (See Section 2.5.3)

### 2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

This issue will be reviewed by ONDQA per memorandum of understanding with OCP.

[10] One subject was excluded from the PK analysis because he had not received study drug in the fasted state and other was withdrawn due to a high triacylglycerol lipase on the day before study drug administration.

### 2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Both the 15 mg and 45 mg to-be-marketed tablet formulation strengths were used in the pivotal trial AP24534-10-201.

### 2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

### 2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

### 2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

The reviewer recommends a comment be sent to the applicant to assess the relative BA between the capsule formulation and the to-be-marketed Iclusig tablet formulation used in the AP24534-07-101 to enrich the PK dataset and provide more information on dose proportionality. Since the 45 mg tablet dose used in the dose finding PK trial AP24534-07-101 was administered as three 15 mg Iclusig tablets rather than the to-be-marketed 45 mg Iclusig tablet used in the pivotal trial AP24534-10-201, the reviewer also recommends a comment be sent to the applicant to evaluate the relative BA of one 45 mg Iclusig tablet relative to concomitant administration of three 15 mg Iclusig tablets.

## 2.6 Analytical Section

### 2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Ponatinib and metabolites AP24600 (primary inactive metabolite) and AP24567 were identified in human plasma. A validated LC/MS/MS method was used to analyze parent compound and AP24567 from studies AP24534-102, -103, and -104. Metabolite AP24600 was analyzed via a validated method for studies 101 and 102, but a non-validated method was used to analyze samples from study 104, which the report was not provided. AP24600 was not quantified in study 103. Analytical methods used to measure the parent drug (and metabolites) in the different studies are listed in Table 16, below.

**Table 16:** Summary of Analytical Methods used in Study 101, 102 and 103

(b) (4)

[redacted]

**Table 16:** Summary of Analytical Methods used in Study 101, 102 and 103

| | | | | | |
|---|---|---|---|---|---|
| 110316VRM_ACM (Partial Method Validation) | **AP24534-07-102, -103, -104** | (b) (4) Assay Validation SOP | **Assay Method** | | |
| | | | **Matrix** | Plasma | |
| | | | **Analyte** | Ponatinib (AP24534) | AP24567 |
| | | | **Calibration Range** | 0.5 – 250 ng/mL | |
| | | | **LLOQ** | 0.5 ng/mL | 0.1 ng/mL |
| | | | **Regression** | Linear, weighted (1/x2) | |
| | | | **Intra- & Inter Assay Precision(%CV)** | ≤ 9.4% | ≤ 10.3% |
| | | | **Intra- & Inter Assay Accuracy (%RE)** | -10.4 – 10.5% | -13.8 – 6.3% |
| | | | **Freeze-thaw stability** | 5 cycles @ -20 C & -70 C | |
| | | | **Benchtop (room temp) stability** | 24 hours | |
| | | | **Storage stability** | -20 C & -70 C for up to 95 days | |
| 120081VRM_ACM | **AP24534-07-101, -102** | (b) (4) Assay Validation SOP | **Assay Method** | | |
| | | | **Matrix** | Plasma | |
| | | | **Analyte** | Ponatinib | AP24600 |
| | | | **Calibration Range** | 0.5 – 250 ng/mL | |
| | | | **LLOQ** | 0.5 ng/mL | |
| | | | **Regression** | Linear, weighted (1/x2) | |
| | | | **Intra-Assay Precision (%CV)** | ≤ 4.1% | ≤ 6.0% |
| | | | **Intra-Assay Accuracy (%RE)** | -5.5 – 6.0% | -3.1 – 6.7% |
| | | | **Inter-Assay Precision (%CV)** | ≤ 4.4% | ≤ 5.7% |
| | | | **Inter-Assay Accuracy (%RE)** | -3.5 – 1.3 % | 0.0 – 2.3% |
| | | | **Freeze-thaw stability** | 5 cycles @ -20 C | |
| | | | **Benchtop (room temp) stability** | 24 hours | |
| | | | **Storage stability** | -20 C & -70 C for up to 26 days | |

### 2.6.2 Are there additional assays (e.g., PD assays) used to identify and measure product in the plasma in the clinical pharmacology studies?

Phosphorylated and non-phosphorylated CRKL (CRK-oncogene like protein) was used as a pharmacodynamic (PD) marker for BCR-ABL kinase activity (secondary endpoint) in Study AP24534-07-101. A validated assay report was provided, which gel electrophoresis and immunoblotting were used to measure CRKL in PBMCs isolated from whole blood. The assay was developed by the laboratory of (b) (4) . Comparison of samples within a single gel (3-5 replicates), between different gels (3 replicates), and different operators (3 replicates) were performed.

Based on the results of the applicants' method validation report, we reject their findings due to insufficient data (e.g., internal standard, freeze thaw stability, dose-response) needed to determine the adequacy of results.

### 2.6.3 Which metabolites have been selected for analysis and why?

Metabolites AP24600 and AP24567 were selected for analysis in plasma. In earlier studies, AP24567 was identified as the primary metabolite and monitored in clinical studies. In later radiolabeled studies, an additional metabolite (AP24600) was identified and subsequently determined to be the major metabolite (inactive) in human plasma. To determine the exposure of AP24600 in humans, archived plasma samples (Studies 101, 102, 104) were assayed for AP24600.

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

Ponatinib is highly bound to human plasma proteins (> 99%). Total concentrations were measured in plasma. Not assessing free concentrations is not optimal given the high degree of protein binding reported with ponatinib; however, it is acceptable at this time since the potential for displacement will be evaluated in vitro as a PMC. If the study finds that displacement is indeed a concern then this issue should be readdressed by the applicant.

### 2.6.5 What bioanalytical methods are used to assess concentrations of the measured moieties?

Plasma ponatinib and AP24567 concentrations measured in clinical studies were analyzed using three validated methods as detailed in Table 16. All methods utilized a LC-MS/MS. The first method (080348VRM_ACM_R1), measured ponatinib and AP24567 in plasma over a range of 0.1 to 50 ng/mL, and was used for study AP24534-07-101 (dose-escalation study). The second method (110316VRM_ACM) used plasma and increased the range of ponatinib to 0.5 to 250 ng/mL and was used for studies 102, 103 and 104. The third validated method (120081VRM _ACM) measured ponatinib and AP24600 in plasma over a range of 0.5 – 250 ng/mL, and was used in studies 101 and 102. The sponsor met the Agency's recommended acceptance criteria of <20% for precision (CV%) and within +20% for accuracy at the lower limit of quantitation and <15% or within +15% at all concentration ranges.[11] Details regarding all three assay methods, analytes, and assay performances are provided in Section 2.6.1.

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

Details of the main bioanalytical methods are discussed in Section 2.6.1.

### 2.6.7 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

- *Method 080348VRM_ACM_R1:* LLOQ and ULOQ were 0.1 ng/mL and 50 ng/mL, respectively, for ponatinib and AP24567.
- *Method 110316VRM_ACM:* LLOQ and ULOQ were 0.5 ng/mL and 250 ng/mL, respectively, for ponatinib and LLOQ and ULOQ of for AP24567 was 0.1 ng/mL and 50 ng/mL, respectively.
- *Method 120081VRM_ACM:* LLOQ and ULOQ were 0.5 ng/mL and 250 ng/mL, respectively.

### 2.6.8 What are the accuracy, precision, and selectivity at these limits?

Details on the accuracy and precision of analytical methods 080348VRM_ACM_R1, 110316VRM_ACM and 120081VRM_ACM are listed in Table 16 and the main bioanalytical methods are discussed in Section 2.6.1.

### 2.6.9 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Details of the main bioanalytical methods are discussed in Section 2.6.1.

### 2.6.10 What is the QC sample plan?

- Method 080348VRM_ACM_R1: QC samples (six replicates each) were prepared at 0.1 ng/mL to 37.5 ng/mL (AP24534 and AP24567) in five runs for intra-assay results and three runs for inter-assay results.
- Method 110316VRM_ACM: QC samples (six replicates each), in three separate runs, were prepared at 0.5 ng/mL to 200 ng/mL for AP24534 and 0.1 ng/mL to 40 ng/mL for AP24567.
- Method 120081VRM_ACM: QC samples (six replicates each), in three separate runs, were prepared at 0.5 ng/mL to 200 ng/mL for both AP24534 and AP24600.

The sponsor met the Agency's recommended acceptance criteria of <20% for precision (CV%) and within +20% for accuracy at the lower limit of quantitation and <15% or within +15% at all concentration ranges. Inter-assay and intra-assay precision and accuracy results are located in Table 16 in Section 2.6.1.

[11] Guidance for Industry: Bioanalytical Method Validation May 2001 (http://1.usa.gov/wyN0hL)

# 3 DETAILED LABELING RECOMMENDATIONS

- **HIGHLIGHTS:** Revised DRUG INTERACTIONS section to include dose modification with concurrent strong CYP3A4 inhibitor and remove CYP3A4 inducer warning.
- **Section 2.1 Dose Modifications:** added dose modification with concurrent strong CYP3A4 inhibitor.
- **Section 7 DRUG INTERACTIONS:** Added general statement regarding metabolic and transporter systems that effect and are affected by ponatinib.
- **Section 7.1 Drugs That Are Strong Inhibitors of CYP3A4 Enzymes:** Revised to include dose modification with concurrent strong CYP3A4 inhibitor, more actionable monitoring recommendations (in consultation with the clinical reviewer) and examples consistent with the revised FDA DDI guidance. Non actionable information moved to section 12.
- **Section 7.2 Drugs That Are Strong Inducers of CYP3A4 Enzymes:** Revised to include stronger cautionary language, more actionable monitoring recommendations and examples consistent with the revised FDA DDI guidance. Non actionable information moved to section 12.
- **Section 7.3 Drugs That Elevate Gastric pH:** This section was added given the seriousness of the potential interaction.
- **Section 7.4 Drugs That are substrates of the P-gp or BCRP transporter systems:** This section was added given the seriousness of the potential interaction.
- **Section 8.6 Hepatic Impairment:** Non actionable information removed and more actionable monitoring recommendations (in consultation with the clinical reviewer) were added.
- **Section 8.7 Renal Impairment:** Non actionable information removed.
- **Section 12.2 Pharmacodynamics:** Section removed. PD assay deemed unreliable.
- **Section 12.3 Pharmacokinetics:**
  - Added statement the absolute BA is unknown.
  - PK parameters revised based on analysis of tablet rather than tablet+capsule data.
  - Extraneous exposure information removed.
  - Additional study context for the food effect trial added.
  - Additional context added for pH based solubility and DDI potential.
  - Distribution subsection condensed and additional context regarding how the volume of distribution was obtained was added.
  - Additional context regarding the metabolism of ponatinib added.
  - Nonactionable information regarding metabolites was removed.
  - Additional context regarding how the clearance was obtained was added.
  - Additional information regarding accumulation added.
  - Non actionable information regarding elimination omitted.
  - In vitro DDI findings and additional clinical trial context to support information in section 7 added.
  - Nonactionable information removed from the special populations subsections.
- **Section 12.6 QT prolongation:** Agree with proposals from IRT and the Clinical reviewer (see Section 2.2.4.3 of this review)

# 4 APPENDICES

## 4.1 Pharmacometrics Review

# OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

| Application Number | NDA 203469 |
|---|---|
| Compound | Iclusig (Ponatinib) |
| Submission Date | 30 Jul 2012 |
| Clinical Division | Oncology Products |
| PM Reviewers | Li Zhang, Ph.D. & Hongshan Li, Ph.D. |
| PM Team Leader (Acting) | Nitin Mehrotra, Ph.D. |

## 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 the proposed dose of 45 mg once daily supported by dose intensity-response relationship for efficacy and safety?

No, the proposed 45 mg daily dose is not supported by dose intensity-response relationship for efficacy and safety. A lower dose, especially for CP-CML patients, may offer a better benefit-risk profile. We agree that a 45 mg QD dose is adequate for AP/BP CML patients in order to provide maximum chance of efficacy since these patients are in the advanced phase of the disease and have lower survival rate than CP-CML patients.

- Based on the dose intensity-efficacy relationship for CP-CML patients, it appears that you may not compromise substantially on efficacy if dose is decreased from 45 to 30 mg QD (Figure 1 and Figure 2). The efficacy rate reached maximum at the 1$^{st}$ quartile of dose intensity (corresponding to 15 mg QD) for major hematologic responses ( Figure 2) and at the 2$^{nd}$ quartile of dose intensity (corresponding to ~30 mg QD) for major cytogenetic responses (Figure 1).
- Furthermore, there is a significant relationship between dose intensity and safety endpoints ( ≥ Grade 3 including thrombocytopenia, ischemia, rash, hypertension, myelosuppression, pancreatitis, lipase elevation, ALT/AST elevation) indicating that the rate of these adverse events are 2-9 fold at 45 mg QD compared to 30 mg QD (Figure 3). The rates of adverse events in the 4th quartile of dose intensity were 2 to 10-fold the rates of ≥ Grade 3 AE in the 2$^{nd}$ or 3$^{rd}$ quartiles of dose intensities (Figure 3). This indicates that a lower dose will likely reduce the risk of these adverse events.
- Moreover, about 75% of patients got dose reduced through the trial due to adverse events. Forty nine percent patients required dose reduction to 30 mg while 25%

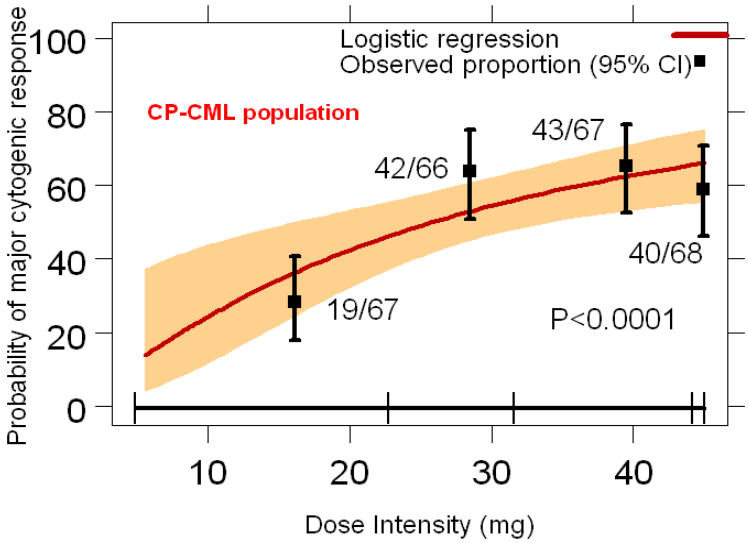
patients required dose reduction to 15 mg. The median time to the first dose reduction was 68 days. The median time to dose reduction to 30 mg was 71 days and the median time to dose reduction to 15 mg was 134 days.

### 1.1.2 Does the dose intensity-efficacy relationship support the 45 mg once daily dose?

No, the dose intensity-efficacy indicates that a lower dose than 45 mg QD may offer a better benefit-risk profile for patients with CP-CML. Dose intensity-efficacy relationships are evident in CP-CML patients and it reached plateau at about 25 mg QD. Even though, dose intensity-efficacy relationships are not obvious in AP-CML/BP-CML/Ph+ ALL patients which may indicate that a lower dose may provide similar efficacy, we agree with the 45 mg QD dose for this population realizing that these patients are in advanced phase of their disease and higher dose (with appropriate dose modification guidelines) will provide maximum chance of efficacy.

Since pharmacokinetic data was not available for study 201, we investigated dose intensity-efficacy relationship in CP-CML patients (n=267), and AP-CML/BP-CML/Ph+ ALL patients (n=177). Dose intensity here is defined as average daily dose (total dose divided by dose days) and ranges from 0.34 to 45.2 mg in CP-CML patients and 1.41 mg to 45 mg AP-CML/BP-CML/Ph+ ALL patients. Two primary efficacy endpoints were used in the dose intensity response analysis: major cytogenetic responses (PPMCYR) for CP-CML patients and major hematologic response (MAHRC) for AP-CML/BP-CML/Ph+ ALL patients. Figure 1 shows there is a statistically significant relationship between dose intensity and probability of major cytogenetic responses in CP-CML patients ($p<0.0001$). The observed data also shows the major cytogenetic response increases with higher dose intensity and appears to reach the plateau at higher doses (30 mg). It is important to note that this is univariate analysis which may be confounded by patient disease status and other risk factors since these are second line patients who had already failed prior TKIs. Multivariate analysis accounting for various risk factors was also explored for CP-CML and it was observed that dose intensity was a significantly related to response after accounting for other risk factors although the relationship became shallow.

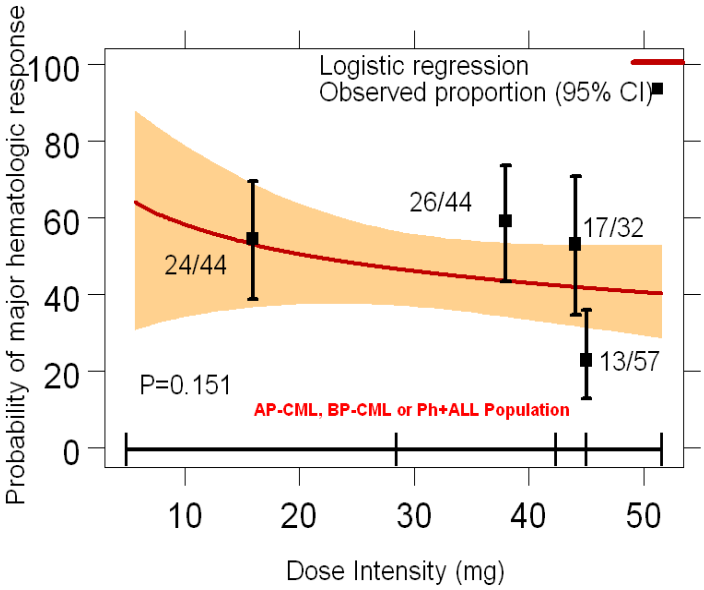
**Figure 1: Relationship of dose intensity and probability of major cytogenetic response. The 4 fraction numbers in the plot are the observed response rates of the 4 quartiles with the numerator as number of responders and the denominator as total number of patients in each quartile. With every unit of log dose increases, the odd of having a response is 1.32 fold.**




Source: FDA reviewer's analysis

Figure 2 shows dose intensity does not appear to be related with major hematological response in AP-CML/BP-CML/Ph+ ALL patients (p=0.151).

**Figure 2: Relationship of dose intensity and probability of major hematologic responses. The 4 fraction numbers in the plot are the observed response rates of the 4 quartiles with the numerator as number of responders and the denominator as total number of patients in each quartile.**




Source: FDA reviewer's analysis

### 1.1.3 Do the dose intensity-safety relationships support the 45 mg once daily dose? - Is the proposed step dose reduction strategy (45 to 30 to 15 mg QD) to manage adverse events appropriate?

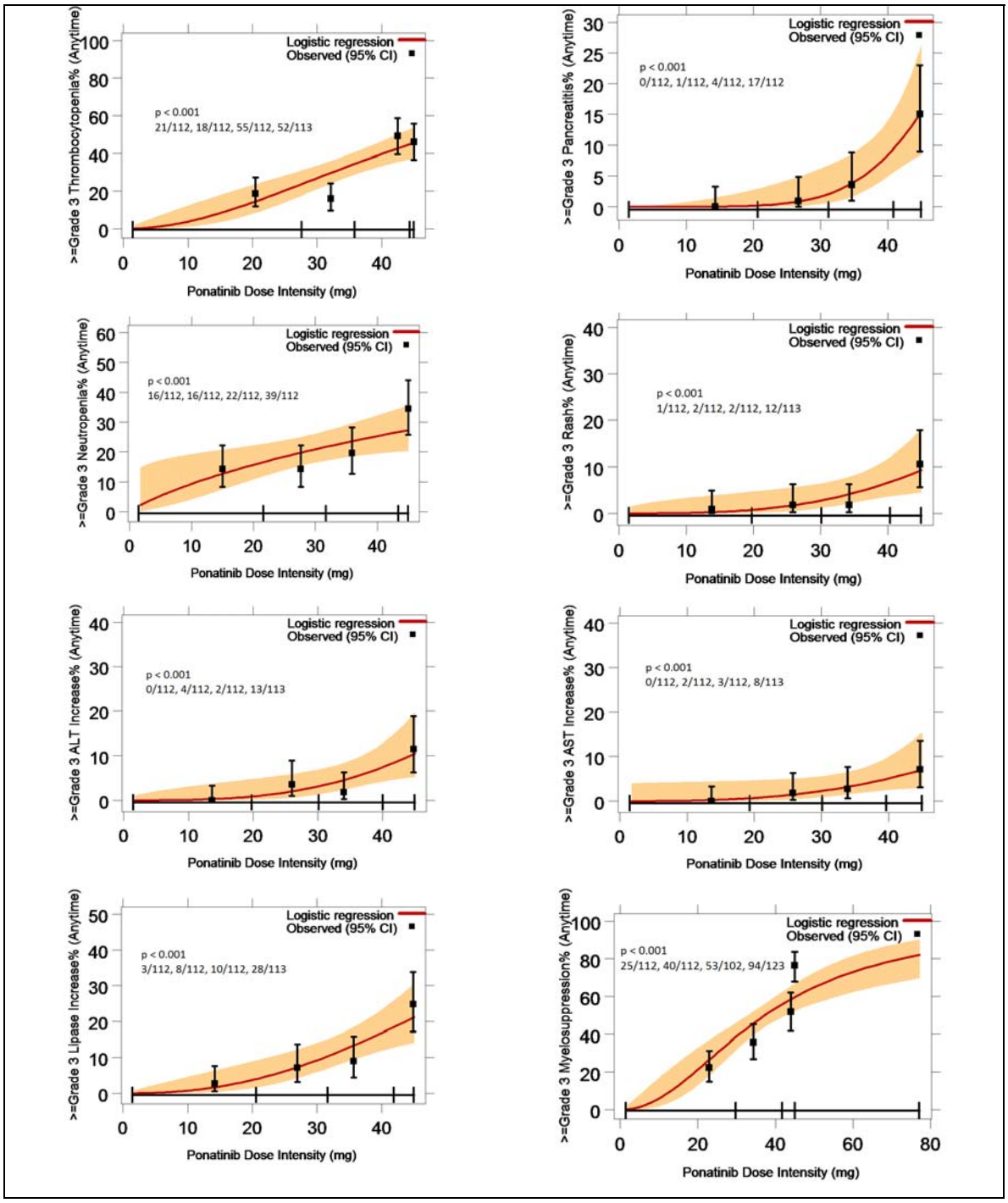
No, dose intensity-safety relationship indicated that there is significant increase in safety events with increase in dose and thus a lower dose than 45 mg will lead to lower adverse event rate. This is also supported by the fact that approximately 75% of the patients had dose reductions in the trial. Dose intensity- safety analyses of relevant adverse events were conducted for trial 201. Based on univariate logistic regression analyses, significant dose intensity-response relationship was observed for variety Grade 3 & 4 adverse events (Figure 3). It is worth noting that these are univariate analysis which may be confounded by patient disease status and other risk factors since these are second line patients who had already failed prior TKIs.

Yes, the dose reduction strategy proposed by the sponsor to manage the adverse events appears reasonable. Based on the logistic regression model, the risk of having these adverse events decreases if dose is decreased from 45 to 30 to 15 mg QD (Table 1). For example, reducing dose from 45 mg QD to 30 mg QD will reduce severe pancreatitis rate by 9-fold.

**Table 1. Predicted probability (%) of Grade ≥ 3 adverse events at 45, 30 and 15 mg QD dose**

| Grade ≥ 3 Adverse Event | Probability at 15 mg QD | Probability at 30 mg QD | Probability at 45 mg QD |
|---|---|---|---|
| Thrombocytopenia | 8.4 | 26.9 | 45.5 |
| Pancreatitis | 0.0 | 1.7 | 15.4 |
| Neutropenia | 12.7 | 20.9 | 27.3 |
| Rash | 0.3 | 2.7 | 9.3 |
| ALT increase | 0.3 | 3.1 | 10.5 |
| AST increase | 0.3 | 2.2 | 7.0 |
| Lipase increase | 0.3 | 2.2 | 7.0 |
| Myelosuppression | 12.9 | 38.7 | 59.7 |

**Figure 3: Dose intensity versus response relationships for some ≥Grade 3 safety endpoints of Study 201. The four fraction numbers against the p value represents the observed adverse event rates in the four quartiles with the numerator as number of responders and the denominator as total number of patients in each quartile.**



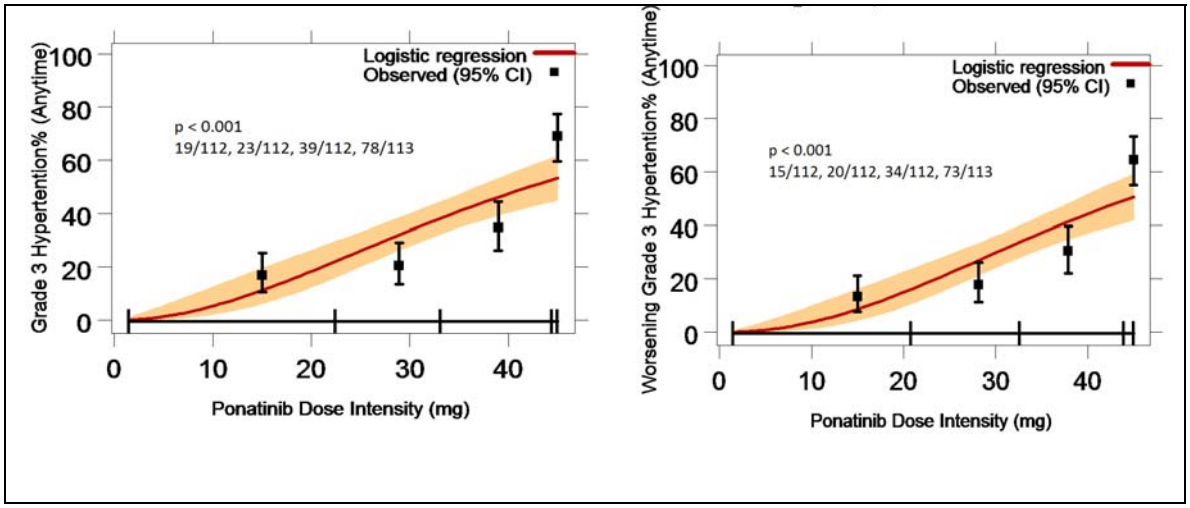

Source: FDA reviewer's analysis

### 1.1.4 Is there any relationship between ponatinib dose intensity and hypertension?

Yes, there are significant dose intensity-response relationships for hypertension in the patient population ($p < 0.001$). Reducing dose from 45 mg QD to 30 mg QD will reduce Grade ≥ 3 hypertension rate from 53% to 34%. Grade 3 or higher hypertension (Figure 4, left) is defined as patient meeting criteria for grade 3 or higher hypertension (systolic BP > 160 or diastolic BP > 100) at any time, regardless of baseline values.

Dose intensity was also related to worsening grade of hypertension as evident from the figure below. Worsening of grade 3 or higher hypertension (Figure 4, right) is defined as 'treatment emergent hypertension' i.e. patient meeting criteria for grade 3 or higher hypertension worsening from baseline ((systolic BP > 160 and baseline systolic BP =< 160) or (diastolic BP > 100 and baseline diastolic BP =< 100)) at any time.

**Figure 4: Effect of Ponatinib on Blood Pressures of Patients in Study 201**

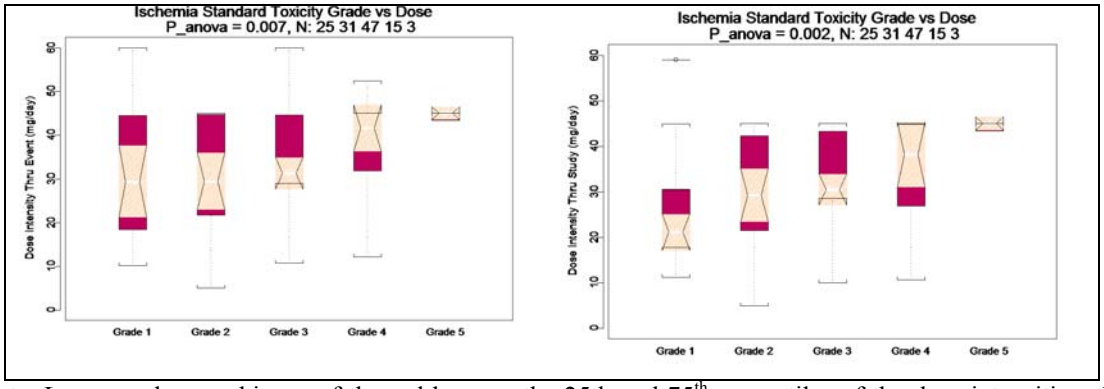



Source: FDA reviewer's analysis

### 1.1.5 Is there a relationship between risk of ischemia and ponatinib dose intensity?

Yes, the relationship between risk of ischemia and ponatinib dose intensity is likely there. Higher ponatinib dose resulted in higher grade of ischemia ($p < 0.01$) as shown in Figure 5 where the data of 70 ischemia patients from Studies 101 and 201 are presented and multiple events might have occurred for a specific patient. It is important to note that this analysis may be confounded by patient disease status since some of these patients may be predisposed to this risk because of their prior medical history. However, no trend was found when all 449 patients were analyzed using logistic regression with severe ischemia event as the categorical variable.

**Figure 5. Effect of Ponatinib on Ischemia Grade of Patients in Study 201**




Note: Lower and upper hinges of the red box are the 25th and 75th percentiles of the dose intensities; the band near the middle of the box is the 50th percentile, and whiskers are drawn to the nearest value not beyond a standard span from the hinges. The standard span is 1.5×(upper hinge - lower hinge). Points beyond the end of the whiskers (outliers) are drawn individually. The slanted shaded orange area represents 95% confidence of the median.

Source: FDA reviewer's analysis

## 1.2 Recommendations

Based on the dose intensity-response relationships for efficacy and safety, we recommend the following PMR.

**PMR**: Dose intensity-response analysis of efficacy and safety endpoints from trial 201 indicated that a lower dose of ponatinib may have a better benefit-risk profile for the indication of CML or Ph+ALL. We recommend that you collect sparse PK in your ongoing trial (AP24534-12-301) from all patients. Exposure-response analysis must be conducted for both efficacy and safety endpoints. Based on the results of these analyses, you may be required to conduct a trial to evaluate lower dose or an alternate dosing regimen of ponatinib.

## 1.3 Label Statements

None.

# 2 PERTINENT REGULATORY BACKGROUND

Ponatinib is a kinase inhibitor indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy. Sponsor was seeking accelerated approval with 6 months of follow-up on all ongoing patients in pivotal phase II trial (PACE). The potential conversion to full approval was scheduled with 2 year follow-up. Initiated randomized phase 3 trial will be in newly diagnosed CML. Sponsor requested priority review. The fast track designation was granted on 30 November 2010. The major cytogenetic response in CP-CML patients is 54%, while major hematologic response in AP-CML patients is 58% and in BP CML / Ph+ ALL patients is 34%.

## 3 RESULTS OF SPONSOR'S POPULATION PK ANALYSIS

For the proposed 2-compartmental model [redacted] (b) (4) [redacted] The final structure modeling was Run 40 as reported before any patient-specific covariates included, and the final covariate model was Run 61 with 5 covariates added on CL and V (refer to $\theta_{16}$, $\theta_{17}$, $\theta_{18}$, $\theta_{19}$ and $\theta_{20}$ in Table 3 ).

**Figure 6: The 2-compartmental model for oral ponatinib proposed by the sponsor**

(b) (4) [redacted]

**Table 2: Key Steps of the Population PK Model Building**

(b) (4)

*Population PK parameter Estimates*

The estimates for the final population PK model are list in Table 3.

**Table 3: Parameter Estimates of the Final PK Model**

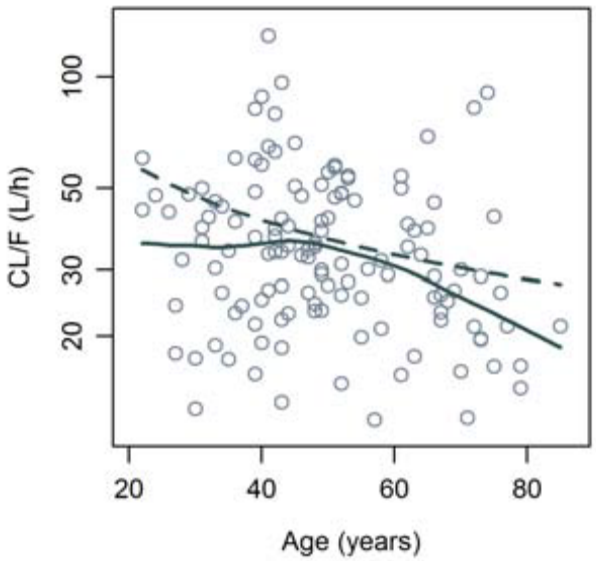
| Parameter | Alias | Estimate | 95% CI |
|---|---|---|---|
| $\theta_1$ | $N_{tr}$ | 2.07 | (1.83 - 2.3) |
| $\theta_2$ | $CL/F$ (L/h) | 37.2 | (32.7 - 41.7) |
| $\theta_3$ | $V_1/F$ (L) | 1100 | (976 - 1220) |
| $\theta_4$ | $MTT$ (h) | 2.23 | (1.97 - 2.49) |
| $\theta_5$ | $Q/F$ (L/h) | 31.5 | (25.7 - 37.2) |
| $\theta_6$ | $V_2/F$ (L) | 537 | (503 - 570) |
| $\theta_7$ | $\theta_{CL,kczl}$ (%) | -22.4 | (-25.3 - -19.5) |
| $\theta_8$ | $\theta_{F,kczl}$ (%) | 31 | (18.8 - 43.2) |
| $\theta_9$ | $\theta_{N_{TR},fed}$ (%) | 117 | (79.8 - 154) |
| $\theta_{11}$ | $MTT_2$ (h) | 4.36 | (4.24 - 4.47) |
| $\theta_{12}$ | $pTCAM2$ (%) | 29.2 | (16.8 - 45.9) |
| $\theta_{13}$ | $\theta_{F,highfat}$ (%) | 10.9 | (-5.47 - 27.2) |
| $\theta_{14}$ | $\theta_{\epsilon,trough}$ (%) | 125 | (101 - 148) |
| $\theta_{15}$ | $\theta_{IOV,patients}$ (%) | 69.5 | (43.5 - 95.6) |
| $\theta_{16}$ | $\theta_{CL,k_{out}}$ ($h^{-1}$) | 0.00318 | (0.00204 - 0.00432) |
| $\theta_{17}$ | $\theta_{CL,Conc}$ (L/pg) | 9.63 | (5.84 - 13.4) |
| $\theta_{18}$ | $\theta_{CL,Age}$ | -0.529 | (-0.781 - -0.278) |
| $\theta_{19}$ | $\theta_{CL,Albumin}$ | 1.07 | (0.535 - 1.6) |
| $\theta_{20}$ | $\theta_{V,BMI}$ | 0.616 | (0.284 - 0.948) |
| $\sigma_{1,1}$ | Proportional Error ($\sigma_{TV,1,1}$) | 0.0161 | (0.0147 - 0.0176) |
| $\sigma_{2,2}$ | Additive Error | 0.0194 | (0.0131 - 0.0257) |
| $\omega_{2,2}$ | $\omega^2_{CL/F}$ | 0.22 | (0.137 - 0.304) |
| $\omega_{3,2}$ | $\omega^2_{CL/F,V/F}$ | 0.168 | (0.0998 - 0.237) |
| $\omega_{3,3}$ | $\omega^2_{V/F}$ | 0.196 | (0.123 - 0.268) |
| $\omega_{4,4}$ | $\omega^2_{MTT}$ | 0.067 | (0.0167 - 0.117) |
| $\omega_{5,5}$ | $\omega^2_{IOV_F}$ | 0.0161 | (0.0104 - 0.0218) |
| $\omega_{8,8}$ | $\omega^2_{IOV_{MTT}}$ | 0.0881 | (0.0597 - 0.117) |
| $\omega_{11,11}$ | $\omega^2_{IOV_{NTR}}$ | 0.186 | (0.133 - 0.238) |
| $\omega_{14,14}$ | $\omega^2_{pTCAM2}$ | 6.57 | (2.48 - 10.7) |
| $\omega_{15,15}$ | $\omega^2_{\epsilon,prop}$ | 0.0172 | (-0.00458 - 0.0389) |
| $\omega_{16,16}$ | $\omega^2_{\theta_{CL,Conc}}$ | 1.55 | (0.645 - 2.46) |

*Parameter values for the final PopPK model estimated using FOCE INTERACTION. The number of transit compartments for the second TCAM model ($N_{tr,2}$) was fixed to 15. $N_{tr}$: Number of transit compartments in the first TCAM. Not necessarily an integer. $MTT$: Mean transit time through the first TCAM. $MTT_2$: Mean transit time through the second TCAM. $CL/F$: Systemic Clearance. $V_1/F$: Apparent volume of distribution in the central compartment. $Q/F$: Inter-compartmental Clearance. $V_2/F$: Apparent volume of distribution in the peripheral compartment. $\theta_{CL,kczl}$: change in clearance with ketoconazole co-administration. $\theta_{F,kczl}$: change in bioavailability with ketoconazole co-administration. $\theta_{N_{tr},fed}$: change in number of transit compartments in first TCAM with high-fat or low-fat breakfast. $pTCAM2$: proportion of the dose modeled via the second TCAM. $\theta_{F,highfat}$: change in bioavailability with high-fat breakfast. $\theta_{\epsilon,trough}$: change in magnitude of residual error for trough samples. $\theta_{IOV,patients}$: change in magnitude of IOV for patients. $\theta_{CL,kout}$: turnover rate for hypothetical enzyme. $\theta_{CL,conc}$: change in hypothetical enzyme production rate with increasing ponatinib concentrations. $\theta_{CL,Age}$: change in clearance with increasing age. $\theta_{CL,Albumin}$: change in clearance with increasing albumin levels. $\theta_{V,BMI}$: change in volume of distribution with increasing BMI levels. $\omega^2_X$: Variance of the between-subject variability of parameter X. $\omega^2_{X,Y}$: Covariance of the between-subject variability of parameters X and Y. $\omega^2_{IOV_X}$: Variance of the between-occasion variability of parameter X.*

Source: Sponsor's population PK report, Page 32

The sponsor identified that age was the most significant covariate on CL/F: clearance with declined with age. "Compared to the estimated clearance 37.2 L/h for a subject of median age in the analysis data set, 48 years, a person of age 70 is predicted to have a clearance of 30.5, a 18.1% decrease whereas a person of age 20 is predicted to have 58.9% higher clearance." That means a ≤ 20-year patient has only 63% exposure of a median age patient (Figure 7).

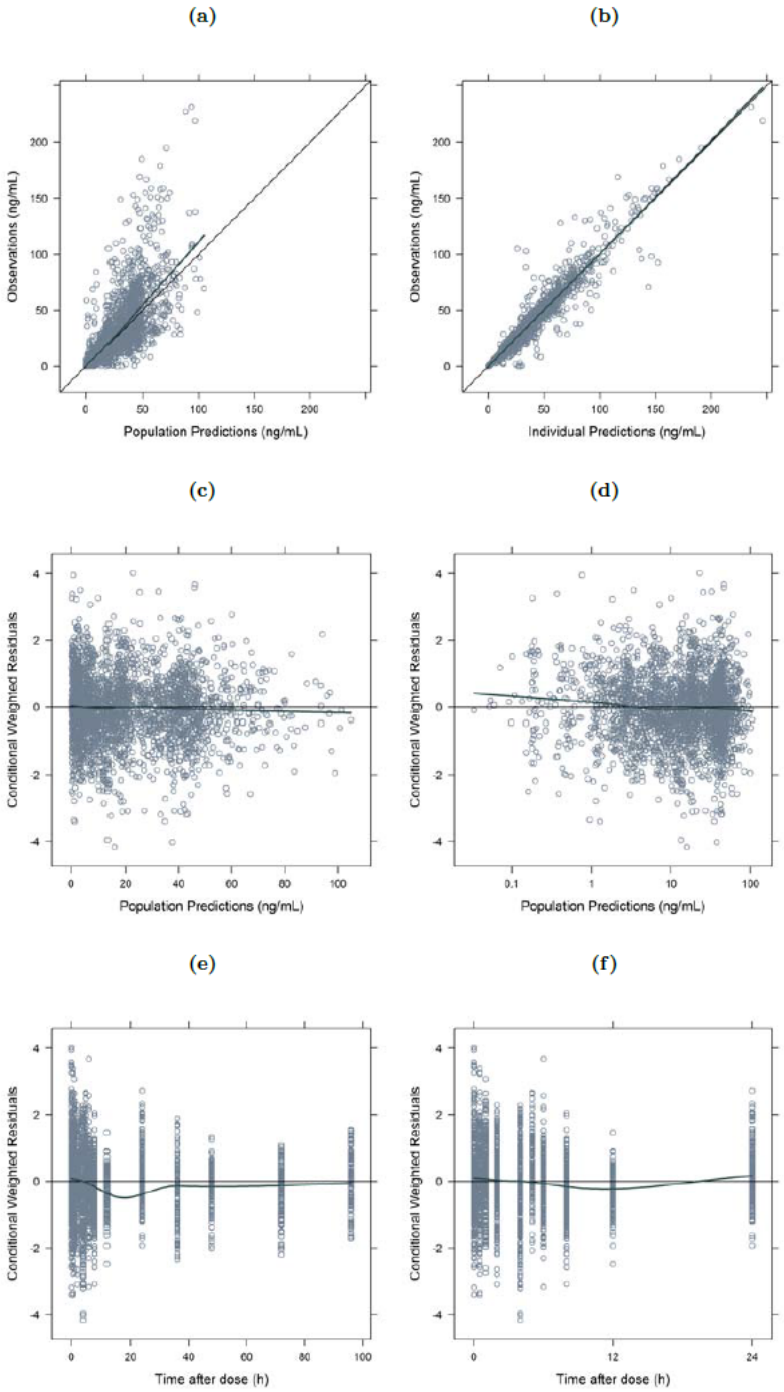
**Figure 7: Age effect on clearance of ponatinib**




Source: Sponsor 's population PK report by qPharmetra, LLC, Page 29

"During the ensuing modeling it was revealed the data were best described by having clearance increase as a function of ponatinib concentration and with time. For a daily dose of 45 mg, a decrease in the steady state concentration of 26% is predicted for a subject with typical change in clearance compared to a situation where no change is assumed. The half-life of the onset of the clearance increase was estimated to 218 hours ($k_{out}$ = 0.00318 $h^{-1}$). The predicted reduction in accumulation ratio between daily doses of 15 and 60 mg matched accumulation ratios calculated by non-compartmental PK analysis of those arms in Study AP24534-07-101 well." The goodness of fit plots is presented in Figure 8.

**Figure 8: Goodness of Fit of the Final Population PK Model**




*Panels a and b show the observed ponatinib concentrations vs. predictions derived from the population means and the individual parameter estimates, respectively. Note that the maximum shrinkage in the individual parameters was 36% for BSV on structural parameters and 69% for IOV. Panels c and d show the conditional weighted residuals vs. population predictions on normal scale (c) and logarithmic scale (d). Panels e and f show the conditional weighted residuals vs. time after dose. In panel f, the scale on the x-axis is zoomed in to show the first 24 hours after dose.*

*Source: Sponsor's population PK report, Page 37*

*Reviewer's Comments*

*Overall, the FDA pharmacometrics reviewer believes that the proposed population pharmacokinetic model, particularly the absorption complexity and the enzyme-involved elimination, is yet to be validated by PK data from long-term Phase II/III trials.*

- *The PK data for the population PK analysis were heavily collected from healthy subjects of food effect study and ketoconazole co administration study and other data were collected from maximum tolerable dose (MTD) finding study. No data were collected from Phase II/III efficacy and safety evaluation studies. It is important to note that the formulation used for the registration trial is different from the formulation used in the trials used on population PK analysis. Therefore, the effect of formulation (if any) cannot be discerned from this population PK analysis.*
- *The proposed pop-PK model of ponatinib is likely over parameterized as evident by several parameters.*
- *The proposed covariate model is not supported by BSV (between subject variability) change between basic structural model and the final covariate model. Meaningful covariates on CL should decrease BSV of CL in the final model. However, the final model (Run 61 as reported) resulted in slightly higher CL BSV value than the basic structure model (Run 40 as reported) for the 5 covariates added to V and CL; the BSV is of CL are 47% for Run 61 and 45% for Run 40.*
- *No conclusion was drawn about the appropriateness of current dose of 45 mg QD, although the sponsor did conduct dose intensity-response analyses for efficacy and safety based on data of Study 201 and Study 101, and did conduct AUC-response analyses for efficacy and safety based on data Study 101 (using population PK simulation to generate AUC data)*
- *While critical NONMEM runs of the population PK report were reproduced in the review process, no independent population PK analyses were executed by the FDA pharmacometrics reviewer. The final pop-PK model was two-compartmental with dual TCAM (with NTR2 fixed as 15) and elimination induction by an enzyme compartment (Figure 6). Covariates included KCZL on CL and F, BRKFST on NTR, TROUGH on $\sigma_{1,1}$ (proportional error). Inter-individual variability included CL, V, MTT (with eta fixed as 0 for NTR). Inter-occasion variability included F, MTT, NTR, $\sigma_{1,1}$. Residual variability included $\sigma_{1,1}$ (proportional error) + $\sigma_{2,2}$ (additive error), where $\sigma_{1,1}$ was Box-Cox transformation with lambda fixed as 14.9. The estimation method was FOCE with INTER. Matrix=S was defined in $Covariance section. The reported results for the final model (Appendix 8 of the pop-PK report for Run 61) was based on a terminated run due to rounding errors (error=134). As recommended by the sponsor, making initial estimates of all parameters aberrant to their final estimations resulted in minimization successful (see Run 62 results generated by PM division at FDA). Matrix=S was still defined in $Covariance of Run 62. The NONMEM message from Run 62 was: "Minimization successful. However, problems occurred with the minimization…." Based on Run 62, Run 63 (generated by PM division at FDA) with NSIG changed from 3 to 2, and with "Matrix=S" deleted did not converged due to rounding errors (error=134).*

- *For oral PK data, the 2-compartmental structure model with two parallel transit-compartment (TCAM) processes (Figure 6) could be too over parameterized by the 10 structural parameters (Ntr, CL/F, V1/F, MTT, Q/F, V2/F, MTT2, pTCAM2, $k_{out}$ and $I_{mag}$) to be estimated. The over-parameterization was evident by the following: Eta was fixed as 0 for Ntr, and Ntr2 was fixed as 15. One-compartment model with one absorption constant rate, plus an occasion parameter for 60 mg dose could be able to capture the data reasonably well, which will reduce the number of parameters and provide adequate precision as well.*

- *Particularly, the elimination enzyme induction model could result in consequence if the prediction is used for improper dose adjustment in clinical practice. Yes, it is hard to explain that the concentration-time curve of 60 mg/day ponatinib in human lays below the curve for 45 mg/day (refer to the results of non-compartmental PK analysis) without any mechanistic explanation. The enzyme compartment of the model does not have any supporting physiological evidence.*
- *To best characterize the exposure-efficacy/safety relationships of ponatinib using exposure instead of dose intensity, the future population PK (pop-PK) model should be able to reliably predict steady-state exposure such as $C_{max\_ss}$, $C_{min\_ss}$, and $AUC_{0-\tau\_ss}$ for a subject with specific covariates. The proposed pop-PK model and corresponding results should be evaluated with additional data from current and future Phase II-III clinical trials. Particularly, time-dependent clearance remains a major PK characteristic to be verified.*

# 4 REVIEWER'S ANALYSIS

## 4.1 Introduction

The purpose of ponatinib pharmacometric review was to investigate the characteristics of the exposure-response relationships including dose intensity-response and AUC (area under plasma ponatinib concentration-time curve)-response for efficacy/safety evaluation; and to investigate the population pharmacokinetics of ponatinib in the patient population.

## 4.2 Methods

### 4.2.1 Data Sets

Data sets used for FDA analyses are summarized in Table 4.

**Table 4. Analysis Data Sets**

| Study Number | Name | Link to EDR |
|---|---|---|
| AP24534-07-101 (101) | ader.xpt | \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\Sponsor Data and Reports |
| AP24534-10-201 (201) | adeff.xpt | \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\Sponsor Data and Reports |
| 201 | adsl.xpt | \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\Sponsor Data and Reports |
| 201 | ader3.xpt | \\cdsnas\pharmacometrics\Reviews\Ongoing PM |

| | | |
|---|---|---|
| | | Reviews\Ponatinib_NDA203469_LZ\Sponsor Data and Reports |
| 201 | aderht.xpt | \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\Sponsor Data and Reports |
| 201 | aderht3xpt | \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\Sponsor Data and Reports |
| 201 | ischemia.xpt | \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\Sponsor Data and Reports |
| 201 | nm4.xpt | \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\Sponsor Data and Reports |

### 4.2.2 Software

SPLUS 8.0, SAS 9.2 and NONMEM 7.2 were used.

### 4.2.3 Models

Multivariate analysis and linear logistic regression were used for exposure-response analysis. The extravenously dosing 2-compartmental model proposed by the sponsor was used for population pharmacokinetic analysis.

### 4.2.4 Analysis

The purpose of this pharmacometric (PM) review is to address key questions based on dose intensity-response analyses of efficacy/safety datasets from the sponsor. The dose intensity-response relationship of each efficacy or safety endpoint was evaluated by logistic regression, general linear modeling, or general least square linear fit. The exposure for Study AP24534-07-101 (abbreviated as Study 101) was described by AUC Intensity (AUCI, average daily area under plasma ponatinib concentration-time profile from day 1 through the response evaluation time) or by Dose Intensity (DI, average daily dose from day 1 through the response evaluation time), of which safety data were analyzed but not included in this review report. The exposure for Study AP24534-10-201 (abbreviated as Study 201) was described by only DI since no pharmacokinetic (PK) samples collected. The response was the overall result of each efficacy or safety endpoint documented for the study. The response rate is the percentage of the responder in the specific subject population or specific subject group.

The relationship of binomial response (i.e., “yes” or “no” which means “responder” or “non-responder” as the response results) versus dose intensity was analyzed by logistic regression. Both linear and log linear models were tested and ultimately log linear model was utilized with log dose intensity as the independent variable. Most of the dose intensity-response analyses for this PM review were executed by logistic regression.

The relationship of other categorical response (i.e., ≥3 types of outcomes of the endpoint) versus dose intensity was analyzed by general linear modeling. In brief, the ordered multilevel response was correlated with the median dose intensity of the corresponding subject bins of the study population by general linear modeling. ANONA and Chisquare test among the bins were implemented for the modeling. Boxplots were presented for visualizing the analysis. Analysis to relate ischemia grade with dose intensity used this approach.

The relationship of continuous response (e.g., blood pressure increase from baseline) versus dose intensity was analyzed by general least square linear regression across the

dose intensity range, for which p values were provided for both intercept and slope of the fitted line. Scatter plot with fitted line was presented to visualize the analysis.

## 4.3 Results

### 4.3.1 What are the characteristics of the dose intensity-response relationship for efficacy of Study 101?

The dose intensity- response for efficacy was evaluated in Study 101 CP-CML patients (n=43), and AP-CML/BP-CML/Ph+ ALL patients (n=22). Two primary efficacy endpoints were used in the exposure response analysis: major cytogenetic responses (MCyR) for CP-CML patients and major hematologic response (MaHR) for AP-CML/BP-CML/Ph+ ALL patients. Reviewer's analysis shows there is a flat trend with AUC intensity and probability of major cytogenetic responses at month 6, month 12 and anytime in CP-CML patients. There is also a flat trend with AUC intensity and probability of major hematologic responses at month 6, month 12 and anytime AP-CML/BP-CML/Ph+ ALL patients. However, there is limited number of patients in study 101 to draw any meaningful conclusions.

### 4.3.2 In addition to dose intensity, what other covariates have impact on primary efficacy endpoints of Study 201?

In addition to dose intensity, FDA reviewer also investigate whether other covariates such as cohort (mutated or resistant/intolerant patient), gender, age, ECOG score, number of prior TKI treatment and race would have impact on primary efficacy endpoints.

Assuming all covariates influence the primary endpoint independently, Table 5 demonstrated statistical P-value from univariate analysis. Dose, cohort, age, number of prior treatment and race have significant statistical impact on major cytogenetic response in CML-CP population; while dose cohort, gender and ECOG have significant statistical impact on major hematological response in AP, BP-CML and Ph+ALL population. The odds ratio of each covariate which is higher or lower than 1, shows the direction of effect of that covariate, for example, age in CML-CP population with lower than 1 odds ratio means patients with older age had lower responses; while dose in CML-CP population with higher than 1 odds ratio means patients with higher doses had higher responses.

**Table 5: The odds ratio and the statistical P-value from univariate analysis of efficacy data Study 201**

| | CML-CP population | | AP, BP-CML and Ph+ALL population | |
|---|---|---|---|---|
| | P-Value | Odds Ratio | P-Value | Odds Ratio |
| DOSE | 0.0002 | 1.01 | 0.036 | 0.99 |
| COHORT | 0.002 | 1.25 | 0.0013 | 0.91 |
| SEX | 0.148 | 0.91 | 0.034 | 1.17 |
| AGECAT | 0.00001 | 0.84 | 0.505 | 1.03 |
| ECOG | 0.09 | 0.9 | 0.0005 | 0.84 |

| | | | | |
|---|---|---|---|---|
| NUMTKI | 0.0006 | 0.87 | 0.897 | 0.99 |
| RACEN | 0.018 | 1.2 | 0.152 | 1.13 |

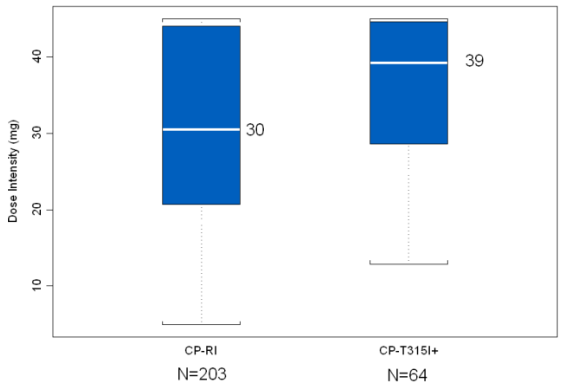
Source: FDA reviewer's analysis

Since dose intensity is not the only parameter which may influence the primary efficacy endpoints, FDA reviewer also studied the relationship between dose intensity and other covariates. The result shows dose has interactions with cohort, age and number of prior treatment in CML-CP population; while no dose related interactions were observed in AP-CML, BP-CML and Ph+ALL population.

Figure 9, Figure 10 and Figure 11 demonstrated different dose intensities in different subgroups stratified by significant covariates in CP-CML population.

Figure 9 shows higher mean dose intensity in CP-CML T3151+ mutated patients than that in CML-CP resistant/intolerant patient (39 mg vs. 30 mg), which also directs a higher response rate (MCyR 70.3%  versus 48.8%).

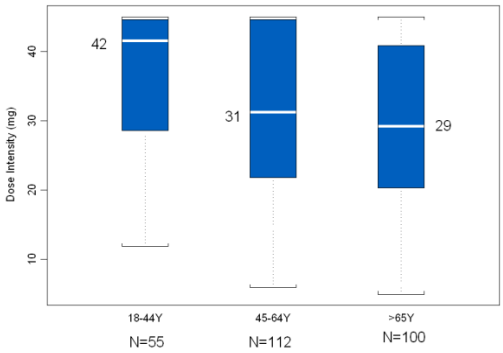
**Figure 9: Dose intensity of CP-RI patients versus CP-T315I+ patients**




Source: FDA reviewer's analysis

Figure 10 shows younger patients can tolerate higher dose, which also appears to receive better efficacy.

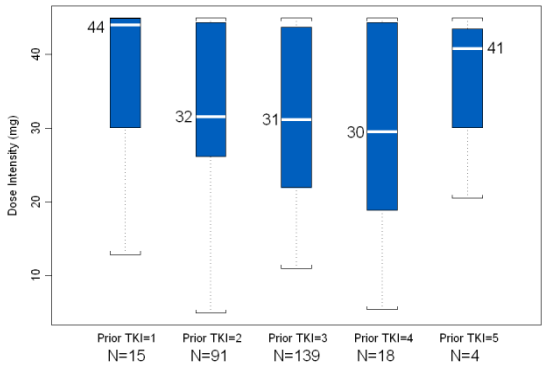
**Figure 10. Dose intensity of patients in different ages**




Source: FDA reviewer's analysis

Figure 11 shows CP-CML patients who receive less prior TKI treatment can tolerate higher dose, which also appears to receive better efficacy.

**Figure 11. Dose intensity of patients with TKI treatment history categories**




Source: FDA reviewer's analysis

## 5 LISTING OF ANALYSES CODES AND OUTPUT FILES

| File Name | Description | Location in \\cdsnas\pharmacometrics\ |
|---|---|---|
| Intensity-Efficacy2.ssc | Dose intensity-Efficacy (Study 201) | Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\ER Analyses\Final Model\Efficacy\201\ |
| Exposure-Efficacy.ssc | Exposure-Efficacy (Study 101) | Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\ER Analyses\Final Model\Efficacy\101 |
| ader.ssc<br>ader3.ssc<br>aderht.ssc<br>aderht3.ssc<br>lipase.ssc<br>lipase.ssc<br>ischemia.ssc | Exposure-Safety (Study 201) | \Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\ER Analyses\Final Model\Safety\201FinalSafetyDataAnalyses |
| 101AUCI_AE.ssc<br>101DI_AE.ssc | Exposure-Safety (Study 101) | \Reviews\Ongoing PM Reviews\Ponatinib_NDA203469_LZ\ER Analyses\Final Model\Safety\101FinalSafetyDataAnalyses |

## 4.2 PBPK Review

APPEARS THIS WAY ON ORIGINAL

# *Physiologically-based pharmacokinetic modeling (PBPK) and Simulation Memo*

Joseph Grillo, Pharm.D., Office of Clinical Pharmacology

Secondary Review by Ping Zhao, Ph.D., Office of Clinical Pharmacology

| | |
|---|---|
| NDA number | 203469 |
| Drug Name: | Ponatinib tablets |
| OCP Reviewer: | Joseph Grillo, Pharm. D. |
| PBPK consult request: | Joseph Grillo, Pharm. D. |
| OCP Team Leader: | Julie Bullock, Pharm. D. |
| OCP Division: | **Division of Clinical Pharmacology 5** |

## *Table of Contents*

## 1. Recommendation

A simulation from PBPK model shown to reasonably predict ponatinib PK, alone and following inhibition by a strong CYP3A4 inhibitor, suggests that a 52% reduction in ponatinib's $C_{max}$ and a 71% reduction in ponatinib's AUC may be expected following induction by a strong CYP3A4 inducer. Assuming dose proportionality, this suggests the exposure following dosing at the proposed 45 mg dose under strong CYP3A4 induction would potentially result in an AUC that would normally be seen at a dose less than 15 mg. Since the applicant is planning to conduct a clinical trial to evaluate the effect of coadministration of ponatinib with a strong CYP3A4 inducer and the pharmacometric analysis suggest reduced efficacy with doses below 15 mg in the chronic phase CML population, we recommend the labeling include strong language suggesting to avoid co administration unless the potential benefit outweighs the risk of potential reduced exposure and that patients be close monitored for reduced efficacy.

## 2. Objectives

The objective of this clinical pharmacology memo is to predict strong CYP3A4 induction on ponatinib exposure using physiologically-based pharmacokinetic (PBPK) model.

## 3. Background

Ponatinib is a tyrosine kinase inhibitor (TKI). The primary target of ponatinib is BCR-ABL, an abnormal tyrosine kinase that is often found in chronic myeloid leukemia (CML) and Ph+ ALL patients. Fecal elimination is the major excretion pathway for ponatinib. In the mass balance trial AP24534-11-104 fecal excretion accounted for 86.6% of the radioactive ponatinib dose (capsule) following a 336 hour total sampling period. Characterization of fecal metabolites from the pre-planned 0-144 hour recovery period reported the following: 23.7% ponatinib, 65.2% metabolites and 11.1% unknown. The amount of ponatinib and metabolites eliminated through urine was approximately 5% of the dose with less than 1% as parent compound and the remainder as metabolites.

In vitro, 52%, 28.4%, 9%, and 2.6% of ponatinib was metabolized by CYP3A4, CYP2C8, CYP2D6, and CYP3A5 at 60 minutes. In addition to phase I metabolism demonstrated by the cytochrome P450 superfamily in vitro, the applicant also believes that esterases, amidases or proteases are involved in the in vivo enzymatic hydrolysis of ponatinib. Based on the metabolite identification from the mass balance trial hydrolysis appears to account for approximately 2.25% of the ponatinib metabolism.

Based on an analysis of the ponatinib pivotal trial by the pharmacometrics division, it appears that there is reduced efficacy in Chronic myelogenous leukemia (CML) - chronic phase (CP) patients at doses below 30 mg per day (Figure 1). This is not obvious in the (CML) - accelerated phase (AP), or blast phase (BP) or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) populations.

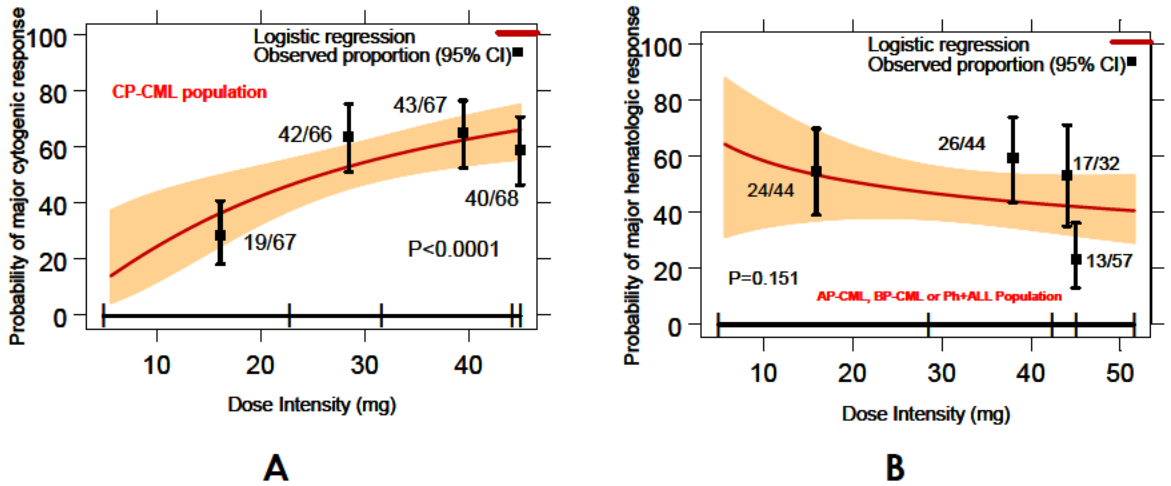



**Figure 1:** Major Cytogenetic Response [A] in CP-CML and Major Hematological Response [B] AP-CML, BP-CML or Ph+ALL Populations

The applicant conducted an open-label, randomized, 2-period, 2-sequence crossover trial to evaluate the effects of concomitant multiple dose administration of ketoconazole, a strong CYP3A inhibitor on the PK profile of single-dose ponatinib administration in healthy subjects. The trial reported an average 78% increase in ponatinib exposure would be expected if ponatinib were co-administered with a strong CYP3A4 inhibitor.

### 4. *PBPK Modeling Building and Simulations*

A PBPK model of ponatinib was developed using SimCYP® software (Version 11, Sheffield, UK). Drug dependent parameters of ponatinib are summarized in Table 1, along with assumptions and source data for model building. Model building and simulations were conducted in a virtual healthy volunteer population with system-dependent parameters (such as organ blood flow, tissue content, enzyme abundance, renal functions, and demographic distribution) that were built in the PBPK software.[5-6]

**Table 1:** Input parameters of ponatinib for PBPK model using SimCYP (V11)

| Parameter (unit) | Value | Assumptions and references |
|---|---|---|
| | | (b) (4) |

(b) (4)

**Figure 2:** Simulated ponatinib concentration time profile in healthy volunteers taking 45 mg single oral dose of ponatinib (representative Healthy population).

**Table 2:** Simulated Ponatinib PK parameters after single oral dose of 45 mg ponatnib using PBPK model

| Parameter | Observed [a] GM [range] | Simulated [b] |
|---|---|---|
| $C_{max}$ (ng/mL) | 54.7 [25.1- 80.2] | 53.51 |
| $T_{max}$ (h) | 6[c] [4 - 12] | 4.30 |
| AUC (ng/mL*h) | 1273 [613 - 2040] | 1391.36 |

[a] Observed values from fasted cohort of the food effect trial AP24534-11-102 [Ref# (3)]
[b] Simulation was conducted using healthy population representative (SimCYP® built-in virtual population database, age 20 years, male, fasted).

In order to evaluate the effect of CYP3A4 metabolism on ponatinib PK, a simulated trial, similar to the design of the submitted report for trial AP24534-11-103 where coadministration of the strong CYP3A4 inhibitor ketoconazole and ponatinib, was conducted. This simulation was conducted using the standard ketoconazole compound profile and the healthy subject population representative (e.g., 20 years old male healthy subject) provided by the SimCYP software. The results of the simulated drug interaction trial reasonably capture the ponatinib PK profile that was reported in the observed trial AP24534-11-103 (see Table 3) giving further confidence in the model.

**Table 3:** Simulated and observed ponatinib exposure ratio ($AUC_R$ and $C_{max}R$) after a single 15 mg oral dose (day 2) of ponatinib in subjects also taking ketoconazole 400 daily

(b) (4)

[redacted]

## 5. *Results: Question-based review*

### *5.1. What is the simulated effect of strong CYP3A4 induction on ponatinib exposure using physiologically-based pharmacokinetic (PBPK) model?*

A PBPK model of ponatinib was constructed as described above. To evaluate the effect of enzyme induction, a trial simulation was conducted using conducted using the standard rifampicin (strong CYP3A4 inducer) compound profile and the healthy subject population representative (e.g., 20 years old male healthy subject) provided by the SimCYP software. The trial was designed so that the virtual patient received a single 45 mg oral dose (day 10) of ponatinib in addition to also taking rifampicin 600 daily (Days 1-15). the results of the simulated drug interaction trial are reported mean ponatinib ratio's (ponatinib+rifampicin/ponatinib)of 0.29 and 0.48 for AUCR and $C_{max}R$, respectively. Therefore, a simulation from PBPK model shown to reasonably predict ponatinib PK, alone and following inhibition by a strong CYP3A4 inhibitor, suggests that a 52% reduction in ponatinib's $C_{max}R$ and a 71% reduction in ponatinib's AUCR may be expected following induction by a strong CYP3A4 inhibitor. Assuming dose proportionality, this suggests the exposure following dosing at the proposed 45 mg dose under strong CYP3A4 induction would potentially result in an AUC that would normally be seen at a dose less than 15 mg.

## References

1. NDA 203469 Quality Overall Summary at the following location: \\Cdsesub1\evsprod\NDA203469\0000\m2\23-qos\ ponatinib-hcl-ash-stevens-inc.pdf
2. NDA 203469 Clinical Pharmacology Summary at the following location: \\Cdsesub1\evsprod\NDA203469\0000\m2\27-clin-sum\ summary-of-clinical-pharmacology-studies.pdf
3. NDA 203469 Final Study report for trial AP24534-11-102 at the following location: \\Cdsesub1\evsprod\NDA203469\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\ap24534-11-102\ ap24534-11-102-csr-body.pdf
4. NDA 203469 Final Study report for trial AP24534-11-102 at the following location: \\Cdsesub1\evsprod\NDA203469\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\ap24534-11-103
5. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp((R)) Population-based ADME Simulator. Expert Opin Drug Metab Toxicol 2009.
6. Jamei M, Dickinson GL, Rostami-Hodjegan A. A framework for assessing inter-individual variability in pharmacokinetics using virtual human populations and integrating general knowledge of physical chemistry, biology, anatomy, physiology and genetics: A tale of 'bottom-up' vs 'top-down' recognition of covariates. Drug Metab Pharmacokinet 2009; 24(1):53-75.

### 4.3 Cover sheet and OCPB Filing/Review Form

APPEARS THIS WAY ON ORIGINAL

# Office of Clinical Pharmacology
# New Drug Application Filing and Review Form

**General Information About the Submission**

| | | | |
|---|---|---|---|
| **NDA/BLA Number:** | NDA 203469 | **SDN:** | 1 & 16 |
| **Sponsor:** | Ariad | **Date of Submission** | 7/30/2012 |
| **Brand Name:** | Iclusig® | **Generic Name:** | Ponatinib tablets |
| **Drug Class:** | pan BCR-ABL inhibitor kinase inhibitor | | |
| **Dosage Form:** | 15 mg and 45 mg round, white, film-coated immediate release tablets | | |
| **Dosing Regimen:** | The recommended dose and schedule for Iclusig is 45 mg administered orally once daily. Continue treatment as long as the patient does not show evidence of disease progression or unacceptable toxicity | | |
| **Route of Administration:** | Oral | | |
| **Indication:** | The treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy | | |
| **OCP Division:** | DCP5 | **OND Division:** | DHP |
| **OCP Reviewer:** | Joseph Grillo, Pharm. D.<br>Rachelle M. Lubin, Pharm. D. | | |
| **OCP Team Leader:** | Julie Bullock, Pharm. D. | | |
| **PM Reviewer:** | Li Zhang, Ph.D. & Hongshan Li, Ph.D. | | |
| **PM Team Leader:** | Nitin Mehrotra, Ph.D. | | |
| **GG Reviewer:** | | | |
| **GG Team Leader:** | | | |
| **Priority Classification:** | ☐ Standard ☐ Priority<br>☒ Breakthrough (3 month goal) | **PDUFA Due Date** | November 15, 2012 |
| **OCP Review Due Date:** | October 25, 2012 | **OND Division Due Date:** | October 30, 2012 |

**Clinical Pharmacology and Biopharmaceutics Information**

| | "X" if included at filing | Number of studies submitted | Critical Comments |
|---|---|---|---|
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | ☒ | | |
| **Tabular Listing of All Human Studies** | ☒ | | |
| **Human PK Summary** | ☒ | | |
| **Labeling** | ☒ | | |
| **Bioanalytical and Analytical Methods** | ☒ | 3 | |
| **I. Clinical Pharmacology** | | | |
| **Mass balance:** | ☒ | 2 | |
| **Isozyme characterization:** | ☒ | 1 | |
| **Blood/plasma ratio:** | ☒ | | Part of Ppb study |
| **Plasma protein binding:** | ☒ | 2 | |
| **Pharmacokinetics (e.g., Phase I) -** | | | |
| ***Healthy Volunteers:*** | | | |
| single dose: | ☐ | | |
| multiple dose: | ☐ | | |
| ***Patients:*** | | | |
| single dose: | ☒ | 1 | SD sampling time only 24 hrs |
| multiple dose: | ☒ | | Combined with SD trial |
| **Dose proportionality -** | | | |
| fasting / non-fasting single dose: | ☒ | | Combined with SD/MD trial. Limited by use of cap/tab |
| fasting / non-fasting multiple dose: | ☒ | | Combined with SD /MD trial. Limited by use of cap/tab |
| **Drug-drug interaction studies -** | | | |
| In-vivo effects on primary drug: | ☒ | 1 | Ketoconazole (CYP3A4 INH), Rifampin (CYP3A4 IND), & Lansoprazole (pH/absorption) trial protocols submitted 6/8/12 and reviewed by OCP. |

| | | | |
|---|---|---|---|
| In-vivo effects of primary drug: | ☐ | | |
| Concomitant therapy: | ☐ | | |
| In-vitro: | ☒ | 3 | CYP INH, CYP IND, Multiple Transporter Sub/INH |
| **Subpopulation studies** - | | | |
| ethnicity: | ☒ | | Pop-pk |
| gender: | ☒ | | Pop-pk |
| BW: | ☒ | | Pop-pk |
| pediatrics: | ☐ | | |
| Age/geriatrics: | ☒ | | Pop-pk |
| Albumin: | ☒ | | Pop-pk |
| renal impairment: | ☐ | | < 5% renal elimination so probably okay |
| hepatic impairment: | ☒ | | HI trial protocol submitted 6/8/12 and reviewed by OCP |
| **PD** - | | | |
| Phase 2: | ☒ | 1 | Pivotal trial. No PK sampling |
| Phase 3: | ☐ | | |
| **PK/PD** - | | | |
| Phase 1/2, proof of concept: | ☐ | | |
| Phase 3 clinical trial: | ☐ | | |
| **Population Analyses** - | | | |
| Data rich: | ☒ | 2 | Pop-pk and E/R reports |
| Data sparse: | ☐ | | |
| **QT evaluation:** | ☐ | 1 | Report. Data from Combined with SD/MD trial |
| **II. Biopharmaceutics** | | | |
| **Absolute bioavailability:** | ☐ | | |
| **Relative bioavailability** - | | | |
| solution as reference: | ☐ | | |
| alternate formulation as reference: | ☒ | | Sponsor provided anecdotal exposure comparison of cap/tab from SD/MD trial. Biowaiver or relative BE not required per Biopharm per MOU |
| **Bioequivalence studies** - | | | Biowaiver or BE trial not required per Biopharm per MOU |
| traditional design: | ☐ | | |
| replicate design: | ☐ | | |
| **Food-drug interaction studies:** | ☒ | 1 | |
| **Bio-waiver request based on BCS** | ☐ | | Biowaiver or BE trial not required per Biopharm per MOU |
| **BCS class** | ☒ | | |
| **Alcohol induced dose-dumping** | ☐ | | |
| **III. Other CPB Studies** | | | |
| **Genotype/phenotype studies** | ☒ | | Report as part of SD/MD trial |
| **Chronopharmacokinetics** | ☐ | | |
| **Pediatric development plan** | ☒ | | Waiver |
| **Literature References** | ☐ | 118 | |
| **Total Number of Studies** | | 18 | |

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 | Not required per Biopharm per MOU |
| 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 | waiver |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | waiver |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | X | | | |
| | **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**
☐ **No**

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

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

- For FDA review of the PopPK study report "Population Pharmacokinetic Analysis of Ponatinib Exposure in Healthy Volunteers and Patients with Advanced Chronic Myelogenous Leukemia or other Hematologic Malignancies", please provide us with the NONMEM control streams for the base model, final model and other relevant intermediate models **[Communicated to the applicant 8/24/12]**.
- Regarding your assay 080348VRM_ACM_R1, it appears the Cmax concentrations (0.05 ng/mL) for AP24567 at the 2 through 8 dosages in cycle 1 of the 101 trial were below the LLOQ of this assay (0.1 ng/mL). Please clarify this discrepancy within 5 business days. **[Communicated to the applicant 09/04/12]**.
- Regarding your assay 110316VRM_ACM, long term frozen sample stability appears 95 days. Please confirm storage time for samples obtained from trials utilizing this assay within 5 business days **[Communicated to the applicant 09/04/12]**.
- Regarding your assay 120081VRM_ACM, long term frozen sample stability appears 26 days yet this assay was developed to evaluate "archived" samples from completed trials. Please confirm storage time for samples obtained from trials utilizing this assay within 5 business days **[Communicated to the applicant 09/04/12]**.
- You state in your biopharmaceutics summary that assay 120081VRM_ACM was utilized to evaluate the metabolite AP24600 trials 101, 102, and 104 yet we are unable to locate PK summary information in your study reports or the raw data in your dataset folder. Please provide the location of this information in your application or submit it within 5 business days **[Communicated to the applicant 09/04/12]**.
- You state in your biopharmaceutics summary that assay 120081VRM_ACM was utilized to evaluate the metabolite AP24567 in trial 102 yet we are unable to locate PK summary information in your study reports or the raw data in your dataset folder. Please provide the location of this information in your application or submit it within 5 business days **[Communicated to the applicant 09/04/12]**.
- We are unable to locate the raw data for urine and fecal concentrations of ponatinib and its metabolites in your dataset folders for trials ARP 257 and AP24534-11-104. Please provide the location of this information in your application or submit it within 5 business days **[Communicated to the applicant 09/04/12]**.
- We are unable to locate the raw data files for the ponatinib and metabolite PK parameters from trial 101 derived from the data set "Pkload." Please provide the location of this information in your application or submit it in sas transfer format within 5 business days. Please use a format similar to the "adpkp" files submitted with your other trial reports. In addition, please also include a field in this data set that clearly indicates whether the capsule or tablet formulation was used **[Communicated to the applicant 09/04/12]**.

**Signatures:**

Joseph Grillo, Pharm.D.
Reviewer
Division of Clinical Pharmacology 5

Julie M. Bullock, Pharm.D.
Team Leader
Division of Clinical Pharmacology 5

Rachelle M. Lubin, Pharm. D.
Reviewer
Division of Clinical Pharmacology 5

**Clinical Pharmacology - NDA Filing Memo**

| | | |
|---|---|---|
| **NDA:** | **203469/000 Original Submission** | **IND: 78,375** |
| **Compound:** | **Iclusig® (ponatinib), 15 mg and 45 mg tablets for oral administration** | |
| **Sponsor:** | **ARIAD Pharmaceuticals, Inc.** | |
| **Filing Date:** | **July 30, 2012** | |
| **Reviewer:** | **Joseph Grillo, Pharm.D. & Rachelle M. Lubin, Pharm. D.** | |

Ponatinib (AP24534) is an, orally-available tyrosine kinase inhibitor (TKI). The primary target of ponatinib is BCR-ABL, an abnormal tyrosine kinase of chronic myeloid leukemia (CML) and Ph+ ALL. Two clinical trials with ponatinib are ongoing in adult patients with hematologic malignancies. A phase 1 study (AP24534-07-101) is ongoing in the United States with enrollment complete at 81 patients. The pivotal phase 2 trial (AP24534-10-201) is being conducted in multiple sites in Asia, Australia, EU, Canada, and the United States, with enrollment complete at 449 patients. In addition, 3 clinical pharmacology trials in healthy subjects have been completed: AP24534-11-102 (Food Effect), AP24534-11-103 (Ketoconazole Interaction) and AP24534-11-104 (14C-ADME). Three additional clinical pharmacology trials for ponatinib in healthy subjects are planned:

- AP24534-12-107, An Open-Label, Nonrandomized, Inpatient/Outpatient Clinical Study to Assess the Effect of Rifampicin on the Pharmacokinetics of Ponatinib, a Pan-BCRABL Tyrosine Kinase Inhibitor, when Administered Concomitantly in Healthy Subjects.
- AP24534-12-108, A Clinical Study to Evaluate the Effect of Multiple Doses of Lansoprazole on the Pharmacokinetics of Ponatinib when Administered Concomitantly to Healthy Subjects.
- AP24534-12-109, Evaluation of Pharmacokinetics and Safety of Ponatinib in Patients with Chronic Hepatic Impairment and Matched Healthy Subjects.

Ponatinib is being submitted for approval for treatment of adults with chronic, accelerated or blast phase CML or Ph+ALL who are resistant or intolerant to prior tyrosine kinase inhibitor therapy. The recommended dose and schedule for ponatinib is 45 mg administered orally once daily. The proposed commercial formulation for ponatinib is an immediate release (IR), film-coated tablet supplied in two strengths, 15 mg and 45 mg.

The applicant states that the results from the phase 2 trial report an overall MCyR rate for CP-CML patients was 53.9%. For CP-CML R/I patients (Cohort A), the MCyR rate was 48.8%, and for CP-CML patients with the T315I mutation confirmed at baseline (Cohort B), the MCyR rate was 70.3% (Table 15). A per protocol analysis confirmed these findings with similar MCyR rates observed: overall MCyR 54.3%, CP CML R/I (Cohort A) 49.3%, CP-CML T315I (Cohort B) 70.3%. The applicant reports that Ponatinib is generally well tolerated in humans and the pancreas was identified as a target organ of toxicity (Pancreatitis was identified in the phase 1 trial as the DLT). Adverse events that occurred in at least 20% of patients overall were decreased platelet count, rash, abdominal pain, headache, constipation, dry skin, fatigue, arthralgia, nausea, pyrexia, decreased neutrophil count, hypertension, and anemia.

The Applicant reports the following regarding the Clinical Pharmacology development of Ponatinib:

Ponatinib hydrochloride is classified as a BCS class 2 compound due to its low solubility and high permeability characteristics. In patients treated continuously with once-daily dosing, ponatinib was readily absorbed with maximum plasma levels being observed approximately 4 hours post-dose. In a clinical trial completed to provide a formal assessment of the effect of food on the ponatinib absorption, neither a high- or low-fat meal altered ponatinib absorption as compared to fasting conditions. In vitro data demonstrate that ponatinib aqueous solubility is dependent on pH, with solubility decreasing as pH increases.

Following the initial dose and under steady-state conditions, various measures of ponatinib exposure (Cmax and AUC) increase in a manner approximately proportional with increasing dose. At the 45 mg clinical dose, the geometric mean steady state Cmax, Cmin, and $AUC_{(0-T)}$ were 77 ng/mL, 34 ng/mL and 1296 ng•h/mL (CV=48%, N=20). Steady-state apparent clearance (CL/F), volume of distribution (V/F),

and elimination half-life (t1/2) for the clinical dose of 45 mg were 35 L/h (CV=55%, N=20), 1101 L and 22 hours, respectively. With continuous once daily administration of 45 mg ponatinib, a 1.5-fold accumulation of AUC from first dose to steady-state conditions was observed.

In vitro distribution studies have demonstrated that binding of ponatinib in human plasma is estimated to be greater than 99% and that the blood to plasma partition ratio of ponatinib was 0.96 in human blood. In vitro studies also indicate that ponatinib is either a non-substrate or a very weak substrate of both P-gp and BCRP, and is not a substrate of OCT-1, OATP1B1 and OATP1B3.

In vitro metabolism studies using human liver microsomes and hepatocytes initially suggested the major human metabolic pathway of ponatinib to be CYP3A4/5-mediated N-demethylation to form AP24567, a metabolite 4-fold less active than ponatinib. However, only low concentrations of AP24567 were observed in human plasma, approximately 1% to 2% of ponatinib. Subsequently, analyses of plasma samples from ADME studies completed late in the development program of ponatinib revealed AP24600, a pharmacologically inactive metabolite formed through esterase/amidase-mediated hydrolysis of the amide bond in ponatinib. It was determined that upon oral administration of ponatinib, AP24600 is the major circulating metabolite in plasma of humans. Following administration of [14C]-ponatinib to healthy subjects, fecal excretion accounted for elimination of 87% of the radioactive dose. The amount of drug and metabolites eliminated through urine was low (5% of the administered radioactive dose). Unchanged ponatinib accounted for 24% and <1% of the administered dose in feces and urine, respectively, with the remainder of the dose composed of metabolites.

As CYP3A4/5 contributes to the metabolism of ponatinib, a drug interaction trial was conducted to evaluate the effects of concomitant administration of multiple doses of ketoconazole, a strong inhibitor of human CYP3A4/5, on the pharmacokinetics of a single dose of ponatinib (AP24534-11-103). Overall, this trial demonstrated a statistically significant, <2-fold, effect of ketoconazole co-administration on the relative bioavailability of ponatinib. In vitro data support that ponatinib is not an inhibitor or an inducer of major CYP enzymes and that the potential for CYP enzyme inhibition- or induction-mediated drug interaction by ponatinib is low at the therapeutic dose of 45 mg. In vitro, ponatinib is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). At therapeutic concentrations, ponatinib did not inhibit the human organic anion transporting polypeptides OATP1B1 or OATP1B3, organic cation transporters OCT1, OCT2, OAT1, OAT3, or bile salt export pump (BSEP) in vitro.

Human ponatinib elimination is mainly hepatic and the amount ponatinib that is eliminated in the urine as either parent drug or metabolites is ~5% of the dose. Ponatinib has not been formally evaluated in patients with hepatic or renal impairment, but a clinical trial in hepatic impairment is ongoing. No specific studies have been performed to evaluate ponatinib pharmacokinetics in children or in the elderly. An exploratory population pharmacokinetic analysis produced a model that suggests that apparent oral clearance of ponatinib declines with age.

Preclinical experiments suggested that ponatinib has a low risk of prolonging QTc interval in patients administered the proposed daily clinical dose of 45 mg. The QT interval prolongation potential of ponatinib was assessed in 39 leukemia patients who received 30 mg, 45 mg or 60 mg ponatinib once daily. There was no significant effect on cardiac repolarization as measured by the lack of a significant change in QTcF (corrected QT by the Fridericia method) at all doses. In addition, the pharmacokinetic-pharmacodynamic models show no exposure-effect relationship, with an estimated QTcF mean change of –6.4 (upper confidence interval –0.9) msec at Cmax for the 60 mg group.

Four measures of patient outcome were evaluated as a guide for dosage escalation: 1) patient safety; 2) achievable plasma exposures; 3) inhibition of phosphorylation of CRKL as a surrogate for BCR-ABL inhibition; and 4) clinical anti-leukemic response. The applicant reports that the phase 2 starting clinical dose of ponatinib of 45 mg per day, with dose reduction to 30 mg or 15 mg allowed if clinically indicated, is supported as a safe and efficacious dose by plasma pharmacokinetic data, pharmacodynamics data, safety measures, and efficacy observations.

## 4.4 Cited References

APPEARS THIS WAY ON ORIGINAL

Cell Communication and Signaling BioMed Central

Review



# Crk and CrkL adaptor proteins: networks for physiological and pathological signaling

Raymond B Birge*[1], Charalampos Kalodimos[2], Fuyuhiko Inagaki[3] and Shinya Tanaka[4]

---

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

---

/s/

---

JOSEPH A GRILLO
12/04/2012

RACHELLE M LUBIN
12/04/2012

LI ZHANG
12/04/2012

HONGSHAN LI
12/04/2012

PING ZHAO
12/04/2012

NITIN MEHROTRA
12/04/2012

JULIE M BULLOCK
12/05/2012

NAM ATIQUR RAHMAN
12/05/2012

| BIOPHARMACEUTICS REVIEW<br>Office of New Drug Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | 203-469 | **Reviewer:** Kareen Riviere, Ph.D. | |
| **Submission Dates:** | 7/30/2012; 9/27/2012; 10/1/2012; 10/16/2012; 11/7/2012 | **Secondary Signature:** Sandra Suarez-Sharp, Ph.D. | |
| **Division:** | DHP | **Team Leader:** Angelica Dorantes, Ph.D. | |
| **Sponsor:** | Ariad Pharmaceuticals, Inc. | **Acting Supervisor:** Richard Lostritto, Ph.D. | |
| **Trade Name:** | Iclusig® Tablets | **Date Assigned:** | 8/1/2012 |
| **Generic Name:** | Ponatinib | **Date of Review:** | 11/19/2012 |
| **Indication:** | Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy | **Type of Submission:** Original 505(b)(1) New Drug Application | |
| **Formulation/strengths:** | IR Tablets/ 15 mg and 45 mg | | |
| **Route of Administration:** | Oral | | |


**SUMMARY**

This submission is a 505(b)(1) New Drug Application for Iclusig® (ponatinib) Tablets, 15 mg and 45 mg strengths. The proposed indication is for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy.

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method and acceptance criterion as well as dissolution data supporting the drug product manufacturing site change. This NDA has Quality by Design elements for both drug substance and drug product manufacturing.

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of the proposed dissolution methodology, the proposed dissolution acceptance criterion, the dissolution data supporting the drug product manufacturing site change, as well as the role of dissolution in the selection of the proposed formulation and (b) (4) for the tablet formulation.


**A. Dissolution Method**

The proposed dissolution method is shown below.

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| 1 | 50 rpm | 900 mL | 37°C | HCl/KCl pH 2.1 buffer |

The proposed dissolution method has adequate discriminating power, and therefore is deemed acceptable.

**B. Acceptance Criterion**

The proposed acceptance criterion is shown below.

| Acceptance Criterion |
|---|
| Q = (b) (4) % at (b) (4) minutes |

This proposed dissolution acceptance criterion is considered too permissive and unable to screen for batches that may be inequivalent. In an IR letter to the Applicant dated October 5, 2012, the ONDQA Biopharmaceutics Team recommended a dissolution acceptance criterion of Q = (b)(4)% at 30 minutes based on the mean in-vitro dissolution profiles for all strengths at release and at 12 months stability studies. In a submission dated November 7, 2012, the Applicant accepted the Agency's recommendation.

**C. Information to Support Approval of the 15 mg Strength (Lower Strength)**

The film-coated tablets were used as the sole drug product in the pivotal efficacy study and in all clinical pharmacology studies with the exception of the human ADME trial. The two tablet strengths (15 mg and 45 mg) are compositionally proportional and have similar in vitro dissolution profiles. The film-coated tablets are the proposed commercial formulation and were used in all clinical studies for ponatinib.

**D. Dissolution Data to Support Manufacturing Site Change**

The manufacturing site change from the (b)(4) site to the (b)(4) site is analogous to a Level (b)(4) site change according to the SUPAC-IR Guidance. The Applicant provided multi-point dissolution profile comparisons with f2 testing results for the product manufactured at the old and new site using the following media: (b)(4) This data did not demonstrate that the (b)(4) and (b)(4) batches were f2 similar. The Applicant subsequently provided information explaining that some batches failed f2 testing at the (b)(4) site because the batch used as a reference product (12 moth stability batch) was not appropriate given that the dissolution of the proposed drug product slows down with age. The Applicant has agreed to limit the drug product shelf life to 12 months, (b)(4) the dissolution acceptance criterion, and use a reference batch that is representative of the product as part of a control strategy to prevent f2 failure of future (b)(4) batches. This strategy is adequate. Therefore, the manufacturing site change is acceptable from a Biopharmaceutics perspective.

**E. Role of Dissolution in the QbD Program**

The proposed commercial tablet manufacturing process consists of three primary manufacturing operations: (b)(4) The Applicant deemed dissolution a critical quality attribute of the proposed commercial formulation. Design of Experiments (DoEs) were performed to establish a formulation design space (b)(4). Dissolution was studied in these DoEs as a response variable.

During the review cycle, the ONDQA review team informed the Applicant that the DoE studies were not performed with a discriminating dissolution method and advised the Applicant to conduct f2 testing to demonstrate equivalent performance (clinical relevance) of product batches manufactured within the proposed formulation design space (b)(4) with the proposed dissolution method. In a submission dated October 1, 2012, the Applicant stated that (b)(4) the formulation (b)(4) DoE studies would be removed from the application and that they would update the application with ranges observed during historical manufacturing and process validation lots. In a submission dated October 16, 2012, the Applicant further clarified that they plan to manufacture drug product lots using the target quantities of drug substance and excipients.

**RECOMMENDATION**

1. Iclusig (ponatinib) 15mg and 45mg strength IR tablets are recommended for approval from a Biopharmaceutics standpoint.
   - The following dissolution method and acceptance criterion were agreed upon for both strengths (refer to submission dated Nov 12, 2012):
     i. Dissolution method: Apparatus I, 50 rpm agitation rate, 900 mL media volume, 37 °C, HCl/KCl pH 2.1 buffer.
     ii. Dissolution acceptance criterion: Q = (b)(4)% at 30 minutes.

2. The manufacturing site change from the (b)(4). site to the (b)(4) site is acceptable from a Biopharmaceutics standpoint.

**Kareen Riviere, Ph.D**
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

**Sandra Suarez Sharp, Ph.D.**
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

cc: Dr. Angelica Dorantes, and Dr. Richard Lostritto

# ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

## 1. Background

### Drug Substance

According to the Applicant, Ponatinib is a BCS class 2 compound (low solubility, high permeability). The chemical structure of ponatinib hydrochloride is shown in Figure 1.

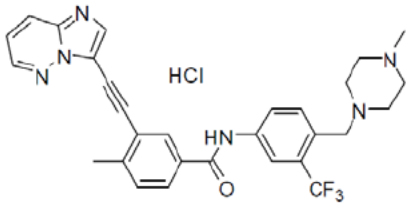



**Figure 1**. Chemical structure of ponatinib hydrochloride.

The solubility profile of ponatinib hydrochloride is shown in Table 1.

**Table 1**. Ponatinib HCl Solubility in Aqueous Buffers at Various pH Values

| Buffer | pH | Strength | Tween 80 | Solubility (mg/mL) | | |
|---|---|---|---|---|---|---|
| | | | | 25°C | 37°C | |
| | | | | HCl Salt Equivalent | | Free Base Equivalent |
| | | | | | | (b) (4) |

***Reviewer's Assessment***:
***Ponatinib HCl is soluble in the citrate, acetate and HCl/KCl buffers tested. Additionally, these buffers meet*** (b) (4) ***actetate, and phosphate buffers.***

### Drug Product

The drug product is a film-coated immediate release tablet that is formulated (b) (4) into two tablet strengths. The composition of the 15 mg and 45 mg ponatinib film coated tablets is shown in Table 2.

**Table 2**. Composition of Ponatinib Film Coated Tablets

| Description | Component | Percent (w/w) | Quantity (mg) | | Function | Quality Standard |
|---|---|---|---|---|---|---|
| | | | 15 mg | 45 mg | | |
| Core Tablet | Ponatinib free base (added as ponatinib HCl)[a] | 15.0 | 15.0 | 45.0 | Active Ingredient | In-house (see 3.2.S.4.1 Specification) |
| | Lactose monohydrate[b] | (b) (4) | | | | NF, Ph. Eur., JP |
| | Microcrystalline cellulose | | | | | NF, Ph. Eur., JP |
| | Sodium starch glycolate, Type B | | | | | NF, Ph. Eur., JP |
| | Colloidal silicon dioxide | | | | | NF, Ph. Eur., JP |
| | Magnesium stearate (b) (4) | | | | | NF, Ph. Eur., JP |
| | **Total** | **100%** | **100 mg** | **300 mg** | | |
| Film Coat | (b) (4) White film coating[c] | -- | 2.5 | 7.5 | Coating Agent | In-house (see 3.2.P.4 Control of Excipients – Noncompendial, Section 1) |
| | Purified Water[d] | -- | q.s.[e] | q.s.[e] | Solvent | USP (Ph. Eur., JP) |
| **Total Tablet Weight (mg)** | | | 102.5 | 307.5 | | |

***Reviewer's Assessment***:
***The 15 and 45 mg strength tablets are proportionally similar in composition.***

## 2. Dissolution Method

The proposed dissolution method is shown below.

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| 1 | 50 rpm | 900 mL | 37°C | HCl/KCl pH 2.1 buffer |

On April 10, 2012, the Applicant submitted an amendment to the dissolution report for poantinib tablets under IND 78375. This reviewer submitted a review of that amendment on June 25, 2012. Below is a summary of this reviewer's assessment:

- **Solubility**: Ponatinib HCl solubility is the highest in aqueous solution at pH values less than 1.7. The solubility of ponatinib HCl is buffer dependent.
- **Medium Selection**: The sponsor should justify their selection of pH 2.1 HCl/KCl buffer.
- **Apparatus and Rotation Speed Selection**: The Sponsor's selection of the basket is acceptable. The selection of the 50 rpm rotation speed is not adequately justified.
- **Discriminating Ability**: The currently proposed dissolution method was able to discriminate the dissolution performance for drug product stored under different conditions. However, it can not discriminate meaningful variations in formulation, hardness values, and particle size.

An IR letter was sent to the Applicant on June 27, 2012, stating that the proposed dissolution method was not acceptable and that additional data were needed to support the selection of the dissolution medium and rotation speed.

**New Data to Support the Selection of Dissolution Medium, Apparatus, and Rotation Speed**

The Applicant provided new data in this NDA original submission to support the selection of the dissolution method parameters. Figure 2 displays dissolution profiles obtained for 45mg ponatinib tablets, lot 110023 using the following aqueous media: HCl/KCl buffer pH 1.2, 1.7 and 2.2; pH 2.7 citrate buffer; pH 4.1 acetate buffer; and pH 6.8 phosphate buffer.

**Figure 2**. Dissolution Profiles for 45 mg Ponatinib Tablets Lot 110023 in Various Media (Paddle; (b) (4) rpm)

(b) (4)

Note: the vertical bars represent the minimum and maximum % released at each sampling time.

The dissolution rate obtained in pH 6.8 phosphate buffer is negligible since the drug substance is not soluble in this medium. The dissolution of ponatinib tablets in pH 4.1 acetate buffer (b) (4) is released within (b) (4) minutes even though ponatinib HCl solubility in this buffer is greater than (b) (4). The dissolution in pH 2.7 citrate buffer is (b) (4) at early time points, but remains incomplete at later time points even though ponatinib solubility in this buffer is (b) (4).

The Applicant postulates that the high solubility of ponatinib HCl in the citrate and acetate buffers could be attributable to the *in situ* conversion of ponatinib HCl to the respective acetate and citrate salts. The incomplete release from the tablet may result from an incomplete conversion to the respective acetate or citrate salt likely mediated by the presence of tablet excipients.

The Applicant observed formation of a (b) (4) using the paddle apparatus and (b) (4) rpm rotation speed; therefore, they investigated the use of the basket. Dissolution profiles were obtained for ponatinib tablets, 45 mg, lot 110023 using Apparatus 1 at a basket rotation speed of 50 rpm using the following buffers: pH 2.0, 2.1, 2.2 and 2.4 HCl/KCl buffers; and, pH 2.5 citrate buffer (refer to Figure 3).

**Figure 3**. Dissolution Profiles for 45 mg Ponatinib Tablets Lot 110023 in Various Media (Basket; 50 rpm)

(b) (4)

Note: the vertical bars represent the minimum and maximum % released at each sampling time.

The Applicant selected pH 2.1 HCl/KCl buffer as the most appropriate medium. They noted that the solubility of ponatinib in this buffer (b) (4) affords sufficient solubility to ensure full release of ponatinib from the 45 mg tablet strength in 900 mL of medium.

The Applicant also evaluated the impact of various basket rotation speeds on the dissolution profile of ponatinib tablets (refer to Figure 4).

**Figure 4**. Effect of Basket Rotation Speed on Dissolution Profiles for 45 mg Ponatinib Tablets Lot 110023

(b) (4)

N

***Reviewer's Assessment:***

***The Applicant's selection of the proposed dissolution medium is acceptable (b) (4). Apparatus 1 with a medium composed of pH 2.1 buffer and a basket rotation speed at 50 rpm provided a suitable dissolution profile for ponatinib tablets since greater than (b) (4) % drug was released over a period of (b) (4) minutes with complete release at 60 minutes. There seems to be no significant difference in the profiles when basket rotation speeds of 50 and (b) (4) rpm are implemented. Thus, the selection of basket and basket rotation speed are also acceptable.***

**Evaluating the Discriminating Ability of the Proposed Dissolution Method**

(b) (4)

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

---

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

---

/s/

---

KAREEN RIVIERE
11/19/2012

SANDRA SUAREZ
11/19/2012

# Office of Clinical Pharmacology
# New Drug Application Filing and Review Form

**General Information About the Submission**

| | | | |
|---|---|---|---|
| **NDA/BLA Number:** | NDA 203469 | **SDN:** | 1 & 16 |
| **Sponsor:** | Ariad | **Date of Submission** | 7/30/2012 |
| **Brand Name:** | Iclusig® | **Generic Name:** | Ponatinib tablets |
| **Drug Class:** | pan BCR-ABL inhibitor kinase inhibitor | | |
| **Dosage Form:** | 15 mg and 45 mg round, white, film-coated immediate release tablets | | |
| **Dosing Regimen:** | The recommended dose and schedule for Iclusig is 45 mg administered orally once daily. Continue treatment as long as the patient does not show evidence of disease progression or unacceptable toxicity | | |
| **Route of Administration:** | Oral | | |
| **Indication:** | The treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy | | |
| **OCP Division:** | DCP5 | **OND Division:** | DHP |
| **OCP Reviewer:** | Joseph Grillo, Pharm. D.<br>Rachelle M. Lubin, Pharm. D. | | |
| **OCP Team Leader:** | Julie Bullock, Pharm. D. | | |
| **PM Reviewer:** | Li Zhang, Ph.D. & Hongshan Li, Ph.D. | | |
| **PM Team Leader:** | Nitin Mehrotra, Ph.D. | | |
| **GG Reviewer:** | | | |
| **GG Team Leader:** | | | |
| **Priority Classification:** | ☐ Standard ☐ Priority<br>☒ Breakthrough (3 month goal) | **PDUFA Due Date** | November 15, 2012 |
| **OCP Review Due Date:** | October 25, 2012 | **OND Division Due Date:** | October 30, 2012 |

**Clinical Pharmacology and Biopharmaceutics Information**

| | "X" if included at filing | Number of studies submitted | Critical Comments |
|---|---|---|---|
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | ☒ | | |
| **Tabular Listing of All Human Studies** | ☒ | | |
| **Human PK Summary** | ☒ | | |
| **Labeling** | ☒ | | |
| **Bioanalytical and Analytical Methods** | ☒ | 3 | |
| **I. Clinical Pharmacology** | | | |
| **Mass balance:** | ☒ | 2 | |
| **Isozyme characterization:** | ☒ | 1 | |
| **Blood/plasma ratio:** | ☒ | | Part of Ppb study |
| **Plasma protein binding:** | ☒ | 2 | |
| **Pharmacokinetics (e.g., Phase I) -** | | | |
| ***Healthy Volunteers:*** | | | |
| single dose: | ☐ | | |
| multiple dose: | ☐ | | |
| ***Patients:*** | | | |
| single dose: | ☒ | 1 | SD sampling time only 24 hrs |
| multiple dose: | ☒ | | Combined with SD trial |
| **Dose proportionality -** | | | |
| fasting / non-fasting single dose: | ☒ | | Combined with SD/MD trial. Limited by use of cap/tab |
| fasting / non-fasting multiple dose: | ☒ | | Combined with SD /MD trial. Limited by use of cap/tab |
| **Drug-drug interaction studies -** | | | |
| In-vivo effects on primary drug: | ☒ | 1 | Ketoconazole (CYP3A4 INH), Rifampin (CYP3A4 IND), & Lansoprazole (pH/absorption) trial protocols submitted 6/8/12 and reviewed by OCP. |

| | | | |
|---|---|---|---|
| In-vivo effects of primary drug: | ☐ | | |
| Concomitant therapy: | ☐ | | |
| In-vitro: | ☒ | 3 | CYP INH, CYP IND, Multiple Transporter Sub/INH |
| **Subpopulation studies** - | | | |
| ethnicity: | ☒ | | Pop-pk |
| gender: | ☒ | | Pop-pk |
| BW: | ☒ | | Pop-pk |
| pediatrics: | ☐ | | |
| Age/geriatrics: | ☒ | | Pop-pk |
| Albumin: | ☒ | | Pop-pk |
| renal impairment: | ☐ | | < 5% renal elimination so probably okay |
| hepatic impairment: | ☒ | | HI trial protocol submitted 6/8/12 and reviewed by OCP |
| **PD** - | | | |
| Phase 2: | ☒ | 1 | Pivotal trial. No PK sampling |
| Phase 3: | ☐ | | |
| **PK/PD** - | | | |
| Phase 1/2, proof of concept: | ☐ | | |
| Phase 3 clinical trial: | ☐ | | |
| **Population Analyses** - | | | |
| Data rich: | ☒ | 2 | Pop-pk and E/R reports |
| Data sparse: | ☐ | | |
| **QT evaluation:** | ☐ | 1 | Report. Data from Combined with SD/MD trial |
| **II. Biopharmaceutics** | | | |
| **Absolute bioavailability:** | ☐ | | |
| **Relative bioavailability** - | | | |
| solution as reference: | ☐ | | |
| alternate formulation as reference: | ☒ | | Sponsor provided anecdotal exposure comparison of cap/tab from SD/MD trial. Biowaiver or relative BE not required per Biopharm per MOU |
| **Bioequivalence studies** - | | | Biowaiver or BE trial not required per Biopharm per MOU |
| traditional design: | ☐ | | |
| replicate design: | ☐ | | |
| **Food-drug interaction studies:** | ☒ | 1 | |
| **Bio-waiver request based on BCS** | ☐ | | Biowaiver or BE trial not required per Biopharm per MOU |
| **BCS class** | ☒ | | |
| **Alcohol induced dose-dumping** | ☐ | | |
| **III. Other CPB Studies** | | | |
| **Genotype/phenotype studies** | ☒ | | Report as part of SD/MD trial |
| **Chronopharmacokinetics** | ☐ | | |
| **Pediatric development plan** | ☒ | | Waiver |
| **Literature References** | ☐ | 118 | |
| **Total Number of Studies** | | 18 | |

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 | Not required per Biopharm per MOU |
| 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 | waiver |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | waiver |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | X | | | |
| | **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**
☐ **No**

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

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

- For FDA review of the PopPK study report "Population Pharmacokinetic Analysis of Ponatinib Exposure in Healthy Volunteers and Patients with Advanced Chronic Myelogenous Leukemia or other Hematologic Malignancies", please provide us with the NONMEM control streams for the base model, final model and other relevant intermediate models **[Communicated to the applicant 8/24/12]**.
- Regarding your assay 080348VRM_ACM_R1, it appears the Cmax concentrations (0.05 ng/mL) for AP24567 at the 2 through 8 dosages in cycle 1 of the 101 trial were below the LLOQ of this assay (0.1 ng/mL). Please clarify this discrepancy within 5 business days. **[Communicated to the applicant 09/04/12]**.
- Regarding your assay 110316VRM_ACM, long term frozen sample stability appears 95 days. Please confirm storage time for samples obtained from trials utilizing this assay within 5 business days **[Communicated to the applicant 09/04/12]**.
- Regarding your assay 120081VRM_ACM, long term frozen sample stability appears 26 days yet this assay was developed to evaluate "archived" samples from completed trials. Please confirm storage time for samples obtained from trials utilizing this assay within 5 business days **[Communicated to the applicant 09/04/12]**.
- You state in your biopharmaceutics summary that assay 120081VRM_ACM was utilized to evaluate the metabolite AP24600 trials 101, 102, and 104 yet we are unable to locate PK summary information in your study reports or the raw data in your dataset folder. Please provide the location of this information in your application or submit it within 5 business days **[Communicated to the applicant 09/04/12]**.
- You state in your biopharmaceutics summary that assay 120081VRM_ACM was utilized to evaluate the metabolite AP24567 in trial 102 yet we are unable to locate PK summary information in your study reports or the raw data in your dataset folder. Please provide the location of this information in your application or submit it within 5 business days **[Communicated to the applicant 09/04/12]**.
- We are unable to locate the raw data for urine and fecal concentrations of ponatinib and its metabolites in your dataset folders for trials ARP 257 and AP24534-11-104. Please provide the location of this information in your application or submit it within 5 business days **[Communicated to the applicant 09/04/12]**.
- We are unable to locate the raw data files for the ponatinib and metabolite PK parameters from trial 101 derived from the data set "Pkload." Please provide the location of this information in your application or submit it in sas transfer format within 5 business days. Please use a format similar to the "adpkp" files submitted with your other trial reports. In addition, please also include a field in this data set that clearly indicates whether the capsule or tablet formulation was used **[Communicated to the applicant 09/04/12]**.

**Signatures:**

Joseph Grillo, Pharm.D.
Reviewer
Division of Clinical Pharmacology 5

Julie M. Bullock, Pharm.D.
Team Leader
Division of Clinical Pharmacology 5

Rachelle M. Lubin, Pharm. D.
Reviewer
Division of Clinical Pharmacology 5

**Clinical Pharmacology - NDA Filing Memo**

| | | |
|---|---|---|
| **NDA:** | **203469/000 Original Submission** | **IND: 78,375** |
| **Compound:** | **Iclusig® (ponatinib), 15 mg and 45 mg tablets for oral administration** | |
| **Sponsor:** | **ARIAD Pharmaceuticals, Inc.** | |
| **Filing Date:** | **July 30, 2012** | |
| **Reviewer:** | **Joseph Grillo, Pharm.D. & Rachelle M. Lubin, Pharm. D.** | |

Ponatinib (AP24534) is an, orally-available tyrosine kinase inhibitor (TKI). The primary target of ponatinib is BCR-ABL, an abnormal tyrosine kinase of chronic myeloid leukemia (CML) and Ph+ ALL. Two clinical trials with ponatinib are ongoing in adult patients with hematologic malignancies. A phase 1 study (AP24534-07-101) is ongoing in the United States with enrollment complete at 81 patients. The pivotal phase 2 trial (AP24534-10-201) is being conducted in multiple sites in Asia, Australia, EU, Canada, and the United States, with enrollment complete at 449 patients. In addition, 3 clinical pharmacology trials in healthy subjects have been completed: AP24534-11-102 (Food Effect), AP24534-11-103 (Ketoconazole Interaction) and AP24534-11-104 (14C-ADME). Three additional clinical pharmacology trials for ponatinib in healthy subjects are planned:

- AP24534-12-107, An Open-Label, Nonrandomized, Inpatient/Outpatient Clinical Study to Assess the Effect of Rifampicin on the Pharmacokinetics of Ponatinib, a Pan-BCRABL Tyrosine Kinase Inhibitor, when Administered Concomitantly in Healthy Subjects.
- AP24534-12-108, A Clinical Study to Evaluate the Effect of Multiple Doses of Lansoprazole on the Pharmacokinetics of Ponatinib when Administered Concomitantly to Healthy Subjects.
- AP24534-12-109, Evaluation of Pharmacokinetics and Safety of Ponatinib in Patients with Chronic Hepatic Impairment and Matched Healthy Subjects.

Ponatinib is being submitted for approval for treatment of adults with chronic, accelerated or blast phase CML or Ph+ALL who are resistant or intolerant to prior tyrosine kinase inhibitor therapy. The recommended dose and schedule for ponatinib is 45 mg administered orally once daily. The proposed commercial formulation for ponatinib is an immediate release (IR), film-coated tablet supplied in two strengths, 15 mg and 45 mg.

The applicant states that the results from the phase 2 trial report an overall MCyR rate for CP-CML patients was 53.9%. For CP-CML R/I patients (Cohort A), the MCyR rate was 48.8%, and for CP-CML patients with the T315I mutation confirmed at baseline (Cohort B), the MCyR rate was 70.3% (Table 15). A per protocol analysis confirmed these findings with similar MCyR rates observed: overall MCyR 54.3%, CP CML R/I (Cohort A) 49.3%, CP-CML T315I (Cohort B) 70.3%. The applicant reports that Ponatinib is generally well tolerated in humans and the pancreas was identified as a target organ of toxicity (Pancreatitis was identified in the phase 1 trial as the DLT). Adverse events that occurred in at least 20% of patients overall were decreased platelet count, rash, abdominal pain, headache, constipation, dry skin, fatigue, arthralgia, nausea, pyrexia, decreased neutrophil count, hypertension, and anemia.

The Applicant reports the following regarding the Clinical Pharmacology development of Ponatinib:

Ponatinib hydrochloride is classified as a BCS class 2 compound due to its low solubility and high permeability characteristics. In patients treated continuously with once-daily dosing, ponatinib was readily absorbed with maximum plasma levels being observed approximately 4 hours post-dose. In a clinical trial completed to provide a formal assessment of the effect of food on the ponatinib absorption, neither a high- or low-fat meal altered ponatinib absorption as compared to fasting conditions. In vitro data demonstrate that ponatinib aqueous solubility is dependent on pH, with solubility decreasing as pH increases.

Following the initial dose and under steady-state conditions, various measures of ponatinib exposure (Cmax and AUC) increase in a manner approximately proportional with increasing dose. At the 45 mg clinical dose, the geometric mean steady state Cmax, Cmin, and $AUC_{(0-\tau)}$ were 77 ng/mL, 34 ng/mL and 1296 ng•h/mL (CV=48%, N=20). Steady-state apparent clearance (CL/F), volume of distribution (V/F),

and elimination half-life (t1/2) for the clinical dose of 45 mg were 35 L/h (CV=55%, N=20), 1101 L and 22 hours, respectively. With continuous once daily administration of 45 mg ponatinib, a 1.5-fold accumulation of AUC from first dose to steady-state conditions was observed.

In vitro distribution studies have demonstrated that binding of ponatinib in human plasma is estimated to be greater than 99% and that the blood to plasma partition ratio of ponatinib was 0.96 in human blood. In vitro studies also indicate that ponatinib is either a non-substrate or a very weak substrate of both P-gp and BCRP, and is not a substrate of OCT-1, OATP1B1 and OATP1B3.

In vitro metabolism studies using human liver microsomes and hepatocytes initially suggested the major human metabolic pathway of ponatinib to be CYP3A4/5-mediated N-demethylation to form AP24567, a metabolite 4-fold less active than ponatinib. However, only low concentrations of AP24567 were observed in human plasma, approximately 1% to 2% of ponatinib. Subsequently, analyses of plasma samples from ADME studies completed late in the development program of ponatinib revealed AP24600, a pharmacologically inactive metabolite formed through esterase/amidase-mediated hydrolysis of the amide bond in ponatinib. It was determined that upon oral administration of ponatinib, AP24600 is the major circulating metabolite in plasma of humans. Following administration of [14C]-ponatinib to healthy subjects, fecal excretion accounted for elimination of 87% of the radioactive dose. The amount of drug and metabolites eliminated through urine was low (5% of the administered radioactive dose). Unchanged ponatinib accounted for 24% and <1% of the administered dose in feces and urine, respectively, with the remainder of the dose composed of metabolites.

As CYP3A4/5 contributes to the metabolism of ponatinib, a drug interaction trial was conducted to evaluate the effects of concomitant administration of multiple doses of ketoconazole, a strong inhibitor of human CYP3A4/5, on the pharmacokinetics of a single dose of ponatinib (AP24534-11-103). Overall, this trial demonstrated a statistically significant, <2-fold, effect of ketoconazole co-administration on the relative bioavailability of ponatinib. In vitro data support that ponatinib is not an inhibitor or an inducer of major CYP enzymes and that the potential for CYP enzyme inhibition- or induction-mediated drug interaction by ponatinib is low at the therapeutic dose of 45 mg. In vitro, ponatinib is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). At therapeutic concentrations, ponatinib did not inhibit the human organic anion transporting polypeptides OATP1B1 or OATP1B3, organic cation transporters OCT1, OCT2, OAT1, OAT3, or bile salt export pump (BSEP) in vitro.

Human ponatinib elimination is mainly hepatic and the amount ponatinib that is eliminated in the urine as either parent drug or metabolites is ~5% of the dose. Ponatinib has not been formally evaluated in patients with hepatic or renal impairment, but a clinical trial in hepatic impairment is ongoing. No specific studies have been performed to evaluate ponatinib pharmacokinetics in children or in the elderly. An exploratory population pharmacokinetic analysis produced a model that suggests that apparent oral clearance of ponatinib declines with age.

Preclinical experiments suggested that ponatinib has a low risk of prolonging QTc interval in patients administered the proposed daily clinical dose of 45 mg. The QT interval prolongation potential of ponatinib was assessed in 39 leukemia patients who received 30 mg, 45 mg or 60 mg ponatinib once daily. There was no significant effect on cardiac repolarization as measured by the lack of a significant change in QTcF (corrected QT by the Fridericia method) at all doses. In addition, the pharmacokinetic-pharmacodynamic models show no exposure-effect relationship, with an estimated QTcF mean change of –6.4 (upper confidence interval –0.9) msec at Cmax for the 60 mg group.

Four measures of patient outcome were evaluated as a guide for dosage escalation: 1) patient safety; 2) achievable plasma exposures; 3) inhibition of phosphorylation of CRKL as a surrogate for BCR-ABL inhibition; and 4) clinical anti-leukemic response. The applicant reports that the phase 2 starting clinical dose of ponatinib of 45 mg per day, with dose reduction to 30 mg or 15 mg allowed if clinically indicated, is supported as a safe and efficacious dose by plasma pharmacokinetic data, pharmacodynamics data, safety measures, and efficacy observations.

---

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

---

/s/

---

JOSEPH A GRILLO
09/28/2012

RACHELLE M LUBIN
09/29/2012

JULIE M BULLOCK
10/02/2012