CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203469Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Addendum to CDTL Memo

Date	Electronic Signature
From	Virginia Kwitkowski, MS, RN, ACNP-BC
Subject	Addendum to Cross-Discipline Team Leader Review to incorporate SGE Consultant Reviews
NDA/BLA # Supplement#	NDA 203469
Applicant	Ariad Pharmaceuticals, Inc.
Date of Submission	Rolling Submission: 07/31/12-09/27/12
PDUFA Goal Date	03/27/13
Proprietary Name / Established (USAN) names	Iclusig®/Ponatinib
Dosage forms / Strength	15 mg and 45 mg immediate release tablets
Proposed Indication(s)	Patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL resistant or intolerant to prior tyrosine kinase inhibitor therapy

The review team did not select this application for Advisory Committee review because the trial design was similar to those previously used to support accelerated approval in the Chronic Myelogenous Leukemia and Ph+ALL indications.

Instead, the team decided to request Special Government Employee input from two clinical experts.

The clinical review team approached Dr. Mikkael Sekeres, M.D., M.S. about participating in the review of this NDA. Dr. Sekeres agreed to participate in the Divisional assignment for ponatinib. Dr. Sekeres was cleared for this assignment by the FDA Advisors and Consultants Staff on November 17, 2012. Dr. Sekeres is the Director of the Leukemia Program of the Cleveland Clinic in Cleveland, Ohio. He is also the current Chair of the FDA Oncologic Drug Advisory Committee. The DHP cleared Briefing Package was sent to Dr. Sekeres via overnight shipping on 11/26/12. The Division received the response from Dr. Sekeres on 12/03/12.

The consult response is as follows:

> **"Question: Discuss whether Iclusig (ponatinib) has a favorable benefit-risk profile for the treatment of adult patients with CML (all phases) or Ph+ ALL resistant or intolerant to prior tyrosine kinase inhibitor therapy.**
>
> Ponatinib is a kinase inhibitor with a broad spectrum of activity, including BCR-ABL, VEGFR, PDGFR, FGFR, KIT, SRC, and others. Other TKIs FDA-approved for the treatment of CML include imatinib, dasatinib, nilotinib, and bosutinib, with imatinib and Dasatinib also

approved for Ph+ ALL. Resistance to TKIs is often mediated through the T315I mutation.

An NDA for accelerated approval was submitted for ponatinib for the treatment of adult patients with chronic phase, accelerated phase, or blast phase CML, or Ph+ ALL resistant or intolerant to prior TKI therapy.

Accelerated approval is for diseases that are serious or life-threatening, and may be granted on the basis of a surrogate endpoint reasonably likely to predict clinical benefit.

CML that is resistant or intolerant to prior TKI therapy, or Ph+ ALL, both meet the criterion for a disease that is serious or life-threatening.

The pivotal trial is a multi-center, single arm, open-label, Phase 2 study of patients with Ph+ CML or ALL. Patients must also be either resistant to TKI (For CP-CML, lack of hematologic response at 3 months, minor or major cytogenetic response at 6 or 12 months, CP CML with loss of response or kinase domain mutation, or evolution to AP- or BP-CML; for AP- or BP-CML, lack of hematologic response at 3 or 1 month, loss of response, or development of kinase domain mutation); or intolerant; or develop the T315I mutation.

CBCs were obtained essentially monthly, and BM Bx/asp every 3 months through cycle 18, then every 6 months for CP-CML; every 2 months for others through 2 years.

The primary efficacy endpoint in CP-CML was major cytogenetic response; for others it was major hematologic response (either complete hematologic response or no evidence of leukemia). Secondary endpoints included hematologic, cytogenetic, and molecular responses; time to and duration of response; and PFS and OS.

Of 449 patients enrolled worldwide, 42% were from the U.S. TRhere were more men than women with ALL and BP-CML; BP-CML patients were younger. Few Asian or African-American or Black patients were represented in the ALL group. Patients in BP-CML had more ECOG PS=2 than other groups. Time from initial diagnosis was shorter in ALL and BP-CML, and the T315I mutation was overrepresented in those groups. Median number of prior TKIs was 3 for all groups except ALL, in whom it was 2 – meaning that this was a very heavily pre-treated overall group of patients.
For CP-CML, the major cytogenetic response rate was 54%; 49% in the resistant cohort and 70% in the T315I cohort. For AP-CML, major hematologic response rate was 52% overall;55% in the resistant cohort

and 39% in T315I mutants. For BP-CML and ALL, the major hematologic response rates were 31% and 41%. Median response durations were not reached; 9.5, 4.7, and 3.2 months, respectively.

On the whole, these are surrogate endpoints that are reasonably likely to predict clinical benefit, and these responses are impressive in this heavily pre-treated population. However, I am not entirely comfortable with the endpoint of hematologic improvement in BP-CML and ALL translating to clinical benefit. I worry that we are lowering the bar for TKIs, as such a surrogate would not be accepted for acute myeloid leukemia, for which the survival is similar, if not slightly better.

Major safety issues included arterial thrombotic events, hepatic, myelosuppression, bleeding, pancreatitis, HTN. CHF, SVTs, QTc prolongation and cardiac conduction defects, VTE, TLS, GI perforation; compromised wound healing, and fluid retention. These led to 73% of patients requiring a dose modification. A rate of grade 3 or 4 arterial ischemia of 6% seems high in this population, as does the fatal acute liver failure in 3 patients (it is not clear how many satisfied Hy's Law beyond this) and 6% clinical pancreatitis and 6% cardiac arrhythmias.

A Phase 3 study in the same population is underway.

On the whole, ponatinib has a favorable benefit-risk profile in CML and Ph+ ALL patients resistant or intolerant to previous TKIs, and I would vote to recommend approval. This is a heavily pretreated population in whom "intolerant" probably is not very relevant, given the number of previous TKIs to which these patients were exposed. (in other words, they were all or nearly all probably resistant at some point in their lives). The adverse event rates are serious and high, though again, in this population, probably acceptable. The clinical meaning of a hematologic response in BP-CML and Ph+ ALL is unclear in the absence of Phase 3 data."

The clinical review team approached Dr. Wyndham Wilson, M.D., Ph.D separately about participating in the review of this NDA. Dr. Wilson is Head of the Lymphoma Therapeutics Section in the Metabolism Branch of the National Cancer Institute, in Bethesda, Maryland. Dr. Wilson is the immediate past Chair of the FDA Oncologic Drug Advisory Committee. Dr. Wilson agreed to participate in the Divisional assignment for ponatinib. On November 16, 2012, the Division was notified by the FDA Advisors and Consultants Staff that Wyndham Wilson was also cleared for a divisional assignment. The DHP cleared Briefing Package was sent to Dr. Wilson via overnight shipping on 11/26/12.

The consult response is as follows:

I reviewed the memorandum dated November 26, 2012 and the response to my inquiry dated December 4, 2012. I have been requested to provide a clinical opinion on the risk/benefit of accelerated approval for ponatinib, which is under review by the Division of Hematology Products.

Ponatinib is a pan-TKI inhibitor that distinguishes itself from approved agents by virtue of its non-cross resistance against BCR-ABL harboring the T315I mutation, which is a major mechanism of resistance to approved TKI agents. Patients that harbor this mutation have a reduced OS compared to those without it, although this data is retrospective and is not based on a clinically validated assay for T315I mutation. Because ponatinib is a pan-TKI inhibitor, including inhibition of VEGF, its toxicity spectrum would be expected to be broader than more specific inhibitors. In particular, it would be expected to display toxicity seen with other VEGF inhibitors.

The indication for ponatinib is for patients with CML and Ph+ALL that is resistant or intolerant to prior TKI therapy. Resistance is defined broadly as failure to achieve adequate response or development of T315I mutation (in patients with inadequate response) on prior TKI therapy, whereas intolerance is defined as discontinuation of prior TKI therapy due to toxicity in the absence of an adequate response.

The primary efficacy endpoint of the trial is response, which included cytogenetic responses and hematological responses, depending on the disease setting. Responses were recorded for 6 different cohorts divided by resistant/intolerant or T315I mutation in CP-CML, AP-CML and BP-CML/Ph+ALL. Ponatinib showed significant activity in all groups with the primary efficacy endpoint ranging from 31% to 70% across the subgroups. Specifically, patients with the T315I mutation and CP-CML or AP-CML had a response rate of 70% and 39%, respectively. Furthermore, the efficacy endpoint was supported by a clinically meaningful duration of response, which was not reached in patients with a MCyR CML, and was 9.5 months in patients with AP-CML and 4.7-3.2 months for patients with BP-CML/Ph+ALL. This study has shown activity of ponatinib that I believe is reasonably likely to predict meaningful clinical benefit.

The major toxicity of ponatinib is related to arterial ischemia and hypertension. There is a disparity between the frequency of treatment emergent events described in the tables for AI and HTN and the summary AE's provided in the briefing document. For example, taking all patients with any grade of TE-AE in Table 5 (occurring at a frequency >=10%), the frequency of arterial ischemia is 28/449 (6%) and hypertension is 268/449 (60%). In the FDA briefing document, the overall frequency of arterial ischemia is reported to be 11.3% and hypertension is 71% (SBP > = 140 mm Hg). Both analyses, however, indicate a significant incidence of AI and HTN, toxicities that are associated with VEGF inhibition. The frequency of

fatal events due to AI was infrequent; one case each of MI, cerebral infarction and cerebral ischemia. Serious arterial ischemia was reported to occur in 7.6% of patients, but this is not further characterized. HTN was frequent and reported by the FDA to be poorly controlled. Eight patients (1.8%) had serious HTN events, and HTN was associated with AI's events in a univariate but not multivariate analysis. Serious bleeding events occurred in 4.2% of patients. GI perforation was not a major toxicity.

The outcome of patients with CML or Ph+ALL who are resistant or intolerant to current state of the art treatment (dasatinib and nilotinib) is unfavorable. There is a need for an effective agent in patients who are no longer responding to or are likely to fail these agents. While the toxicity of ponatinib is significant, the effects of disease progression in these diseases are major and lead to premature death compared to patients who are responding. The absence of validated thresholds for the clinical significance of a detectable T315I mutation may result in a small number of patients unnecessarily being exposed to ponatinib. While ponatinib has serious AI and HTN effects, it is likely that better control of HTN will reduce the frequency of serious AI's. Overall, there is an important unmet medical need for new agents in patients with resistant or intolerant CML/Ph+ALL. Hence, I feel there is a positive risk benefit for ponatinib in this setting and I would favor accelerated approval with appropriate confirmatory trials and a black box warning for AI and HTN.

Summary of SGE Opinions: Both Dr. Wilson and Dr. Sekeres stated that there is a positive risk/benefit assessment for ponatinib in the proposed indications. Dr. Wilson supported boxed warnings for the arterial and venous thrombotic events and hypertension.

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/s/

VIRGINIA E KWITKOWSKI
12/05/2012

Cross-Discipline Team Leader Review

Date	Electronic Signature
From	Virginia Kwitkowski, MS, RN, ACNP-BC
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 203469
Applicant	Ariad Pharmaceuticals, Inc.
Date of Submission	Rolling Submission: 07/31/12-09/27/12
PDUFA Goal Date	03/27/13
Proprietary Name / Established (USAN) names	Iclusig®/Ponatinib
Dosage forms / Strength	15 mg and 45 mg immediate release tablets
Proposed Indication(s)	Patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL resistant or intolerant to prior tyrosine kinase inhibitor therapy
Recommended:	*Accelerated Approval*

Cross Discipline Team Leader Review

1. Introduction

On September 27, 2012, Ariad Pharmaceuticals, Inc. submitted a New Drug Application (NDA) under the 505(b)(1) regulations for ponatinib. The application was a rolling submission with the last section received, completing the application, on September 27, 2012.

The indication proposed by Ariad was: *Iclusig 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.*

Ponatinib is a new molecular entity tyrosine kinase inhibitor with a broad spectrum of *in vitro* kinase inhibition. Ponatinib inhibits the kinase activity of native and mutant forms of BCR-ABL tested, including the T315I mutant. Ponatinib inhibited additional kinases with IC50 concentrations below 20 nM, including VEGFRs, FGFRs, PDGFRs and EPH receptor family members and RET, KIT, SRC, RAF and FLT3. Ponatinib also elicited anti-tumor activity in mice bearing tumors expressing native or T315I mutant BCR-ABL.

2. Background

Source Primary Clinical Review of R. Angelo de Claro, M.D.

CML Background

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the dysregulated production of mature and maturing granulocytes. The leukemic cells in cells in CML typically have a distinct cytogenetic abnormality, the Philadelphia chromosome.

The National Cancer Institute estimates that 5,430 men and women (3,210 men and 2,220 women) will be diagnosed and 610 men and women will die of CML in 2012. From 2005-2009, the median age at diagnosis for chronic myeloid leukemia was 64 years of age. Approximately 2.8% were diagnosed under age 20; 7.7% between 20 and 34; 9.5% between 35 and 44; 14.0% between 45 and 54; 17.0% between 55 and 64; 18.5% between 65 and 74; 20.9% between 75 and 84; and 9.6% 85+ years of age.

Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) is the largest genetically defined subtype in adult ALL, with about 30 percent of adults overall and 50 percent of adults with B-lineage ALL. It is estimated that 6,050 men and women (3,450 men and 2,600 women) will be diagnosed with and 1,440 men and women will die of acute lymphocytic leukemia in 2012.

The treatment of CML and Ph+ALL have been revolutionized with the advent of tyrosine kinase inhibitors (TKI). The following TKIs are FDA-approved for the treatment of CML: imatinib (2001), dasatinib (2006), nilotinib (2007), and bosutinib (2012). The following TKIs

are FDA-approved for the treatment of Ph+ALL: imatinib (2001) and dasatinib (2006). FDA granted accelerated approval for omacetaxine mepesuccinate in 2012 for the treatment of adult patients with CP-CML and AP-CML with resistance and/or intolerance to two or more TKIs.

The BCR-ABL T315I mutation represents a major mechanism of resistance to TKI therapy. Nicolini et al examined the medical records of 222 patients from 9 countries to describe the clinical course of patients with CML or Ph+ALL with T315I mutation. The median overall survival from the time of T315I mutation detection was 22.4, 28.4, 4.0, and 4.9 months, respectively for patients with CP-CML, AP-CML, BP-CML, and Ph+ALL.
End of Text from Source Primary Clinical Review of R. Angelo de Claro, M.D.

The Division filed the application as a priority review. The official filing date is 11/27/12, which represents 60 days from receipt of the application.

The review team did not select this application for Advisory Committee review because the trial design was similar to those previously used to support accelerated approval in the Chronic Myelogenous Leukemia and Ph+ALL indications. Instead, the team decided to request Special Government Employee input from both clinical experts and a patient representative. The clinical review team approached Dr. Mikkael Sekeres, M.D., M.S. and Dr. Wyndham Wilson, M.D., Ph.D. about participating in the review of this NDA. Dr. Sekeres is the Director of the Leukemia Program of the Cleveland Clinic in Cleveland, Ohio. He is also the current Chair of the FDA Oncologic Drug Advisory Committee. Dr. Wilson is Head of the Lymphoma Therapeutics Section in the Metabolism Branch of the National Cancer Institute, in Bethesda, Maryland. Dr. Wilson is the immediate past Chair of the FDA Oncologic Drug Advisory Committee. Both Dr. Sekeres and Dr. Wilson agreed to consult with the Division on the review of ponatinib. The Advisors and Consultants staff identified Ms. Paige Brown as an appropriate patient representative for consultation on this NDA.

On November 7, 2012, the Division was notified by the FDA Advisors and Consultants Staff that Mikkael Sekeres and Paige Brown were cleared for the divisional assignment. On November 16, 2012, the Division was notified by the FDA Advisors and Consultants Staff that Wyndham Wilson was also cleared for a divisional assignment. The clearance was too close to the due date for the Primary Clinical Review by Dr. de Claro to include the consultations in his review.

On 11/26/12, the medical briefing packages were sent via UPS Overnight to Dr. Sekeres and Dr. Wilson. I emailed them both to let them know of the pending arrival of the shipment. Their consultation is pending at the time of finalization of this review.

Ms. Brown was provided the briefing package on 11/27/12. Her response was received on 11/30/12 (see Section 9.0).

Prior Approval History for Indications
Since 2003, the FDA has approved four oral tyrosine kinase inhibitors (TKIs) for the treatment of Philadelphia chromosome positive chronic myelogenous leukemia. For the approved CML

TKI drugs, FDA has required 24 months of median follow-up data in order to grant regular approval (or to convert from accelerated approval to regular approval). Lesser amounts of follow-up data have resulted in the FDA granting accelerated approval. The trials have all been single-arm for the initial accelerated approvals. MCyR has been accepted as the efficacy endpoint for patients with Chronic Phase CML. Either MaHR or CHR have been accepted as efficacy endpoints for Accelerated Phase and Blast Phase CML in previous approvals.

To date, ponatinib has not been marketed in any foreign countries.

3. CMC/Device

The Office of New Drug Quality Assessment CMC review was conducted by Donghao (Rober) Lu, Ph.D (Drug Substance) and Amit K. Mitra, Ph.D. (Drug Product) of Branch II/ONDQA.

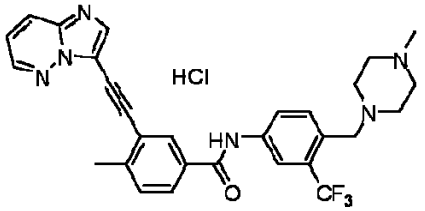
The overall recommendation from CMC is approval.

Name, USAN: Ponatinib Hydrochloride

Molecular Formula: $C_{29}H_{28}ClF_3N_6O$ (HCl salt), $C_{29}H_{27}F_3N_6O$ (free base)

Molecular Weight: 569.02 g/mol (HCl salt), 532.56 g/mol (free base)

Structural Formula:



Recommendations

A. Recommendation and Conclusion on Approvability
The ponatinib hydrochloride drug product is recommended for APPROVAL from the standpoint of chemistry, manufacturing and controls.

Include the following language in the action letter:
Based on the provided stability data, an expiration dating period of 12 months is granted for the drug product when stored at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant made the following post approval agreement. ARIAD will submit the updated method "*Identification, Content Uniformity, Assay and Impurities Method for Ponatinib (AP24534) Tablets, 15*mg and 45 mg" (AM1281) post approval, minimally within 3 months, to the application via a Supplement, Changes Being Effected – 30 Days (CBE-30). The method validation remains unchanged and is current in the Application.

Drug Substance

The drug substance is ponatinib hydrochloride. The chemical name is 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl) phenyl}benzamide hydrochloride. It has a molecular formula of C29H28ClF3N6O and its molecular weight is 569.02.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. The synthesis route and the use of reagents are adequate for the manufacturing of ponatinib hydrochloride drug substance. As this is a new molecular entity, a methods validation request was sent (subsequently determined to be acceptable) for the HPLC method for the determination of assay and organic impurities.

The impurities detected during the development of the drug substance were evaluated. Analytical methods were developed for the control of the impurities listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level was adequately presented.

Ponatinib hydrochloride drug substance was placed under the ICH recommended conditions for stability test. The drug substance was physically and chemically stable based on evaluation of the testing data. A retest period of (b) (4) months was acceptable for the drug substance.

Drug Product

The proposed commercial ponatinib drug product is an immediate release film coated tablets at two different strengths. The 15 mg tablet is described as: "white ¼ inch (6.35 mm) round film-coated tablets, debossed "A5" on one side and plain on the other side". The 45 mg tablet is described as: "white 3/8 inch (9.53 mm) round film coated tablets, de-bossed "AP4" on one side and plain on the other side".

The core tablets of the two product strengths are proportional in composition. The tablets contain a nominal 15 mg or 45 mg of the active ingredient, ponatinib free base, provided as ponatinib HCl. The inactive components of tablets are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, Type B, colloidal silicon dioxide, magnesium stearate, and (b) (4) white film coating which contains talc, polyethylene glycol, polyvinyl alcohol and titanium dioxide. All excipients are of compendial grade. An Information Request was sent to the applicant on the functional attributes of the excipients and their impact of drug product performance. The applicant's response is satisfactory according to the current regulatory standard.

The formulation and manufacturing process have changed over the course of product development with only 3 dosage forms/formulations administered in clinical studies: Drug in capsule (2 mg), capsules (5 and 15 mg) and film coated tablets (15 and 45 mg). The core tablet formulation was developed using some elements of Quality by Design. However, the regulatory dissolution method was not used in determination of the response and a complete linkage of raw material attributes and the process parameters to product quality was not achieved. The film coating process was developed using (b) (4). The applicant submitted 12 months long term stability data with the submission. During stability studies, the applicant, changed the dissolution method at the 12 months time point. Also, during the course of development, the applicant chose to commercialize the drug product from a different facility than that of the developmental facility. There were minor variations in the manufacturing process parameters also. But overall, all manufacturing process steps remained the same. The applicant provided 3 months stability data and dissolution information to bridge the commercial site to the developmental site. Details of the bridging information by f2 test are documented in the Biopharmaceutics review. Based on the limited stability data from the commercial site, a shelf life of 12 months is recommended by the reviewer and the applicant agreed to the 12 months tentative shelf life.

Description of How the Drug Product is Intended to be Used
The drug product is proposed to be marketed in 60 and 180 counts for 15 mg tablets, and 30 and 90 counts for the 45 mg tablets. Both strengths are packaged in high density bottles.

The applicant has provided sufficient stability data for a 12 months tentative shelf life under long term storage conditions. The storage conditions are described as follows: Store at controlled room temperature 20-25^{o}C (68^{o} to 77^{o} F); excursions permitted between 15^{o} to 30^{o}C (59^{o} to 86^{o}F).

Basis for Approvability Recommendation
The applicant has responded satisfactorily to all Information Request letters.
The Office of Compliance has provided an overall acceptable recommendation. Based on the above, this application is recommended for approval from the standpoint of chemistry, manufacturing and controls.

The Biopharmaceutics Review (ONDQA) was conducted by Kareen Riviere, Ph.D., with Secondary Review by Sandra Suarez-Sharp, Ph.D. Team Leader and Acting Supervisor concurrence was received by Angelica Dorantes, Ph.D. and Richard Lostritto, Ph.D., respectively.

Source: Biopharmaceutics Review by Kareen Riviere, Ph.D.
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) design spaces for the tablet formulation.

Dr. Riviere concludes the following:
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.

There are no outstanding CMC issues precluding regulatory action.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviews were conducted by M. Stacey Ricci, M.Eng., Sc.D. and Pedro L. Del Valle, Ph.D. The Team Leader memo was written by Haleh Saber, Ph.D.

Source Pharmacology/Toxicology Review by Dr. Ricci and Dr. Del Valle

In support of the commercial development program for ponatinib, *in vitro* studies and animal studies (in the mouse, rat, dog, and monkey) were conducted to evaluate the pharmacology, general toxicology, reproductive effects and genotoxicity of ponatinib.

Ponatinib pharmacology was evaluated using a series of *in vitro*, cell based and *in vivo* studies, results of which include:

- Ponatinib inhibits the kinase activity of native BCR-ABL or different mutant BCRABL proteins, including the T315I mutation, as demonstrated *in vitro* using recombinant proteins or cell-based survival assays.
- Comparative studies were conducted using ponatinib, dasatinib, nilotinib or imatinib that demonstrated ponatinib alone has activity towards inhibiting T315I mutant activity at sub-micromolar concentrations.
- Ponatinib was tested against a panel of kinases comprising approximately half of the human kinome, and it inhibited 41 kinases (other than BCR-ABL and its variants) with IC50 values ≤ 20 nM. These kinases include RET, FLT3, KIT and members of the VEGFR, FGFR, PDGFR, EPH and SRC families of kinases (see the Appendix for a full list of kinases tested).

Safety pharmacology studies conducted included studies in mice, rats and dogs and the hERG assay. There were no dose-dependent ponatinib-related effects noted on pulmonary function in conscious rats, neurologic effects in mice, or cardiac function in telemeterized dogs. A transient increase in QTc was observed in one dog that received the highest dose used (10 mg/kg; 200 mg/m2). Ponatinib inhibited hERG current in a dose-dependent manner beginning at the 1000 nM concentration and had an estimated IC50 = 2330 nM. ARIAD estimates that the mean Cmax plasma concentration of a human dose of 45 mg ponatinib is 145 nM (77 ng/ml), which is ~20-fold lower than the hERG IC50 value. The potential for ponatinib to block hERG channel activity is low.

Pharmacokinetic parameters were measured in single dose (intravenous or oral) PK studies using rats and monkeys and as part of the repeat dose toxicology studies using rats and monkeys (oral). Ponatinib was absorbed slowly with a T_{max} of 6 and 4 hours, respectively, in the rat and monkey following an oral dose. The oral bioavailability in rats and monkeys was 54% and 21%, respectively. The terminal half-life of ponatinib in plasma after an intravenous dose was 9.7 hours in rats and 5.3 hours in monkeys. Blood clearance was moderate in rats but was slow in monkeys. *In vitro* plasma protein binding was high (>99.7%) in all species tested (mouse, rat, monkey and human). Qualitatively, all metabolites observed in human plasma were also detected in either rat or monkey. AP24600 was the major metabolite in plasma of humans and rats but not monkeys. AP24600 had no effect on cells expressing native or T315I mutant BCR-ABL. Ponatinib was eliminated predominantly by metabolism in rats, monkeys and humans. Tissue distribution studies using [14C]-ponatinib in rats demonstrated that ponatinib is widely distributed throughout the body with maximum tissue concentration observed by 8h post-dose. Tissues with the highest relative tissue concentrations were small intestine, uveal tract of the eye, brain (meninges), lung, liver, pituitary and adrenal glands, white and red pulp of spleen, Harderian gland, kidney cortex and thyroid.

Single-dose and repeat-dose general toxicology studies using mice, rats and monkeys were conducted. The repeat dose 28-Day or 6-Month studies administered AP24534 to either Sprague-Dawley (SD) rats or cynomolgus monkeys daily. An embryo-fetal development (EFD) toxicology study was conducted using the SD rat, and a phototoxicity study was conducted using Long Evans rats.

Single dose studies in rats resulted in mortality or morbidity of 80% of males and 100% females that received the high dose of 100 mg/kg. Histopathology results in these animals indicated immunosuppression as the likely cause of death (due to lymphoid depletion) and associated bacterial sepsis. Necrosis involving the exocrine pancreas and intestinal crypt epithelial cells was also observed. No mortalities were observed following single dose studies in monkeys administered single doses up to 45 mg/kg. Ponatinib-related mortalities were also observed in the repeat-dose studies: rats receiving ≥ 0.75 mg/kg/day (4.5 mg/m2) and in monkeys receiving 5 mg/kg/day (60 mg/mg2). A common cause for the moribundity and early mortalities in repeat-dose studies was not established, but toxicities common to both rat and monkey repeat-dose studies included immunosuppression manifest as lymphoid depletion of

the thymus, spleen and lymph nodes, increased neutrophils, eosinophils and monocytes and clinical signs of weight loss and skin effects. Hyper- and hypo-plastic changes were noted in femoral bone in both rat studies.

Serious clinical safety issues related to ponatinib use include the cardiovascular, hepatic and pancreatic systems.

In the embryo-fetal development study, ponatinib was administered orally to pregnant rats at doses of 0, 0.3, 1, and 3 mg/kg. Systemic exposures (AUC) at 3 mg/kg were equivalent to the AUC in patients receiving the recommended human dose. Soft tissue and skeletal alterations and differences in the number of ossification site averages were observed in the mid and high dose groups and maternal toxicity, including mortality, was observed at the high dose. Additional fetal toxicities observed at the high dose included increased post-implantation loss (early, late and total resorptions); reduced body weight; gross external alterations; multiple soft tissue and skeletal alterations, as well as differences in the number of ossification site averages.

Ponatinib was not genotoxic when evaluated in three separate assays (Ames assay for mutagenicity, in vitro chromosomal aberration assay or in vivo mouse micronucleus assay). Carcinogenicity studies were not completed because of the short life expectancy of CML and Ph+ ALL patients that have failed prior TKI therapy. Results from a phototoxicity study indicate that ponatinib does not cause dermal toxicity but ocular effects were observed at the mid and high doses used (5 and 10 mg/kg).

A pregnancy category D has been assigned to this drug. Due to the teratogenicity findings in rats, an embryofetal developmental study in a second species was deemed not necessary.

Per the reviews of Dr. Ricci, Dr. Del Valle, and Dr. Saber, no additional non-clinical studies are needed to support the approval of Iclusig in the proposed indications.

There are no outstanding pharmacology/toxicology issues precluding regulatory action.

5. Clinical Pharmacology/Biopharmaceutics

The primary clinical pharmacology review was conducted by Joseph Grillo, Pharm. D (Primary) and Rachelle Lubin, Pharm.D. The CDER DCRP QT Interdisciplinary Review Team review was completed by Monica Fiszman on 11/30/12.

Source Review of Dr. Grillo and Dr. Lubin

Iclusig (ponatinib) is an orally administered tyrosine kinase inhibitor (TKI) that primary 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 as long as the patient does not show evidence of disease progression or unacceptable toxicity. Iclusig will be marketed as 15 mg and 45 mg round, white, film-coated tablets.

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. Pharmacokinetic sampling was not done. 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). 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. Other important thrombotic, cardiac, gastrointestinal, hepatic, and myelosuppressive safety issues were also observed with the use of ponatinib.

An FDA 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 addition, the dose intensity-safety relationship indicated that there is significant increase in safety events (i.e., thrombocytopenia, pancreatitis, neutropenia, rash, ALT elevation, AST elevation, lipase elevation, and myelosuppression) with increase in dose. The reviewer finds that the proposed 45 mg daily dose is not supported by dose intensity-response relationship for efficacy and safety discussed below. A lower dose, especially for CP-CML patients, may offer a better benefit-risk profile.

The absolute bioavailability (BA) of ponatinib is unknown. Peak concentrations of ponatinib are observed within 6 hours after Iclusig oral administration. A food effect on BA was not established in a dedicated clinical trial. Drugs that elevate the gastric pH may reduce ponatinib's bioavailability.

Ponatinib is greater than 99% bound to plasma proteins in vitro and the potential for displacement related drug interactions is unknown. The geometric mean ($mean_{geo}$) apparent steady state volume of distribution of ponatinib is 1223 L. Ponatinib is a weak substrate for both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) 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. The $mean_{geo}$ terminal elimination half-life of ponatinib was approximately 24 hours with a 90% median accumulation observed with repeat dosing. 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 ketoconazole (400 mg daily), a strong CYP3A inhibitor, to 22 healthy volunteers increased ponatinib $AUC_{0-\infty}$ and C_{max} by 78% and 47%, respectively, compared to administration of ponatinib alone. Based on these findings, the reviewer recommends that the starting dose be reduced to 30 mg once daily. The effect of CYP3A4 enzyme induction on the metabolism of ponatinib was not specifically evaluated 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.

QT-IRT Consultation Summary: (Source: Review by Monica Fiszman)
QT-IRT has reviewed the additional safety and ECG data from study AP24534-07-101. From this data, IRT concludes 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, an additional QT study is not recommended. However, as mentioned in our previous review, there were unknown factors which had potential to increase exposure of ponatinib (i.e., food, hepatic impairment and administration of CYP3A4 inhibitors). 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 10-201. IRT has not reviewed this subsequent data.

QT-IRT's proposed label
12.6 Cardiac Electrophysiology
The QT interval prolongation potential of ponatinib was assessed in 39 leukemia patients who received 30 mg, 45 mg, or 60 mg Iclusig once daily. No large changes in the mean QTc interval (i.e., >20 ms) from baseline were detected in the study. However, a small increase in the mean QTc interval (i.e., <10 ms) cannot be excluded because of study design limitations.

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.

Post Marketing Requirements

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

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.

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.

4. Collect sparse PK in your 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, you may be required to conduct a trial to evaluate lower dose or an alternate dosing regimen of ponatinib.

Post Marketing Commitments

Evaluate the in vitro potential for the displacement of ponatinib, at a therapeutic concentration, 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.

There are no outstanding Clinical Pharmacology issues precluding regulatory action.

6. Clinical Microbiology

Not relevant to anti-cancer agents.

7. Clinical/Statistical- Efficacy

The clinical review was conducted by R. Angelo de Claro, MD. The statistical review was conducted by Kyung Yul Lee, Ph.D (Team Leader Mark Rothmann, Ph.D.) of DB5. \

Ponatinib has been under investigation by Ariad in the United States since 2007 under IND 78375.

A ***pre-IND*** meeting was held between Ariad and the Division of Drug Oncology Products on September 4, 2007. At this meeting, there was discussion regarding a starting dose for the proposed Phase 1 trial, the dose escalation scheme, plan for intra-patient dose-escalation, proposed safety assessment, pharmacodynamic markers, fast track designation, and product registration strategy (including use of a single-arm trial in patients with CML and Ph+ ALL who have failed or cannot receive available chemotherapies or transplant procedures. The Agency stated (in response to the proposed registration plan) that "whether single-arm studies would support approval would depend upon patient population and available therapies", and suggested an EOP1/2 meeting to discuss the development plan.

FDA granted orphan drug designation to ponatinib for treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) and treatment of chronic myeloid leukemia on November 20, 2009.

A Type B, ***End of Phase 2*** meeting was held by the FDA Division of Hematology Products, Division of Drug Oncology products, members of the CDRH Office of In Vitro Diagnostics, and Ariad Pharmaceuticals on May 14, 2010 to discuss their proposed Phase 2 pivotal trial of ponatinib patients with (patients resistant or intolerant to dasatinib or nilotinib; or patients with the BCR-ABL T315I mutation. At the meeting the following key clinical discussion/agreements occurred:

- The adequacy of the clinical pharmacology studies to support the marketing application will be a review issue. The Sponsor should submit the QTc evaluation plan to the FDA for review, include sparse sampling for PK in any efficacy or safety trials to explore exposure-response relationships for AP24534 and any active metabolites.
- A single-arm trial may be adequate to support accelerated or full approval for a proposed indication, depending on the response rate, duration of response and risk-benefit ratio and available therapy at the time of NDA action. However, the adequacy would be a review issue. Please see FDA response to question 4 below regarding your proposed patient populations. Also, please provide the details of any confirmatory trials you are planning if accelerated approval is planned for any of the indications.
- The Agency agreed with the definitions of "resistant or intolerant to dasatinib or nilotinib" as long as the Sponsor collected the data in patients with historic positive results for the T315I mutation but negative results with the direct sequencing method in the central laboratory for the study.
- The Agency agreed that the direct sequencing method is the current gold standard for testing for the T315I mutation and enrolling patients based on central laboratory results, but that patients who historically tested positive for the T315I mutation but have a negative central laboratory result should not be placed in the T315I cohort in the trial. The Agency informed the Sponsor, "If you intend to seek an indication specifically for the T315I mutation population, we recommend that you design this Phase 2 trial in combination with an *in vitro* diagnostic for which you will submit an application for marketing approval to the Center for Devices and Radiological Health. It is unlikely that you would gain approval of AP24534 for the T315I mutation population without an approved diagnostic with known performance characteristics to be able to identify the appropriate patient population in the post-marketing setting. We recommend that you initiate discussions with CDRH regarding such an *in vitro* diagnostic prior to initiation of this phase 2 trial."
- The Agency agreed with the proposed study endpoints (major cytogenetic response rate for chronic phase patients and major hematologic response rate for accelerated phase, blast phase, and Ph+ ALL patients) and stated that they could be considered clinically meaningful depending upon the sample size, response rate, and associated toxicities.
- The Agency agreed that the safety data of approximately 370 patients would likely be acceptable to support the NDA.
- The Agency agreed that the proposed single-arm trial may provide adequate evidence based on a surrogate endpoint for purposes of accelerated approval, contingent upon demonstration of an important, verifiable response of meaningful duration and an acceptable safety profile.
- The Agency communicated to the sponsor that more than one indication can be approved with one NDA submission.
- The Agency agreed that given the orphan designation, a pediatric study plan is not required. The Agency strongly encouraged the Sponsor to investigate whether the drug has activity in a pediatric population.

On July 22, 2010, following the EOP1/2 meeting, Ariad submitted a proposal to amend the entry criteria for the PACE trial and requesting Agency feedback. The question posed was:

"The primary endpoint of the AP24534 pivotal Phase 2 trial for patients with chronic phase CML is major cytogenetic response. We propose that the study incorporate enrollment of chronic phase CML patients in partial cytogenetic response at baseline, with the stipulation that such patients must achieve a complete cytogenetic response in order to be considered responders in the primary endpoint analysis of cytogenetic response. Does the Agency agree that the revised patient entry criteria to include patients in partial cytogenetic response at baseline are acceptable and will allow the evaluation of this trial for a marketing application employing the statistical methodology discussed in the May 14 End of Phase 1 Meeting?". The Divison of Drug Oncology Products responded as follows, via email, on August 13, 2010: "As indicated in your email submission dated 7/22/10, there are instances where patients with CML in chronic phase who have a PCyR on a TKI may be resistant. However, not every patient with PCyR is resistant. We suggest amending your protocol to define which patients in PCyR are resistant. Please submit the amended protocol for review."

A search of DARRTS was not successful in identifying subsequent submissions or communications indicating that the Agency had agreed to the proposed change.

On 11/30/2010, Ariad was granted Fast Track Designation for the investigation of AP24534 for CML and Ph+ ALL patients who have a T315I BCR-ABL mutation.

On February 16, 2012, a **Type B pre-NDA** meeting was held with the Division of Hematology Products and Ariad, to discuss the details of the Phase 3 development program for ponatinib. The following key agreements/discussions occurred at the meeting:

- The adequacy of the clinical pharmacology program to support the marketing application will be a review issue.
- The Agency instructed Ariad to submit the protocols for the three clinical pharmacology studies (rifampicin interaction study, lansoprazole study, and the hepatic impairment study) you plan to conduct post-approval to the IND for agency review and concurrence. These studies should ongoing by the time the NDA is submitted.
- The Agency provided a list of the QT data that would need to be submitted for review. Ariad agreed.
- The Agency recommended that the sponsor submit the efficacy and the safety data from the 449 patients, with at least 6-months of follow-up data, enrolled in the PACE trial. The Agency explained that a broader definition of intolerance would have also been acceptable; i.e., patients with intolerance regardless of response. Include data on prior therapies received for all patients, including complete documentation of resistance, intolerance, or both, to prior anti-CML treatments.
- The Agency informed Ariad that they are required to submit raw and analysis datasets for all clinical trials (including clinical pharmacology) included in the NDA.
- The Agency recommended that (b) (4) schedule a pre-PMA meeting with OIVD to discuss the logistics and coordination of the PMA filing.

Ariad has conducted 3 clinical pharmacology / pharmacokinetic trials in healthy volunteers, one Phase 1 in adult patients with refractory or advanced CML and other hematologic malignancies, and one Phase 2 trial in adult patients with CML or Ph+ALL (Trial 10-201).

The application contained the available results of these 5 trials (the PK trials are completed and the clinical trials are ongoing). The clinical review was primarily based on the efficacy and safety data of the Clinical Trial 10-201 (PACE Trial). An additional Phase 1 dose-escalation clinical trial (07-101) was also reviewed as support to the PACE trial safety data.

As noted above, during the End of Phase 1/2 Meeting, the Division recommended that an *in vitro* diagnostic be developed for marketing approval to support the approval of ponatinib in patients with a T315I mutation. Ariad did eventually partner with (b) (4) to develop a companion diagnostic test for PMA submission to CDRH at the same time as the ponatinib NDA submission.

Later, during pre-NDA discussions, Ariad had indicated that they would be seeking an indication for patients with CML and the T315I mutation, a population of patients with no available therapy.

Ariad presented their NDA application during an Applicant orientation meeting at FDA on 08/06/12. In the presentation they stated that ponatinib had substantial activity in all populations tested (activity was not limited to patients with the T315I mutation). Therefore, they were seeking an indication for patients with CML previously treated with one or more prior TKIs. This altered indication would no longer require a companion diagnostic, because any patient who had been treated with at least one prior TKI would be eligible for treatment with ponatinib. The Division had internal meetings and decided that the indication would be supported without an *in vitro* diagnostic for the T315I mutation because the test is not needed to select a population who would benefit from the drug.

Source Primary Clinical Review of R. Angelo de Claro, M.D.
Trial 10-201 (The PACE Trial) enrolled 449 patients from 68 sites worldwide: Australia, Belgium, Canada, France, Germany, Italy, South Korea, United Kingdom, United States, the Netherlands, Spain, and Sweden. U.S. patients accounted for 187 (42%) of the 449 total patients. The next top-enrolling countries were France (54 patients), Germany (38 patients), Italy (38 patients), and the United Kingdom (30 patients).

The primary efficacy analysis population consisted of 444 patients out of the total 449 patients enrolled in Study 10-201. Five patients were excluded from the primary efficacy analyses due to non-confirmation of T315I mutation using a central laboratory test, and these patients did not have prior therapy with dasatinib or nilotinib.

The median time from time of initial diagnosis for the efficacy population was 6.1 years (range 0.3 to 28.5 years). Patients in the T315I-mutation-positive cohorts tended to have a shorter time from initial diagnosis and a lower number of prior TKI therapies. The most common exposure to prior TKI therapy in the efficacy population include: imatinib (96%), dasatinib (84%), and nilotinib (66%).

Refer to Dr. de Claro's review for Demographics tables (Section 6.1.2).

The primary efficacy endpoint for patients with Chronic Phase CML in the PACE trial was Major Cytogenetic Response. The FDA analysis of the primary results of this endpoint were the same as the Applicant's.

Table 1 FDA and Applicant's Primary Endpoint Analysis in Patients with CP-CML

	Overall (N=267)	Resistant or Intolerant	
		R/I Cohort (N=203)	T315I Cohort (N=64)
Cytogenetic Response			
Major[a] (MCyR) % (95% CI)	54% (48, 60)	49% (42, 56)	70% (58, 81)
Complete (CCyR) % (95% CI)	44% (38, 50)	37% (31, 44)	66% (53, 77)

[a] Primary endpoint for CP-CML cohorts was MCyR, which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

The primary efficacy endpoint for patients with Accelerated Phase CML was Major Hematologic Response, which combines Complete Hematologic Response and No Evidence of Leukemia.

Table 2 Applicant's Primary Endpoint Analysis in Patients with AP-CML

	Accelerated Phase CML		
	Overall (N=83)	Resistant or Intolerant	
		R/I Cohort (N=65)	T315I Cohort (N=18)
Hematologic Response			
Major[a] (MaHR) % (95% CI)	58% (47, 69)	60% (47, 72)	50% (26, 74)
Complete[b] (CHR) % (95% CI)	47% (36, 58)	46% (34, 59)	50% (26, 74)
Major Cytogenetic Response[c] (MCyR) % (95% CI)	39% (28, 50)	34% (23, 47)	56% (31, 79)

[a] Primary endpoint for AP-CML and BP-CML/Ph+ALL Cohorts was MaHR, which combines complete hematologic responses and no evidence of leukemia.
[b] CHR: WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, No extramedullary involvement (including no hepatomegaly or splenomegaly).
[c] MCyR combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

Dr. de Claro, the clinical reviewer, did not agree with the Applicant's efficacy analysis of the AP-CML population data. This disagreement was due to some patients who were missing baseline data and some who had already achieved the primary response at time of enrollment. The adjudication details are provided below. I concur with Dr. de Claro's disagreement with the Applicant's conclusion for this cohort. Patients without baseline disease assessments needed to establish the response to the treatment should not be evaluable for response and patients with the primary endpoint (in this case MaHR) at baseline, should also not be evaluable for response.

Table 3 FDA Adjudication of Major Hematologic Response in Patients with AP-CML

SUBJID	Cohort	Applicant's analysis	FDA analysis	Justification
938-012	AP R/I	MaHR (NEL)	Non-responder	MaHR at baseline
948-007	AP T315I	MaHR (CHR)	Non-responder	No labs or bone marrow prior to first dose.
955-002	AP R/I	MaHR (NEL)	Non-responder	No labs or bone marrow prior to first dose.
956-001	AP R/I	MaHR (CHR)	Non-responder	MaHR at baseline
957-010	AP T315I	MaHR (CHR)	Non-responder	MaHR at baseline

Table 4 FDA Primary Endpoint Analysis in Patients with AP-CML

	Accelerated Phase CML		
	Overall (N=83)	Resistant or Intolerant	
		R/I Cohort (N=65)	T315I Cohort (N=18)
Hematologic Response			
Major[a] (MaHR) % (95% CI)	52% (41, 63)	55% (43, 68)	39% (17, 64)
Complete[b] (CHR) % (95% CI)	43% (33, 55)	45% (32, 57)	39% (17, 64)

The primary endpoint for patients with Blast Phase CML and Ph+ ALL was Major Hematologic Response. The Applicant presented the results for patients with BP-CML and

Ph+ALL in a combined fashion. The FDA primary endpoint analysis separated the results of patients with BP-CML from patients with Ph+ ALL due to differences in underlying disease biology and also for consistency with prior FDA action with regards to labeling prior TKI approvals for BP-CML and Ph+ ALL. In addition, 82% of the patients (51/62) with BP-CML had myeloid blast phase, 18% had lymphoid blast phase, which further supports the separated efficacy and safety analyses of patients with Ph+ALL from patients with BP-CML.

Table 5 Applicant's Primary Endpoint Analysis in Patients with BP-CML or Ph+ ALL

	Blast Phase CML or Ph+ ALL		
	Overall (N=94)	Resistant or Intolerant	
		R/I Cohort (N=48)	T315I Cohort (N=46)
Hematologic Response			
Major[a] (MaHR) % (95% CI)	34% (25, 45)	35% (22, 51)	33% (20, 48)
Complete[b] (CHR) % (95% CI)	26% (17, 36)	27% (15, 42)	24% (13, 39)

Major Cytogenetic Response[c] (MCyR) % (95% CI)	31% (22, 41)	27% (15, 42)	35% (21, 50)

[a] Primary endpoint for AP-CML and BP-CML/Ph+ALL Cohorts was MaHR, which combines complete hematologic responses and no evidence of leukemia.
[b] CHR: WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, No extramedullary involvement (including no hepatomegaly or splenomegaly).
[c] MCyR combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

The FDA analysis results are provided below in Table 6 and Table 7.

Table 6 FDA Primary Endpoint Analysis in Patients with BP-CML

	Blast Phase CML		
	Overall (N=62)	**Resistant or Intolerant**	
		R/I Cohort (N=38)	**T315I Cohort (N=24)**
Hematologic Response			
Major (MaHR) % (95% CI)	31% (20, 44)	32% (18, 42)	29% (13, 51)
Complete (CHR) % (95% CI)	21% (12, 33)	24% (11, 40)	17% (5, 37)

Table 7 FDA Primary Analysis in Patients with Ph+ ALL

	Ph+ ALL		
	Overall (N=32)	**Resistant or Intolerant**	
		R/I Cohort (N=10)	**T315I Cohort (N=22)**
Hematologic Response			
Major (MaHR) % (95% CI)	41% (24, 59)	50% (19, 81)	36% (17, 59)
Complete (CHR) % (95% CI)	34% (19, 53)	40% (12, 74)	32% (14, 55)

I agree with Dr. de Claro's statement that "Further subgrouping of patients with BP-CML or Ph+ALL to resistant/intolerant or T315I cohorts lead to small patient numbers and do not provide additional information beyond data as presented.."

Duration of Response

CP-CML. The median duration of MCyR was not reached in patients with CP-CML. Only 6 of the 144 patients with CP-CML who achieved MCyR had an event (disease progression or loss of response).

AP-CML. The median duration of MaHR was 9.5 months (95%CI; 5.5, 17.7 months) in the 43 patients with AP-CML who achieved MaHR. Twenty-one of the 43 patients (49%) experienced an event.

BP-CML. The median duration of MaHR was 4.7 months (95%CI; 2.7, NE) in patients with BP-CML who achieved MaHR. Nine of the 19 patients (47%) who achieved a response experienced an event.

Ph+ ALL. The median duration of MaHR was 3.2 months (95%CI; 1.8, 4.7) in patients with Ph+ ALL who achieved MaHR. Twelve of the 13 patients (92%) who achieved a response experienced an event.

The Clinical Reviewer disagreed with the Applicant's analyses of duration of major hematologic response (DOMAHR). This disagreement was due to the data handling of investigator assessments for progression. The Applicant excluded investigator assessment of progression in their DOMAHR analyses, while the FDA included the investigator assessments. Censoring patients prior to investigator-assessed progression lead to informative censoring: As shown in Table 8, the patients assessed to have investigator-assessed progression underwent subsequent chemotherapy, and 2 patients died subsequently from PD. Finally, FDA included the investigator assessments for progression because the cohort assignments for Study 10-201 used investigator assessments in addition to objective data.

Table 8 FDA Adjudication for Duration of Major Hematologic Response

SUBJID	Cohort	Applicant's analysis	FDA adjudication	Justification*
008-002	Ph+ ALL R/I	Censored on D127	Event on D96	Investigator-assessed PD on D96, received cytarabine and mitroxantrone starting on D101, death due to PD on D
017-010	Ph+ ALL T315I	Censored on D176	Event on D117	Investigator-assessed PD on D117
048-007	BP-CML T315I	Censored on D100	Event on D67	Investigator-assessed PD on D67, received cytarabine and mitoxantrone starting on D69, death due to PD on D
078-001	BP-CML T315I	Censored on D114	Event on D84	Investigator-assessed PD on D84, received cytarabine and daunorubicin starting on D99
128-003	AP-CML R/I	Censored on D195	Event on D164	Investigator-assessed PD on D164, received busulfan, fludarabine, and ATG conditiong starting on D169

*In all cases, the last dose of ponatinib was on the date of investigator-asssessed PD.
Note: Reference date is first dose date of ponatinib.

Overall Survival and Progression-Free Survival were secondary endpoints for the PACE trial. Time-to-event endpoints, such as OS and PFS are not interpretable in single-arm trials due to lack of a control group. The reader is referred to OS analysis reported in Dr. de Claro's review.

Other secondary endpoints included Molecular Response, Hematologic response (CP-CML), and Cytogenetic response (AP-CML, BP-CML, Ph+ ALL).

I agree with Dr. de Claro's conclusion that major molecular response data cannot be adequately evaluated in Study 10-201 because performance data for the RQ-PCR assay was not submitted in the application and that hematologic response was not evaluable in patients with CP-CML because 42% of the patients (113/267) were already in complete hematologic response at baseline. The results for complete cytogenetic response are shown in Table 1.

The clinical review team is not confident that the Applicant has identified the proper dose for marketing. This concern is based upon the exposure and tolerability data provided in the NDA. Patients from all disease cohorts were not able to maintain the treatment intensity of the starting ponatinib dose of 45 mg per day. Patients with CP-CML were only able to receive treatment at 45 mg per day dose level for 50% of the entire treatment duration, and received reduced doses of ponatinib for 36% of the treatment duration. This explains the average ponatinib daily dose of 32.1 mg for the CP-CML cohort. Similar patterns were observed in the other cohorts.

Dose modifications (dose delay >2 days or dose reduction) were more common (>70%) in patients in the CP-CML and AP-CML cohorts as compared to the BP-CML (55%) and Ph+ALL (25%) cohorts.

Adverse events were the most common cause for the dose modifications. Three hundred-twenty-six patients (73%) required a dose modification due to adverse events. The most common adverse events that lead to dose modification (≥5%) were thrombocytopenia (29%), neutropenia (13%), lipase increased (11%), rash (11%), abdominal pain (10%), pancreatitis (6%), and ALT, AST, or GGT increased (6%).

Dr. Grillo (Clinical Pharmacology) agrees and stated the following in his review:

> "The reviewer finds that the proposed 45 mg daily dose is not supported by dose intensity-response relationship for efficacy and safety discussed below. A lower dose, especially for CP-CML patients, may offer a better benefit-risk profile. The reviewer agrees that a 45 mg QD dose is adequate for AP/BP CML patients. This dosing concern is strengthened by the fact that about 75% of patients had their dose reduced throughout above pivotal 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 optimal dose will

be explored further as a PMR through the collection of additional PK sampling in the ongoing phase 3 trial AP24534-12-301."

The Statistical review by Dr. Lee agreed with the efficacy conclusions by Dr. de Claro. Selected portions below are from the Executive Summary by Dr. Lee.

The starting dose was oral 45 mg once daily until progression. This study was conducted North America, Europe/Australia, and Asia. The primary objective was to examine the efficacy of ponatinib for patients with resistant or intolerant to dasatinib or nilotinib (R/I) or those with the T315I mutation (T315I). The primary endpoints were the major cytogenetic response (MCyR) rates based on the null and alternative rates of 20% and 35%, respectively in the R/I CP-CML cohort and 10% and 35%, respectively in the T315I CP-CML cohort and major hematologic response rates based on the null and alternative rates of 10% and 30%, respectively in the APCML and BP-CML/Ph + ALL cohorts.

For R/I CP-CML, the study met its objective in ruling out MCyR rates of 20% and 10%, respectively for the R/I and T315I cohorts. For R/I AP-CML disease, the study met its objective in ruling out MaHR rates of 10% for all cohorts. Given the applicant's analyses and the additional analyses performed by this reviewer, I conclude that the drug has shown activity in all the studied cohorts.

The key statistical issues and findings that impact demonstration of efficacy/safety were as follows:

- The primary endpoint of MCyR had a rate of 48.8 % in the R/I CP-CML patients (Cohort A) and 70.3% in the T315I CP-CML patients (Cohort B). The overall response rate for the CPCML was 53.9% with an exact 95% CI of (47.8, 60.0). The complete cytogenetic response (CCyR) rate for the entire CP-CML cohort was 44.2% (95% CI: 38.1, 50.4), 37.8% in the R/I CP-CML cohort (95% CI: 30.8, 44.1) and 65.6% in the T315I CP-CML patients (95% CI: 52.7, 77.1), respectively.
- The primary endpoint of MaHR had a rate of 60.0 % in the R/I AP-CML patients (Cohort C) and 50.0% in the T315I AP-CML patients (Cohort D). The overall response rate for the AP CML cohort was 57.8% with an exact 95 % CI of (46.5, 68.6). The complete hematologic response (CHR) rate for the AP-CML was 47.0% (95% CI: 35.9, 58.3), 46.2% in the R/I cohort (95% CI: 33.7, 59.0) and 50% in the T315I (95% CI: 26.0, 74.0), respectively. Based on FDA analyses, 43 patients (51.8%) had MaHR in the AP-CML. Among 43 MaHR, 36 (43.4%) had CHR and 7 patients (8.4%) had NEL. In the R/I cohort, 29 patients (44.6%) had CHR and 7 patients (10.8%) had NEL. In the T315I cohort, all 7 MaHR patients (38.9%) had CHR.
- The primary endpoint of MaHR had a rate of 35.4 % in the R/I BP-CML/Ph+ ALL patients (Cohort E) and 32.6% in the T315I BP-CML/Ph+ ALL patients (Cohort F). The overall response rate for the BP-CML/Ph+ ALL patients was 34.0 % with an exact 95 % CI of (24.6, 44.5). The CHR rate for the BP-CML/Ph+ ALL patients was 25.5% (95% CI: 17.1, 35.6), 27.1% in the R/I BP-CML/Ph+ ALL cohort (95% CI: 15.3, 41.9) and 23.9% in the T315I BP-CML/Ph+ ALL cohort (95% CI: 12.6, 38.8), respectively.

- The planned sample size of the AP-CML T315I cohort was 40 patients based on 10% of null MaHR rate and 30% of alternative MaHR rate with the power of 89% at an alpha of 0.05, but only 18 patients were used for analyses. Enrolling fewer patients into cohort AP-CML T315I than originally planned reduced the power/sensitivity to rule out a MaHR rate of 10%. However, the observed response rate in this cohort (and in the other cohorts) was much greater than the assumed response rate that was used to plan the sample size for the cohort. The 95% confidence interval for the MaHR rate in the AP-CML T315I cohort was (26%, 74%) easily ruling out a MaHR rate of 10%. Additionally, it should be noted that had the T315I cohort been fully enrolled to 40 patients without having any additional patients achieving a MaHR, the 95% confidence interval for MaHR rate would have been (11%, 38%) and thus, a 10% MaHR rate would have still been ruled out.
- As enrolment into the T315I cohort was still ongoing when enrolment into the R/I cohort had reached its planned sample size of 100, the sponsor continued enrolment into the R/I cohort. An additional analysis of MCyR was performed by the applicant based on the first 100 patients enrolled into the R/I cohort. The first 100 enrolled R/I CP-CML patients would have, on average, longer follow-up and would have had more time to achieve response. Recall that the data cutoff date was less than two months after the last patient was enrolled. The MCyR rate was 48.0% in the R/I CP-CML cohort based on the first 100 enrolled in the CP-CML R/I cohort. An analysis based on the planned sample size in an open-label setting can help verify the integrity of the results.
- An additional analysis of MaHR was performed by the applicant based on the first 40 patients enrolled into the R/I cohort and T315I BP-CML/Ph+ ALL cohort. An analysis based on the planned sample size in an open-label setting can help verify the integrity of the results. The first 40 enrolled into the cohort patients would have, on average, longer follow-up and would have had more time to achieve response. The MaHR rate was 60% in the R/I AP-CML cohort, 40% in the R/I BP-CML/Ph+ALL cohort and 30% in the T315I BP-CML/Ph+ALL cohorts, respectively. The sensitivity analysis results for 6 cohorts based on per-protocol populations were similar to the primary analysis results.

- For duration of MCyR in the CP-CML cohort, among 144 MCyR patients, 6 patients (4.2%) had events (5 from R/I and 1 from T315I). The median duration of MCyR was not reached for the entire CP-CML cohort. For duration of MaHR, among 48 MaHR patients in the APCML cohort, 22 patients (45.8%) had events (17 from R/I and 5 from T315I) and the median duration of MaHR in the AP-CML cohort was 9.5 months (9.5 months for R/I and 5.7 months for T315I). Among 32 MaHR patients in the BP-CML/Ph+ ALL cohorts, 17 patients (53.1%) had events (7 from R/I and 10 from T315I) and the median duration of MaHR in the BP-CML/Ph+ ALL cohorts was 4.7 months (NA for R/I and 4.1 months for T315I).

- The duration of MaHR based on FDA analysis, among 43 MaHR patients, 21 patients (48.8%) had events in the AP-CML cohort. The median duration of MaHR was 9.5 months based on FDA analysis in the AP-CML cohort. Among 32 MaHR patients, 21

patients (65.6%) had events in the BP-CML/Ph+ ALL cohorts. The median duration of MaHR was 3.5 months based on FDA analysis in the BP-CML/Ph+ ALL cohorts. Among 19 MaHR patients in the BP-CML cohort, 9 patients (47.4%) had events. Among 13 MaHR patients, 12 patients (92.3%) had events. The median MaHR were 4.7 months and 3.2 months, for the BP-CML and Ph+ ALL cohorts, respectively.

8. Safety

I concur with Dr. de Claro's conclusions regarding the safety review of ponatinib.

The following text is from the safety review by Dr. de Claro:

Safety Summary

The safety profile of Iclusig was evaluated in 449 patients with previously treated CML (all phases) or Ph+ALL enrolled in the Study 10-201, a single-arm Phase2 clinical trial. A summary of the key safety findings based on the original data cut-off date of April 27, 2012 are listed below:

- The ponatinib dose was 45 mg PO once daily. The median exposure duration was 9 months for patients with CP-CML or AP-CML, and 3 months for patients with BP-CML or Ph+ALL.

- The major safety issues identified include: arterial thromboembolic events (i.e., myocardial infarction, stroke, peripheral arterial disease), arterial stenosis, hepatic toxicity, myelosuppression, hemorrhage, pancreatitis, hypertension, congestive heart failure, supraventricular tachyarrhythmias (i.e., atrial fibrillation, atrial flutter, atrial tachycardia, supraventricular tachycardia), cardiac conduction defects including QTc prolongation, venous thromboembolism, tumor lysis syndrome, gastrointestinal perforation, compromised wound healing, and fluid retention.

- The cardiovascular safety profile for Iclusig is notable for arterial ischemic events. Based on the July 23, 2012 updated data cut-off date, 8% of patients experienced serious ischemic events. Arterial thromboembolic events have been reported with other kinase inhibitors that inhibit VEGF-receptor kinase activity.

- Seventy-three percent of patients required a dose modification due to adverse events. The most common adverse events that lead to dose modification include thrombocytopenia, neutropenia, lipase elevation, rash, abdominal pain, pancreatitis, and elevated liver enzymes.

- The 120-day safety update submission (data cut-off date July 23, 2012) was notable for the following: increase in frequency of arterial thromboembolic events compared to the original submission, and two cases of fatal acute hepatic failure.

The safety profile for Iclusig cannot be adequately evaluated in the single-arm clinical trials submitted in this application. Further characterization of the safety profile of Iclusig will be evaluated with the ongoing Phase 3 randomized active-controlled trial of Iclusig versus imatinib in patients with newly-diagnosed CML.

The safety population was defined as all patients who received at least 1 dose of study medication. Adverse events (AEs) and concomitant medications were collected from the time of informed consent through the 30-day Follow-up Visit.

Baseline Disease Characteristics of the Safety Population
The baseline disease characteristics and prior treatment history demonstrate a heavily-pretreated population. The median time from initial diagnosis for the overall population was 6.1 years.

The pharmacology-toxicology review noted a broad spectrum of kinase inhibition for ponatinib, which includes inhibition of the VEGFR-family of kinases. The safety profile for ponatinib is notable for similar features to kinase inhibitors active against the VEGFR-kinases. These similar features include arterial thromboembolic events, hypertension, gastrointestinal perforation, and compromised wound healing. The following listing includes FDA-approved drugs and biologics with anti-VEGF activity.

Dr. de Claro had the following recommendations regarding communication of the safety profile of ponatinib from this single-arm trial:

Labeling Recommendation: Box warning is recommended for arterial thromboembolic events and arterial stenosis due to the clinical severity of the events and potential for additional morbidity risk (including fatalities) with longer-term follow-up. Arterial ischemic events and arterial stenosis were observed in Study 10-201, 07-101, and in the expanded access program.

Reviewer Comment: Given the safety signal for recurrent ischemic events observed during ponatinib treatment, re-evaluation of benefit-risk should be done at the initial ischemic event. For patients with alternative treatment options, ponatinib discontinuation is recommended.

Reviewer Comment: Possible mechanisms of action for the arterial ischemic events and arterial stenosis include the broad spectrum of kinase inhibition, VEGFR-kinase inhibition, and insolubility of ponatinib in aqueous solutions. Ponatinib was designed to target native and mutated bcr-abl, however, in vitro testing revealed a broader spectrum of kinase inhibition, which included the VEGFR-family of kinases. Arterial ischemic events have been associated with kinase inhibitors that target VEGFR (refer to USPI for sorafenib, pazopanib, axitinib, and regorafenib). Also, the occurrence of other adverse events typically more associated with pan-kinase inhibition or VEGFR-kinase inhibition such as hypertension, proteinuria, oral mucositis, and gastrointestinal perforation, further supports the above hypothesis. Hypertension, arterial ischemic events, proteinuria, and gastrointestinal perforation have also been observed in drugs with VEGF-specific inhibition (i.e. bevazicumab and ziv-aflibercept).

However, the relative contribution of VEGFR-kinase inhibition cannot be determined. Another possible explanation may be the relative insolubility of ponatinib in aqueous solutions (Refer to Section 4.1 and **Error! Reference source not found.**). This insolubility may lead to precipitation of ponatinib in the circulation and subsequent deposition in areas of turbulent flow such as in the arterial system.

Labeling Recommendation: Box warning is recommended for hepatic toxicity given the cases of fatal acute hepatic failure and the frequency of hepatic transaminase elevation

Labeling Recommendation: The Applicant's proposed dose modifications for myelosuppression in the label are acceptable and are consistent with other drugs in this class.

Labeling Recommendation: Warnings and precautions section should be revised to provide more granular data regarding clinical course for pancreatitis and lipase elevation. Dose modification criteria should be modified to reflect actual practice observed in the clinical trial.

Reviewer Comment: Additional analysis using SMQ 13.0 algorithm method for acute pancreatitis was performed. Twenty-five patients who were classified as having "lipase elevation only" met the following SMQ criteria for pancreatitis: lipase elevation associated with a concurrent symptom (i.e., abdominal distention, abdominal pain, nausea, vomiting). A standard definition for pancreatitis for future or ongoing clinical trials with ponatinib would be helpful in further characterization of pancreatic events.

Reviewer Comment: Pancreatic events, mainly elevated lipase, have also been reported with imatinib, dasatinib, or nilotinib. The USPI for nilotinib includes lipase elevation in the Warnings and Precautions section.

Reviewer Comment: The association of treatment-emergent hypertension with ponatinib treatment is notable. The USPI for other FDA-approved TKIs for CML (imatinib, dasatinib, nilotinib, and bosutinib) do not include hypertension as a significant adverse event. However, other kinase inhibitors such as sorafenib, sunitinib, pazopanib, axitinib, and regorafenib are associated with hypertension. The broader spectrum of kinase inhibition observed with ponatinib as compared to other bcr-abl TKIs, may explain why hypertension was only observed with ponatinib. Specifically, inhibition of VEGF-pathway kinases would be consistent with VEGF-inhibitor like AEs observed with ponatinib such as arterial thromboembolic events and gastrointestinal perforation.

Reviewer Comment: Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES), is included in the USPI Warnings and Precautions of the following drugs that inhibit VEGF signaling: pazopanib, axitinib, regorafenib, bevazicumab, and ziv-aflibercept. No cases of RPLS have been reported in patients treated with ponatinib. Given that ponatinib inhibits VEGFR1 and VEGFR2, in addition to the strong association of ponatinib treatment with hypertension (a known risk factor for development for RPLS), a case could be made to include RPLS in the ponatinib label as an anticipated Warning and Precaution. This approach is recognized in the FDA

Guidance for Warnings and Precautions (Section II.A.3) wherein an anticipated adverse reaction may be included in the label.

Patients on ponatinib treatment who developed altered new-onset consciousness, visual disturbances, seizures, whether or not associated with hypertension should undergo urgent neuroimaging to evaluate for the presence for RPLS.

Reviewer Comment: The frequency of QTc prolongation and rhythm abnormalities (including conduction delays and supraventricular tachyarrhythmias) was likely underestimated in Study 10-201 due to the paucity of ECG monitoring. Also, ECG monitoring in Study 10-201 occurred predominantly at earlier timepoints. Only 22% of the patients had ECGs performed after day 90.

For further details, the reader is referred to the review by R. Angelo de Claro, MD.

9. Advisory Committee Meeting

The review team did not select this application for Advisory Committee discussion because the trial design was similar to those previously used to support accelerated approval in the Chronic Myelogenous Leukemia and Ph+ALL indications. Instead, the team decided to request Special Government Employee input from two clinical experts and a patient representative. See Section 2 for further information.

Results of Patient Advocate Consultation:

First, in answer to the question:
From a patient's perspective, please discuss the ***benefit-risk profile*** for Iclusig for 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.

> "From a patient perspective, the potential of benefits with Iclusig would most likely lead me to try it, particularly if I were a patient with the T3151 mutation. I would also be inclined to try it with AP-CML or BP-CML or with PH+ALL. As a chronic phase patient, I would choose to try other TKIs (probably 2) before trying this, due to what seems to me to be increased risk compared to the other treatments and longer term progression/survival/safety data available on other options. I could be wrong, but I don't recall as much cardiovascular risk associated with previous TKIs. I think CP-CML patient would most likely choose a medication with a longer history and more data. With the more difficult to treat

indications, Iclusig appears to have efficacy in a substantial number of patients. I'm excited to see what future research will show.

My comments are:
In this review, I wish Survival data and Duration data were broken down beyond CP-CML, AP-CML, BP-CML and PH+ALL, as I would really like to see response duration and survival data on the CML patients with the T3151 mutation.
In general, with oncologic drug improvements, there needs to be some line between resistent and intolerant. While I know risk and side effects are important to understand, it would paint a clearer picture to me to see efficacy from a drug in a patient population whose disease did not respond to prior therapies. It would also help compare drugs that might appear might have the same efficacy, but differences in side effects and risks.
Thank you so much and please let me know if you need additional information or have any questions. "

Pediatrics
Ponatinib has not been evaluated in pediatric patients. Ponatinib is exempt from the pediatric study requirements in 21CFR314.55 because it was granted orphan drug designation for the treatment of CML (09-2947) and Ph+ALL (09-2948) on 11/20/09. ARIAD does intend to submit a pediatric study request outlining proposed studies for ponatinib in the pediatric population in Q3 2012.

10. Other Relevant Regulatory Issues

Financial Disclosures: The Applicant submitted financial disclosure information from all 471 investigators. Only one investigator had financial interests to disclose, (b) (6) from site (b) (6). He disclosed that he has equity in ARIAD Pharmaceuticals, Inc valued in the amount of $120,488.56 in December 2011. Dr. (b) (6) site enrolled (b) (6) patients in Study (b) (6). The financial conflicts identified were not likely to have affected the results of the clinical trial because this Investigator only treated of the study patients.

GCP Issues:
Study 10-201 and Study 07-101
The protocol and its amendments, as well as the patient informed consent forms, were reviewed and approved by the Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) of the participating trial centers.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization (ICH), Good Clinical Practices (GCP), and, where applicable, the Food and Drug Administration (FDA) regulations (21 Code of Federal Regulations, Parts 50 and 56) for the protection of the rights and welfare of human patients participating in biomedical research.

All patients or their legal representatives voluntarily consented prior to enrollment in the study.

Clinical Site Inspections/DSI Audits:
The following sites were inspected by the FDA Office of Scientific Investigations (OSI) as part of the NDA review:

1. University of Texas MD Anderson Cancer Center (PI: Jorge Cortes, M.D.)

2. Moffitt Cancer Center (PI: Javier Pinilla-Ibarz, M.D., Ph.D.)

3. ARIAD Pharmaceuticals.

Based on the inspection findings for the clinical sites and the NDA Applicant, OSI determined that the clinical trial data collected appeared generally reliable.

There are no other outstanding regulatory issues with this application.

11. Labeling

- Proprietary name: Iclusig® was deemed acceptable by the Division of Medication Error Prevention and Analysis on 08/21/12 and the letter is in DARRTS.
- DDMAC was consulted for review of the product labeling. They attended labeling meetings and provided input into the label. The Division did not have major disagreements with their recommendations. The formal review has not been entered into DARRTS at the time of CDTL memo finalization.
- A Patient Labeling Consult Request was requested. The patient labeling group had input into the labeling discussions. The formal review has not been entered into DARRTS at the time of CDTL memo finalization.
- The Division of Professional Drug Promotion consultant (Gina McKnight) review was received and discussed in detail at the labeling meeting on 11/29/12. The recommendations were integrated into the labeling where appropriate.
- An OSE consult was submitted on 08/14/12. The DRISK review was entered to DARRTS on 11/28/12. The review stated that DRISK does not recommend a REMS for ponatinib.
- The DMEPA review was put into DARRTS on 11/27/12. Their recommendations for changes to the carton and container were sent to the Sponsor.

- Physician labeling:
    - On 11/14/12, Ariad submitted a waiver request from the one-half page highlights requirements of 21 CFR 201.58. This was requested because of the need to include all of the information required in this section (e.g., Indication and Use, Dosage and Administration, Warnings and Precautions, Adverse Reactions).
    - The proposed PI that was submitted by Ariad with the NDA was found to be substantially deficient with regard to the safety information provided. The label was rejected by the Division, a Face to Face meeting was requested by the Division and a briefing document was sent to the Applicant in advance of the meeting. The Division had a face-to-face meeting with ARIAD to discuss the benefit-risk of ponatinib for ARIAD's proposed indication. Specifically, the Division discussed its concerns regarding the risks including liver failure, arterial occlusive and thromboembolic events observed in the safety population. The Sponsor also discussed its position described in a formal written response to the Division.

    In conclusion, The Division asked the Sponsor to Submit a revised proposed labeling (PI and PPI) that includes the safety issues identified by the Division as described in the FDA meeting package. The Sponsor agreed to provide a revised label to the FDA.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Accelerated Approval for "Patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL resistant or intolerant to prior tyrosine kinase inhibitor therapy"

- Risk Benefit Assessment

With the amended labeling, the risk/benefit assessment is favorable for Iclusig in the indication sought. The response rates demonstrated in the PACE trial were higher than drugs that we have previously approved for CML or Ph+ALL. The single-arm trial safety data submitted for review cannot adequately describe the risks associated with Iclusig use. The Division opted caution in labeling Iclusig by not allowing for Investigator attribution of toxicities. The ongoing randomized trial should further clarify the risks associated with Iclusig.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The Applicant did not propose a REMS and the Division did not conclude that a REMS was needed.

Recommendation for MedGuide: The Division decided that a MedGuide will be included with the labeling to ensure that patients receive written advisories about the risks of Iclusig.

- Recommendation for other Postmarketing Requirements and Commitments (see below)

FDA proposed Post Marketing Requirements for NDA 203469/ Iclusig® (Ponatinib tablets)

PMR (1) Description:	Longer duration followup: (Under Subpart H) Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of Study AP24534-10-201 with 24 months of minimum follow-up for each patient. If 24 months of follow-up is not possible for certain patients, provide justification for each patient.	
PMR Schedule Milestones:	Final Protocol Submission:	06/2012 (submitted)
	Study/Trial Completion:	12/2013
	Final Report Submission:	06/2014

PMR (2) Description:	(Under FDAAA): Submit 12 months of safety follow-up for all ongoing patients the randomized controlled trial AP24534-12-301 that isolates the effect of the drug adequately to characterize the safety of Iclusig	
PMR Schedule Milestones:	Final Protocol Submission:	04/2013
	Study/Trial Completion:	08/2015
	Final Report Submission:	02/2016

PMR (3) Description:	(Under FDAAA): Assess the QT effect of Iclusig	
PMR Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY
	Other: _____	MM/YYYY

PMR (4) Description:	(Under FDAAA): Characterize the effect of Iclusig on platelet function by evaluating the effect of ponatinib on platelet aggregation *in vitro*.	
PMR Schedule Milestones:	Final Protocol Submission:	02/2013
	Study Completion:	09/2013
	Final Report Submission:	12/2013

PMR (5) Description:	(Under FDAAA): 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.	
PMR Schedule Milestones:	Preliminary Protocol Submission	06/2012 (submitted)
	Final Protocol Submission:	06/2012
	Study/Trial Completion:	06/2013
	Final Report Submission:	12/2013

PMR (6) Description:	(Under FDAAA): 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.	
PMR Schedule Milestones:	Preliminary Protocol Submission	06/2012 (submitted)
	Final Protocol Submission:	06/2012
	Study/Trial Completion:	06/2013
	Final Report Submission:	12/2013

PMR (7) Description:	(Under FDAAA): To characterize exposure:response for ponatinib: Collect sparse PK from ponatinib treated patients in your ongoing trial AP24534-12-301. 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 necessary.	
PMR Schedule Milestones:	Preliminary Protocol Submission	02/2013
	Final Protocol Submission:	04/2013
	Study/Trial Completion:	08/2015
	Final Report Submission:	02/2016

PMR (8) Description:	(Under FDAAA): Conduct a dedicated clinical trial in humans to determine the effect of multiple doses of lansoprazole on the pharmacokinetics of ponatinib in healthy subjects.	
PMR Schedule Milestones:	Preliminary Protocol Submission	06/2012 (submitted)
	Final Protocol Submission:	06/2012
	Study/Trial Completion:	06/2013
	Final Report Submission:	12/2013

FDA proposed Post Marketing Commitments for NDA 203469/ Iclusig® (Ponatinib tablets)

PMC (1) Description:	Evaluate the in vitro potential for the displacement of ponatinib, at a therapeutic concentration, from its protein binding sites in human plasma following addition of frequently used highly protein-bound co-medications. Positive findings from this in vitro study may require additional trials in vivo.	
PMC Schedule Milestones:	Preliminary Protocol Submission	02/2013
	Final Protocol Submission:	04/2013
	Study/Trial Completion:	01/2014
	Final Report Submission:	03/2014

The rationale for the trials is provided next to the title of each PMR. At the time of finalization of this memo, the PMRs were not all agreed upon. The Applicant has further questions regarding the QT PMR.

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/s/

VIRGINIA E KWITKOWSKI
12/03/2012