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RESEARCH**

APPLICATION NUMBER:

203469Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA #/Product Name: NDA 203469/ Iclusig[®] (Ponatinib tablets)

PMR Description: To characterize exposure:response for ponatinib:
Collect sparse PK from ponatinib treated patients in the ongoing trial AP24534-12-301 to characterize exposure-response for Iclusig[®] (ponatinib).
The 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	<u>02/2013</u>
	Final Protocol Submission:	<u>04/2013</u>
	Trial Completion:	<u>08/2015</u>
	Final Report Submission:	<u>02/2016</u>
	Other: _____	<u>MM/YYYY</u>

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

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

There is an unmet medical need for drugs to treat of (b) (4) CML and Ph+ALL patients. This drug has received orphan status for the later and is being considered for accelerated approval with limited data.

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

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Exploratory dose intensity-response analyses of efficacy and safety endpoints from trial 201 indicated that a lower dose of ponatinib may have a better benefit-risk profile for the indication of CML or Ph+ALL. Dose intensity-safety relationships indicated that there is a significant increase in Grade ≥ 3 adverse events (thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression) with an increase in dose. Moreover, about 75% of patients received dose reductions from 45 mg during the trial due to adverse events. Forty nine percent of patients required dose reduction to 30 mg while 25% patients required dose reduction to 15 mg.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

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The PMR describe above recommends the sponsor to collect sparse PK in all patients from a clinical trial such as their ongoing trial AP24534-12-301 and to perform exposure-response analysis for efficacy and safety.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Sponsor is conducting a trial to evaluate ponatinib in adult patients with newly diagnosed chronic myeloid leukemia in chronic phase. We are recommending sponsor to collect sparse PK in all patients to conduct exposure-response analysis for efficacy and safety to explore a possibility of a lower dose or an alternate dosing regimen.
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

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

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

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

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PMR/PMC Development Coordinator:

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

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/s/

MONSURAT O AKINSANYA
12/14/2012

PMR/PMC Development Template

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

NDA #/Product Name: NDA 203469/ Iclusig® (Ponatinib tablets)
PMR Description: 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	<u>06/2012</u>
Final Protocol Submission:	<u>06/2012</u>
Study/Trial Completion:	<u>06/2013</u>
Final Report Submission:	<u>12/2013</u>
Other: _____	<u>MM/YYYY</u>

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

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

There is an unmet medical need for drugs to treat of (b) (4) CML and Ph+ALL patients. This drug has received orphan status for the later.

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

In vitro studies suggest ponatinib is a substrate of CYP3A4 with approximately 52% of it metabolism occurring via this pathway. FDA generated simulations from a physiologically based pharmacokinetic (PBPK) model, that reasonably predicts ponatinib PK alone and following inhibition by a strong CYP3A4 inhibitor, suggests that a 52% reduction in ponatinib’s C_{max} and a 71% reduction in ponatinib’s AUC may be expected following induction by a strong CYP3A4 inducer. Assuming dose proportionality, this implies that the exposure following dosing at the proposed 45 mg dose under strong CYP3A4 induction would potentially result in an AUC that would normally be seen at a dose less than 15 mg. The FDA pharmacometric analysis suggests reduced efficacy with doses below 15 mg in the chronic phase CML population.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An open-label, non-randomized, 2-period, fixed order crossover, inpatient/outpatient study to be performed in healthy subjects. The study will consist of 2 treatment periods separated by a 13-day washout period between ponatinib doses. Each subject will participate in the study for approximately 6 weeks. Approximately 20 healthy subjects will be enrolled, with the intent to ensure evaluable data from at least 16 subjects.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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PMR/PMC Development Coordinator:

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

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MONSURAT O AKINSANYA
12/14/2012

PMR/PMC Development Template

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

NDA #/Product Name: NDA 203469/ Iclusig® (Ponatinib tablets)

PMR Description: 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	<u>06/2012</u>
	Final Protocol Submission:	<u>06/2012</u>
	Trial Completion:	<u>06/2013</u>
	Final Report Submission:	<u>12/2013</u>
	Other: _____	<u>MM/YYYY</u>

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

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

There is an unmet medical need for drugs to treat of (b) (4) CML and Ph+ALL patients. This drug has received orphan status for the later.

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

The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility. Drugs that elevate the gastric pH may reduce its bioavailability.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An open-label, non-randomized, 2-period, fixed order, crossover, inpatient/outpatient study to be performed in healthy subjects. The study will consist of 2 treatment periods separated by a 14-day washout period between ponatinib doses. Approximately 20 healthy subjects will be enrolled, with the intent to ensure evaluable data from at least 16 subjects.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
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 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

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

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MONSURAT O AKINSANYA
12/14/2012

PMR/PMC Development Template

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

NDA # 203469
Product Name: Iclusig

PMR (4) Description: Longer duration followup:
Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of Study 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:	<u>06/2012</u>
Trial Completion:	<u>12/2013</u>
Final Report Submission:	<u>06/2014</u>
Other:	<u>MM/YYYY</u>

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

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

CML and Ph+ ALL are life-threatening conditions. In Study 10-201, there were 89 deaths on overall survival analysis: 17 in patients with CP-CML (6%), 12 in patients with AP-CML (14%), 43 in patients with BP-CML (69%), and 17 in patients with Ph+ ALL (53%). Patients with T315I-mutant CML and Ph+ALL have an unmet medical need because there are no drugs approved for the treatment of T315I-mutant CML or Ph+ ALL and the drugs that are currently approved for CML are not active in the patients who have the mutation.

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

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OHOP has previously accepted 2 year efficacy and safety follow-up for conversion of accelerated approval to regular approval for bcr-abl tyrosine kinase inhibitors to treat CML. The goal for this PMR would be to obtain 2-year follow-up data from Study 10-201.

Also, for this approval, the Applicant will be required to submit the results of a randomized trial (PMR2) in addition to PMR1 for conversion to regular approval.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Two-year follow-up of results of Study 10-201 (ongoing).

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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)
2-year follow-up of Study 10-201
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

Other

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

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

PMR/PMC Development Coordinator:

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

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MONSURAT O AKINSANYA
12/14/2012

PMR/PMC Development Template

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

NDA/BLA #	203469
Product Name:	Iclusig
PMR (5) Description:	Characterize the effect of Iclusig [®] (ponatinib) on platelet function by evaluating the effect of Iclusig [®] (ponatinib) on platelet aggregation <i>in vitro</i>
PMR Schedule Milestones:	Final Protocol Submission: <u>02/2013</u>
	Study/Trial Completion: <u>09/2013</u>
	Final Report Submission: <u>12/2013</u>
	Other: _____ <u>MM/YYYY</u>

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

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

CML and Ph+ ALL are life-threatening conditions. In Study 10-201, there were 89 deaths on overall survival analysis: 17 in patients with CP-CML (6%), 12 in patients with AP-CML (14%), 43 in patients with BP-CML (69%), and 17 in patients with Ph+ ALL (53%). Patients with T315I-mutant CML and Ph+ALL have an unmet medical need because there are no drugs approved for the treatment of T315I-mutant CML or Ph+ ALL and the drugs that are already approved for CML are ineffective in patients with the mutation.

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

FDAAA PMR: Risk of platelet dysfunction

Hemorrhagic events occurred in patients on Iclusig treatment even during periods where platelet counts were $\geq 50 \times 10^9/L$. Neelakantan published a description of 5 patients treated with Iclusig who developed prolonged closure times on PFA-100 testing. Further characterization of the effect of Iclusig on platelet function is also recommended due to concomitant requirement for anti-platelet drugs in patients who develop ischemic events.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required:

1. *in vitro* platelet function assay

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

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MONSURAT O AKINSANYA
12/14/2012

PMR/PMC Development Template

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

NDA #/Product Name: NDA 203469/ Iclusig[®] (Ponatinib tablets)

PMR 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.

PMR Schedule Milestones:	Preliminary Protocol Submission	<u>02/2013</u>
	Final Protocol Submission:	<u>04/2013</u>
	Study Completion:	<u>01/2014</u>
	Final Report Submission:	<u>03/2014</u>
	Other:	<u>MM/YYYY</u>

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
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There is an unmet medical need for drugs to treat of (b) (4) CML and Ph+ALL patients. This drug has received orphan status for the later.

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

Ponatinib is highly protein bound. However, the potential for displacement of ponatinib from its protein binding sites by other highly protein-bound comedications, thus increasing free (i.e., active) ponatinib exposure, is unknown. Assuming the proposed 45 mg daily dose, dose proportionality, and 99.92% plasma protein binding, then a decrease in the bound fraction from 99.92% to 99.89% would theoretically result in free drug exposures similar to that expected at the doses exceeding the MTD as defined by the applicant. Further, a reviewer initiated descriptive exploratory analysis of patients requiring dose modification versus aspirin use in the pivotal trial AP24534-10-201 suggest that approximately 70% of patients who received aspirin required a dose reduction compared to approximately 50% who did not received aspirin.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

In vitro study of 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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

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(signature line for BLAs)

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/s/

MONSURAT O AKINSANYA
12/14/2012

PMR/PMC Development Template

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

NDA #/Product Name: NDA 203469/ Iclusig® (Ponatinib tablets)

PMR Description: Conduct a dedicated hepatic impairment trial, since drug clearance may be reduced with 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	<u>06/2012</u>
	Final Protocol Submission:	<u>06/2012</u>
	Study/Trial Completion:	<u>06/2013</u>
	Final Report Submission:	<u>12/2013</u>
	Other: _____	<u>MM/YYYY</u>

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

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

There is an unmet medical need for drugs to treat of (b) (4) CML and Ph+ALL patients. This drug has received orphan status for the later.

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

Fecal elimination is the major excretion pathway for ponatinib. In a human mass balance trial fecal excretion accounted for 86.6% of the radioactive ponatinib dose (b) (4) following a 336 hour total sampling period. The applicant states in its clinical pharmacology summary, “cumulative phase 1 safety data were consistent with 60 mg (a 33% increase above the proposed dose) exceeding the maximum tolerated dose (MTD). A clinical trial of CYP3A4 inhibition (one metabolic pathway) results in exposures exceeding what would be expected from a 33% dose increase. It is possible that hepatic impairment, where all metabolic pathways may be effected, can meet or exceed this value.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An open-label, single-dose, parallel-group, inpatient, nonrandomized study conducted in patients with chronic hepatic impairment and in healthy subjects at a single investigational site. Patients with hepatic impairment (3 Child-Pugh categories) will be matched with healthy subjects by age, sex, body mass index (BMI), and, if possible, smoking habits. A total of 27 study participants will be enrolled in the study, including 18 subjects with hepatic impairment (6 each with Child-Pugh classes A, B, and C) and 9 matched healthy controls.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

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

Continuation of Question 4

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

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

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

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

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

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

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

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

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

 RCK
(signature line for BLAs)

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/s/

MONSURAT O AKINSANYA
12/14/2012

PMR/PMC Development Template

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

NDA # 203469
Product Name: Iclusig

PMR (8) Description: To characterize the safety of Iclusig[®] (ponatinib), submit longer safety follow-up data of at least 12 months for all ongoing patients in the randomized controlled trial AP24534-12-301 that adequately isolates the effect of the drug.

PMR Schedule Milestones:	Final Protocol Submission:	04/2013
	Trial Completion:	08/2015
	Final Report Submission:	02/2016
	Other: _____	MM/YYYY

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

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

CML and Ph+ ALL are life-threatening conditions. In Study 10-201, there were 89 deaths on overall survival analysis: 17 in patients with CP-CML (6%), 12 in patients with AP-CML (14%), 43 in patients with BP-CML (69%), and 17 in patients with Ph+ ALL (53%). Patients with T315I-mutant CML and Ph+ALL have an unmet medical need because there are no drugs approved for the treatment of T315I-mutant CML or Ph+ ALL and the drugs that are approved for CML are ineffective in patients with the mutation.

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

DHP identified safety concerns with Iclusig which 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.

DHP cannot adequately assess these safety concerns because the efficacy data comes from single-arm clinical trials such as the ongoing Study 10-201 clinical trial. The Applicant has initiated Study 12-301, a Phase 3 randomized clinical trial of ponatinib vs. imatinib in patients with newly-diagnosed CP-CML but safety characterization of the drug is not yet available.

In addition, the Applicant should modify existing clinical trial to include safety monitoring for treatment-emergent thyroid dysfunction, proteinuria, fasting hyperglycemia, and dyslipidemia. Refer to PMR3 for additional ECG monitoring.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required: Clinical Study Report of Study 12-301 (interim and final)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

-
- Other
-

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

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

PMR/PMC Development Coordinator:

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

RCK _____
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/s/

MONSURAT O AKINSANYA
12/14/2012

PMR/PMC Development Template

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

NDA #	203469
Product Name:	Iclusig
PMR (9) Description:	Conduct a QT analysis of patients in trial AP24534-12-301 to assess the QT effects of Iclusig® (ponatinib)
PMR Schedule Milestones:	Final Protocol Submission: 04/2013
	Trial Completion: 08/2015
	Final Report Submission: 02/2016
	Other: _____ MM/YYYY

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

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

CML and Ph+ ALL are life-threatening conditions. In Study 10-201, there were 89 deaths on overall survival analysis: 17 in patients with CP-CML (6%), 12 in patients with AP-CML (14%), 43 in patients with BP-CML (69%), and 17 in patients with Ph+ ALL (53%). Patients with T315I-mutant CML and Ph+ALL have an unmet medical need because there are no drugs approved for the treatment of T315I-mutant CML or Ph+ ALL and the drugs that are already approved for CML are ineffective in patients with the mutation.

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

FDAAA PMR: Risk of QTc prolongation

Twenty-five patients (6%) in Study 10-201 experienced treatment-emergent QTc prolongation. There were no cases of *Torsades de Pointes* in the safety population of 530 patients. Given the additional safety signal for myocardial ischemia which would further increase risks for ventricular tachycardia or fibrillation, adequate characterization of the effect of Iclusig on the QT interval is required.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required:

1. single-dose QT study in healthy volunteers
2. steady-state QT study in Iclusig arm of Study 12-301

Applicant should amend Study 12-301 to continue monthly ECG monitoring beyond cycle 3, and include sparse PK sampling.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

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

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)
QT data from Study 12-301
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

Other

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

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

PMR/PMC Development Coordinator:

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

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/s/

MONSURAT O AKINSANYA
12/14/2012

PMR/PMC Development Template

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

NDA #/Product Name: NDA 203469/ Iclusig® (Ponatinib tablets)

PMC Description: Submit an updated method “*Identification, Content Uniformity, Assay and Impurities Method for Ponatinib (AP24534) Tablets, 15mg and 45 mg*” (AM1281) to the application via a Supplement, Changes Being Effectuated – 30 Days (CBE-30)

PMC Schedule Milestones:	Preliminary Protocol Submission	N/A
	Final Protocol Submission:	N/A
	Study Completion:	N/A
	Final Report Submission:	02/2013

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

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

There is an unmet medical need for drugs to treat of (b) (4) CML and Ph+ALL patients. This drug has received orphan status for the later.

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

For CMC PMC see #4 – “Other”

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
In vitro binding displacement
 - Other
The applicant agreed to modify method “*Identification, Content Uniformity, Assay and Impurities Method for Ponatinib (AP24534) Tablets, 15 mg and 45 mg*” (AM1281) to include the impurity marker preparation procedure.
-

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

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

PMR/PMC Development Coordinator:

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

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MONSURAT O AKINSANYA
12/14/2012

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

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

Memorandum

Date: **December 4, 2012**

To: Lara Akinsanya, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Richard Lyght, Pharm.D. – Regulatory Review Officer
Division of Direct to Consumer Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft Iclusig (ponatinib) tablet for oral use Medication Guide

This consult is in response to DHP's August 14, 2012, request for OPDP review of the draft Iclusig Medication Guide. DCDP comments are based on the proposed draft marked-up labeling submitted by DMPP December 3, 2012.

We have made comments directly on the draft labeling below.

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Richard Lyght at 301-796-2874 or at richard.lyght@fda.hhs.gov.

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

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/s/

RICHARD A LYGHT
12/04/2012

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

PATIENT LABELING REVIEW

Date: December 3, 2012

To: Ann T. Farrell, M.D.
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): Iclusig (ponatinib)

Dosage Form and Route: Tablets for oral use

Application Type/Number: NDA 203-469

Applicant: ARIAD Pharmaceuticals Inc.

1 INTRODUCTION

On July 13, 2012 the Agency granted ARIAD Pharmaceuticals Inc.'s proposal to submit their Original New Drug Application (NDA) 203-469, for Iclusig (ponatinib) Tablets, as a Rolling Review consisting of two submissions. The initial portion of this rolling NDA was submitted on July 30, 2012, and the final portion was submitted on September 27, 2012. The Applicant seeks priority review for Iclusig (ponatinib) Tablets for the proposed indication of 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.

On November 15, 2012, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Iclusig (ponatinib). Based on discussions at the November 20, 2012 labeling meeting, DHP agreed with DMPP's recommendation to convert the Applicant's submitted PPI to a Medication Guide (MG). The recommendation was made to ensure that patients will be provided with information about the serious risks associated with the drug, based on the Boxed Warning in the Prescribing Information (PI).

This review is written in response to a request by DHP for DMPP to review the Applicant's proposed PPI for Iclusig (ponatinib), and to convert it to a MG.

2 MATERIAL REVIEWED

- Draft Iclusig (ponatinib) Tablets Patient Package Insert (PPI) received on July 30, 2012 and received by DMPP on November 26, 2012.
- Draft Iclusig (ponatinib) Prescribing Information (PI) received on July 30, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on November 26, 2012.
- Approved TASIGNA (nilotinib) comparator labeling dated May 1, 2012, and Approved STIVARGA (regorafenib) comparator labeling dated September 27, 2012.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more

accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review, we converted the PPI to a MG as requested by DHP, and have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

BARBARA A FULLER
12/03/2012

SHARON R MILLS
12/03/2012

LASHAWN M GRIFFITHS
12/03/2012



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: November 30, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Lara Akinsanya, RPM
DDOP

Subject: QT-IRT Consult to NDA 203469

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

This memo responds to your consult to us dated August 14, 2012 regarding sponsor's response. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT consult review, February 12, 2012 (under IND 78375)
- Study AP24534-07-101 (CSR, Section 14.3.3)

QT-IRT Comments for NDA 203469

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.

BACKGROUND

QT-IRT reviewed study AP24534-07-101 and concluded that an additional dedicated QTc study may not be necessary for ponatanib. However QT-IRT's final decision on whether to waive a dedicated QT study was to be made once all data are available, since sponsor did not provide the ECGs and adverse event data and intended to submit it as part of the NDA submission.

Sponsor's proposed label



Data submitted by the sponsor

Safety Analysis

In this submission sponsor provided the following safety information concerning study AP24534-07-101

Table 1 Summary of Narrative Patients (from Narrative Patient Data)

Summary of Adverse Events	Number of Patients	Number of Events
Adverse Events	60	250 ₂
Serious Adverse Events	57	228 ₁
Discontinued Due to Adverse Events	21	42 ₁
Adverse Events with Outcome of Death	17 ₄	21
Adverse Event of Special Interest	6 ₃	8 ₃

¹ 005-0008 pancreatitis on (b) (6) was removed from the clinical db & 011-0004 dyspnea on (b) (6) was changed to (b) (6) following the data close of 23 Mar 2012.

² Fifteen patients were removed due to non-serious tachycardia determined not to be ventricular, an event of special interest

³ Events counted manually: 011-007 ventricular tachycardia, 011-0020 ventricular tachycardia, 011-008 syncope, 011-0013 syncope x3, 011-0009 convulsion, 048-0005 convulsion.

⁴ Deaths due to Neoplasm Progression within (b) (6) days of discontinuation of study drug = 7 patients, 005-007, 005-0014, 005-0030, 005-0031, 048-0006, 011-0009, 011-0018. All except 011-0009, 011-0018 discontinued due to this event.

Review of Narratives

Ventricular tachycardia: There were two reports of ventricular tachycardia (subjects 011-0007 and 011-0020). In subject 011-007 the event took place more than 10 days after discontinuation of study medication and was confounded by a pre-existing condition, i.e. a cardiologist diagnosed a non-occlusive coronary disease and concomitant medications such as ondansetron. For subject 0020 the event took place (b) (6) days after study drug discontinuation and subject was taking tramadol which can prolong the QT interval (tramadol-subject 011-0020).

Syncope: Subject 011-008 experienced syncope while on study medication. Investigator reports that event was associated with hypoglycemia. Event is confounded by remarkable history of chronic A-Fib and moderate aortic stenosis. Subject 011-0013 suffered three episodes of syncope while on study drug that were confounded by concomitant medications and co-morbidities (pancreatitis and bacteremia/sepsis).

Review of ECG assessment

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. Statistics shows that less than 2% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

Thank you for requesting our input into the development of this product under NDA. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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/s/

MONICA L FISZMAN
11/30/2012

KEVIN M KRUDYS
11/30/2012

NORMAN L STOCKBRIDGE
11/30/2012

1
2 *****Pre-decisional Agency Information*****
3
4

5 Memorandum

6 **Date:** November 29, 2012
7
8 **To:** Lara Akinsanya, Regulatory Project Manager
9 Division of Hematology Products (DHP)
10
11 **From:** Gina McKnight-Smith, Regulatory Review Officer
12 Division of Professional Drug Promotion (DPDP)
13
14 Kathleen Davis, Regulatory Review Officer, DPDP
15 Division of Professional Drug Promotion (DPDP)
16
17 **CC:** Karen Rulli, Professional Review Team II Leader, DPDP
18
19
20
21 **Subject:** Comments on draft labeling (Package Insert) for Iclusig® (ponatinib) Tablet for Oral Use
22 NDA 203469
23

24
25 In response to your consult dated August 4, 2012, we have reviewed the draft Package Insert (PI) for
26 Iclusig and offer the following comments. DPDP has made these comments using the PI version
27 provided via email link on November 26, 2012.
28

29 Thank you for the opportunity to consult on this proposed labeling
30

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/s/

GINA P MCKNIGHT-SMITH
11/29/2012

KATHLEEN T DAVIS
11/29/2012

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

Label and Labeling Review

Date: November 26, 2012

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

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

Division Director: Carol A. Holquist, RPh.
Division of Medication Error and Prevention Analysis

Drug Name and Strength: Iclusig (Ponatinib) Tablets
15 mg, 45 mg

Application Type/Number: NDA 203469

Applicant/sponsor: Ariad Pharmaceuticals

OSE RCM #: 2012-1926

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

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1 INTRODUCTION

This review evaluates the proposed container label, carton, (b) (4) and insert labeling for Iclusig NDA 203469 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted labels and labeling for Iclusig (Ponatinib) under NDA 203469 submitted on July 30, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the July 30, 2012 original NDA submission.

- Active Ingredient: Ponatinib
- Indication of Use: 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.
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 15 mg, 45 mg
- Dose and Frequency: Take 45 mg by mouth daily; if toxicities occur, decrease the dose to 30 mg once daily or 15 mg once daily.
- How Supplied:
 - 15 mg: 60 count and 180 count bottles
 - 45 mg: 30 count and 90 count bottles
- Storage: Store at 20° C to 25° C (68° F to 77° F); excursions permitted to 15° to 30° C (59° F to 86° F)
- Container and Closure System: Child resistant (HDPE) bottles

2 METHODS AND MATERIALS REVIEWED

We reviewed the Iclusig container labels, carton and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

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

- Container Labels submitted November 7, 2012 (Appendices A and B)
- Insert Labeling submitted July 30, 2012.

3 RESULTS AND RECOMMENDATIONS

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

- A. Container Labels 15 mg and 45 mg
1. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
 2. Delete the line that appears between the proprietary name and the established name as it is intervening matter in accordance with 21 CFR 201.10(a).
 3. Remove the route of administration “for oral use” from the finished dosage form statement. The route of administration should appear on the label if the intended route of administration is other than oral.
 4. Delete the yellow graphic that appears above the letter ‘i’ in the proprietary name as this graphic distracts the end user’s attention from the proprietary name, making it difficult to read.
 5. Revise the proprietary name on the container label to title case (i.e. Iclusig) to improve the readability of the proprietary name.
 6. Revise the container label to follow the recommended format: proprietary name followed by established name and dosage form immediately underneath the proprietary name. For example,

Iclusig
(Ponatinib) Tablets
 7. Delete or minimize the red circle graphic in the Applicant’s logo appearing below the statement of strength on the container label. This graphic distracts from the most important information on the principle display panel such as the proprietary name, established name, and statement of strength.

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

8. The proprietary name and the 45 mg strength share the same blue color font. However, the use of the same color font for the proprietary name and product's strength minimizes the difference between the strengths, which may lead to wrong strength selection errors. Thus, revise the color font of the proprietary name or the 45 mg strength, so that the strength and the proprietary name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.
9. Remove the (b) (6) the Dosage and Use information. This is standard information that appears on all labels; thus, does not require special highlighting.
10. Move NDC number to be further away from the net quantity. Currently, NDC number and the net quantity appear together, which reduces the readability of the NDC number.
11. Unbold the statement of net quantity. Currently the net quantity is in bold font and has more prominence than other important information such as established name and NDC number.

B. Insert Labeling

1. Section 2: Dosage and Administration

- a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.² As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:
 - Revise all instances of trailing zeroes appear in Section 2.1 (Dose Modifications),. Trailing zeros are dangerous dose designations that could be misinterpreted as a 10 fold dose if the trailing zero is not seen (e.g., 2.0 times institutional upper limit of normal (IULN) may be misinterpreted as 20 times the IULN in Section 2.1).
 - Revise the '<' and '≥' symbols appearing in the body of the text of sections 2.1 (Dose Modifications), to read "less than" and "greater than or equal to".
 - We note the use of the abbreviations throughout the insert labeling. Prior to the use of these abbreviations, the Applicant should provide the intended meaning to mitigate confusion and misinterpretation [e.g. Absolute neutrophile count (ANC)].

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

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

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/s/

KEVIN WRIGHT
11/26/2012

YELENA L MASLOV
11/26/2012

CAROL A HOLQUIST
11/27/2012

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

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

Application: 203469

Application Type: New NDA

Name of Drug: Iclusig[®] (ponatinib) Tablet for Oral Use

Applicant: ARIAD Pharmaceuticals

Submission Date: September 27, 2012

Receipt Date: September 27, 2012

1.0 Regulatory History and Applicant's Main Proposals

Iclusig[®] Ponatinib is a novel synthetic orally-active tyrosine kinase inhibitor (TKI) intended 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.

ARIAD is seeking *accelerated approval*. Ponatinib received orphan drug designation the treatment of CML and Ph+ALL on 20 November 2009, therefore this NDA is not subject to an application fee and is exempt from the pediatric assessment.

2.0 Review of the Prescribing Information (PI)

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

3.0 Conclusions/Recommendations

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

All SRPI format deficiencies of the PI were conveyed to the applicant in an Information Request dated September 17, 2012. The applicant was asked to correct these deficiencies and resubmit the PI in Word format by September 28, 2012. A revised PI addressing all the noted deficiencies was submitted by the applicant on September 27, 2012.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

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

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

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

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

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

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

Comment:

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

Comment:

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

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

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

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

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

Comment:

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment: *Name of product were not in uppercase*

Product Title

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

Comment:

Initial U.S. Approval

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

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC)

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Indications and Usage

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

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

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

Comment:

Contraindications

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

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

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

Comment:

Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

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

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

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

Comment: *Patient Package Insert was submitted and this section did not reflect addition of FDA-approved patient labeling.*

Revision Date

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

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Section 12.4 was used for Cardiac Electrophysiology

YES

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

Comment:

YES

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A

42. All text is **bolded**.

Comment:

N/A

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

Comment:

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES

45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

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

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

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *Did not include Patient Information in parenthesis*

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

/s/

MONSURAT O AKINSANYA
10/05/2012

JANET K JAMISON
10/05/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 203469 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Iclusig Established/Proper Name: Ponatinib Dosage Form: Tablets for oral use Strengths: 15 mg and 45 mg		
Applicant: ARIAD Pharmaceuticals Agent for Applicant (if applicable): N/A		
Date of Application: September 27, 2012 Date of Receipt: September 27, 2012 Date clock started after UN:		
PDUFA Goal Date: March 27, 2013	Action Goal Date (if different): November 15, 2012	
Filing Date: November 26, 2012	Date of Filing Meeting: August 29, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): 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.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				N/A – not on AIP list
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?				N/A – Orphan Designation

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>✓</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>✓</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>✓</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>✓</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>✓</p>																		

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

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

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			✓	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			✓	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			✓	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			✓	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			✓	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	✓			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			✓	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			✓	
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>		✓		Orphan Drug
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?			✓	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			✓	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			✓	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		✓		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	✓			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		✓		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels			

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

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

	<input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				N/A
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			✓	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			✓	

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

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			✓	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	✓			CDRH – 8/22/12 ORP- 8/22/12 QT-IRT- 8/14/12
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		✓		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): February 16, 2012	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		✓		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 29, 2012

NDA #: 203469

PROPRIETARY NAME: Iclusig

ESTABLISHED/PROPER NAME: Ponatinib

DOSAGE FORM/STRENGTH: 15 and 45mg tablets for oral use

APPLICANT: ARIAD Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

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.

BACKGROUND: On July 30, 2012, ARIAD Pharmaceuticals submitted part 1 of their new NDA rolling submission for ponatinib. Part 2 of the application was submitted on September 27, 2012. ARIAD is seeking *accelerated approval*. Ponatinib received orphan drug designation the treatment of CML and Ph+ALL on 20 November 2009, therefore this NDA is not subject to an application fee and is exempt from the pediatric assessment.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lara Akinsanya	Y
	CPMS/TL:	Janet Jamison	Y
Cross-Discipline Team Leader (CDTL)	Virginia Kwitkowski		Y
Clinical	Reviewer:	Angelo De Claro	Y
	TL:	Virginia Kwitkowski	Y
Clinical Pharmacology	Reviewers:	Joseph Grillo Rachelle Lubin	Y Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Kyung Lee	Y

	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewers:	Stacey Ricci Pedro DelValle	Y Y
	TL:	Haleh Saber	Y
Product Quality (CMC)	Reviewer:	Amit Mitra	Y
	TL:	Janice Brown	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Steven Donald	Y
	TL:	Bryan Riley	N
Facility Review/Inspection	Reviewer:	Anthony Orenca	Y
	TL:	Susan Thompson	Y
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright	Y
	TL:	Yelena Maslov	Y
Other reviewers	Karen Riviere – Biopharmaceutics Jennifer Dickey – CDRH Gina Mcknight & Adora Ndu - OPDP		Y Y Y
Other attendees	Anthony Murgo, Ann Farrell, Edvardas Kaminskas, Robert Kane, Diane Leaman, Jessica Boehmer, Beatrice Kallungal, Ebla Ali- Ibrahim, Debasis Ghosh		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

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

needed?	<input type="checkbox"/> NO
BIostatistics Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<p><input type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter

Appendix A (NDA and NDA Supplements only)

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

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

MONSURAT O AKINSANYA
10/05/2012

JANET K JAMISON
10/05/2012

CLINICAL INSPECTION SUMMARY

DATE: September 26, 2012

TO: Diane Hanner, Regulatory Project Manager
Angelo De Claro, M.D., Medical Officer
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C, Team Leader
Division of Hematology Products (DHP)

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

THROUGH: Susan D. Thompson, M.D.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203469
APPLICANT: ARIAD Pharmaceuticals, Inc.
DRUG: ponatinib
NME: yes
THERAPEUTIC CLASSIFICATION/REVIEW: Priority Review (fast track)
INDICATION: chronic myelogenous leukemia
CONSULTATION REQUEST DATE: August 14, 2012
INSPECTION SUMMARY GOAL DATE: October 19, 2012 (original)
DIVISION ACTION GOAL DATE: November 15, 2012 (Early Action)
PDUFA DATE: To be determined

I. BACKGROUND:

The myelogenous type of leukemia may manifest in the acute (including an accelerated and blast phase) or chronic phase. The most common phenotype of Philadelphia chromosome positive leukemia is chronic myelogenous leukemia (CML), which is most frequently associated with a 210 kD BCR-Abl fusion protein. BCR-Abl is a transcript resulting from the 9:22 chromosomal translocation responsible for formation of the Philadelphia (Ph) chromosome. This fusion protein (BCR-Abl), with constitutive tyrosine kinase activity, consists of the breakpoint cluster region (BCR) and Abelson kinase (Abl).

Ponatinib is a tyrosine kinase inhibitor with potent activity against BCR-ABL with mutations including *T315I*, and also against *fms-like tyrosine kinase 3* (FLT3). Other tyrosine kinase inhibitors experimentally available or approved include imatinib, dasatinib, nilotinib, and bosutinib. Ponatinib produces synergistic cytotoxicity with multidrug resistance-associated ATP-binding cassette (ABC) proteins and ABCB1 and ABCG2 substrate chemotherapy drugs, and enhanced apoptosis induced by these drugs, including daunorubicin, mitoxantrone, and topotecan.

A single adequate study was submitted in support of this NDA. Two U.S. clinical sites plus the Sponsor were selected for clinical audit.

Protocol AP24534-10-201 (PACE Trial):

The PACE trial was a multicenter, international, single-arm, open-label, clinical trial of oral ponatinib in patients ≥ 18 years of age with Philadelphia-chromosome positive (Ph+) disease. Patients were enrolled into the following groups resistant or intolerant to dasatinib or nilotinib: (1) resistant or intolerant to dasatinib or nilotinib who were in the chronic phase (Cohort A), (2) resistant or intolerant to dasatinib or nilotinib who were in the accelerated phase (Cohort C), (3) resistant or intolerant to dasatinib or nilotinib who were in the blast phase (Ph+ acute lymphoblastic leukemia) (Cohort E). Patients were enrolled into the following groups with the T315i mutation: (1) T315i mutation patients in the chronic phase (Cohort B), (2) T315i mutation patients in the accelerated phase (Cohort D), and (3) T315i patients in the blast phase (Ph+ acute lymphoblastic leukemia) (Cohort F).

The primary endpoint for patients with CML-Chronic Phase (Cohorts A and B) was major cytogenetic response (MCyR) defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR). For patients with CML-Accelerated Phase, CML-Blast Phase, or PH+ ALL (Cohorts C, D, E, and F), the primary endpoint was major hematologic response (MaHR) defined as complete hematologic response (CHR) or no evidence of leukemia (NEL).

II. RESULTS:

Name of CI City, State	Protocol/ Study Site	Insp. Date	Final Classification*
Jorge Cortes, M.D. Houston, TX	Protocol AP24534-10-201 Site #005	September 12-19, 2012	Pending Preliminary NAI
Javier Pinilla-Ibarz, M.D., Ph.D. Tampa, FL	Protocol AP24534-10-201 Site #017	September 5-11, 2012	Pending Preliminary VAI

Name of CI City, State	Protocol/ Study Site	Insp. Date	Final Classification*
ARIAD Pharmaceuticals, Inc., Cambridge, MA	Sponsor	August 24 to 31, 2012	Pending Preliminary NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI = Deviations(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Preliminary = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

CLINICAL STUDY SITE INVESTIGATORS

1. Javier Pinilla-Ibarz, M.D., Ph.D./Site #017

Tampa, FL

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from September 5-11, 2012. A total of 22 subjects were screened and enrolled, and 9 subjects were still on treatment, at the end of the study.

An audit of 22 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, and study monitoring visits. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents, for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. The primary study endpoint was not ascertained definitively by an independent adjudication committee. Per DHP, however, Sponsor collected all the raw data, and performed the analyses of the primary and secondary efficacy endpoints. There was no under-reporting of serious adverse events. There were no limitations during conduct of the clinical site inspection by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for not conducting the clinical investigation according to the study protocol. Specifically, these relevant regulatory deficiencies could be categorized as follows:

(1) Site #017 did not report a serious adverse event (SAE) in a timely manner. For example:

(a) Subject 17-004 experienced a SAE on 4/29/2011, but Sponsor was notified on 5/3/2011. Subject also took hydroxyurea 24 hours prior to or after the initial study drug dose.

(b) Subject 17-010 experienced a SAE on 4/7/2011, but Sponsor was notified on 4/29/2011.

(2) Site #017 did not collect or analyze hematology specimens, chemistry specimens, or obtain electrocardiograms (ECGs), as appropriate. The clinical site did not also perform Eastern Cooperative Oncology Group (ECOG) questionnaire patient assessments, physical examinations or vital sign assessments on specific or follow-up visits, as required by study protocol. For example:

(a) Subject 17-004's ECG on Visit C2D1 was not done.

(b) Subject 17-008's ECOG assessment, physical examination, vital signs, and ECG at the follow-up visit were not performed.

(c) Subject 17-009's ECGs on Visits C2D1 and C3D28 were not done.

(d) Subject 17-011's ECG on Visit C2D1, and physical exam and ECOG assessments at follow-up visits were not conducted.

(e) Subject 17-014's ECG on Visit C2D1, hematology samples on visit C1D8, and chemistry samples on Visit C3D1 were not done.

(f) Subject 017-018's hematology and chemistry samples at Visit C2D15, and hematology samples at Visits C3D15, C5D15 and C6D15 were not performed.

(g) Subject's 017-021's hematology and chemistry samples at Visits C2D15 and C3D15 were not done.

(3) Bone marrow aspirate samples were inadequate (The study protocol states that a bone marrow aspirate should be repeated, if possible, when less than 20 metaphase cells were available for evaluation). For example:

(a) Subject 17-018's bone marrow aspirate had one cell metaphase analyzed.

(b) Subject 17-021's bone marrow aspirate had four cell metaphases analyzed.

The DHP Review Team considered the above ORA field staff observations as not critical. Further, the missing bone marrow aspiration and incomplete visit procedures were considered clinical and scientific review-specific items that will be assessed by DHP in the NDA review cycle. Items #2 and #3 above were already noted, by DHP, in the NDA submission to the Agency.

Thus, the above observations were discussed with the DHP Review Team, who did not consider that the above findings would likely have a significant impact on safety and efficacy assessments for this NDA.

c. Assessment of data integrity:

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

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Jorge Cortes, M.D./ Site #005
Houston, TX

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from September 12-19, 2012. A total of 46 subjects were screened, 35 subjects were enrolled, and 16 subjects completed the study.

An audit of 46 subjects' records was conducted; however, only 25 subjects' concomitant medication source records were reviewed. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, and study monitoring visits. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings and no discrepancies were found. Source documents for the primary study endpoint were verifiable at the study site. The primary study endpoint was not ascertained definitively by an independent adjudication committee. Per DHP, however, Sponsor collected all the raw data, and performed the analyses of the primary and secondary efficacy endpoints. There was no under-reporting of serious adverse events. There were no limitations during conduct of the clinical site inspection by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

c. Assessment of data integrity:

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

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

SPONSOR

3. ARIAD Pharmaceuticals, Inc.
Cambridge, MA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from August 24 to 31, 2012.

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

b. General observations/commentary:

The Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites, and monitoring of the investigator sites was considered adequate. No salient issues were identified. There was no evidence of under-reporting of adverse events.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued at the end of the Sponsor inspection.

c. Assessment of data integrity:

The study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For Study Protocol AP24534-10-201, a Phase 2 single-arm, open-label trial, two U.S. clinical investigator sites and Sponsor were inspected in support of this application.

No regulatory deficiencies were observed for Jorge Cortes, M.D. (Site #005) and the Sponsor. Minor regulatory deficiencies in not conducting the investigation per study protocol plan were observed for the domestic study site of Javier Pinilla-Ibarz, M.D., Ph.D (Site #017). DHP noted that these observations were not critical.

Based on review of inspectional findings for these clinical investigators and the NDA Applicant, the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above, for the sites are based on the preliminary communications from the field investigators; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
09/26/2012

SUSAN D THOMPSON
09/26/2012

DSI CONSULT: Request for Clinical Inspections

Date: August 14, 2012

To: Lauren Iacono-Connor, Ph.D., Division Director (Acting), Division of Good Clinical Practice Compliance
Susan Thompson, Branch Chief (Acting), Good Clinical Practice Assessment Branch
Anthony Orencia, M.D.
Office of Scientific Investigations, CDER

Through: R. Angelo De Claro, M.D., Medical Officer, DHP
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Lead Clinical Analyst, Clinical Team Leader, DHP
Ann Farrell, M.D., Division Director, DHP

From: Lara Akinsanya, M.S.

Subject: **Request for Clinical Site Inspections**

I. General Information

Application# NDA 203469 (IND 078375)
Applicant: ARIAD Pharmaceuticals, Inc.: (Ponatinib)

Contact information:

Andrew Slugg, Director, Regulatory Affairs

ARIAD Pharmaceuticals, Inc.

26 Landsdowne Street

Cambridge, MA 02139

Office: +1 617 503 7097

Mobile: +1 617 710 1840

NME: YES

Study Population: Chronic Myelogenous Leukemia

Study Population includes < 17 years of age (No)

Is this for Pediatric Exclusivity (No)

Applicant's Proposed Indication: Iclusig® (ponatinib) is a novel synthetic orally-active tyrosine kinase inhibitor (TKI) intended 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.

PDUFA: TBD (**HIGH PRIORITY**)

Action Goal Date: November 15, 2012 (Early Action Date)

Inspection Summary Goal Date: October 19, 2012

II. Background Information

Ponatinib is a synthetic, orally-active tyrosine kinase inhibitor. Ponatinib was designed to inhibit native BCR-ABL, as well as mutated forms of the protein that cause resistance, including T315I.

The Applicant submitted a New Drug Application (rolling submission) for Ponatinib on July 30, 2012. The complete clinical modules for the application were submitted on July 30, 2012. OHOP intends to take early action on this application, with a goal action date of November 15, 2012.

OHOP granted expanded access (Treatment Protocol) for ponatinib (IND 78375) for the proposed indication on March 26, 2012.

III. Protocol/Site Identification

Site # (Name, Address, Phone number, email, fax#)	Protocol #	# of Subjects	Comments
Site 005: University of Texas, MD Anderson Cancer Center PI: Jorge Cortes, MD Dept. of Leukemia 1515 Holcombe Blvd, Unit 428 Houston, TX 77030 USA Telephone: 713-794-5783 Fax: 713-794-4297 Email: jcortes@mdanderson.org	10-201	31	Highest enrolling site (31 pts), Highest number of patients who met primary endpoint (18 pts), Enrolled to at least 5 of 6 cohorts, Highest number of patients with SAE (22 pts), Site with highest number of major protocol deviations (8)
Site 017: Moffitt Cancer Center PI : Javier Pinilla-Ibarz, MD PhD 12902 Magnolia Dr. Tampa, FL 33612 USA Telephone : 813-745-1387 Fax : 813-745-6817 Email : javier.pinilla@moffitt.org	10-201	22	High enrolment (22 pts, 2nd highest in US, 3rd highest overall), Enrolled to at least 5 of 6 cohorts, Second highest number of patients with SAE (14 pts), Second highest for any protocol deviations (105)

IV. Site Selection/Rationale

Rationale for DSI Audits

Regardless of previous history of inspections at Dr. Cortes' site (MD Anderson), DHP requests specifically that Dr. Cortes be inspected for this new molecular entity. DHP determined that clinical sites for Dr. Pinella-Ibarz and Dr. Cortes will be critical to CDER's efficacy and safety decision-making for this ponatinib NDA NME.

Domestic Inspections: 2 sites requested

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects
High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): New Molecular Entity

International Inspections: No

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

V. Tables of Specific Data to be Verified (if applicable)

None.

Should you require any additional information, please contact Lara Akinsanya (regulatory project manager) at 301-796-9634 or R. Angelo de Claro, MD (medical reviewer).

Concurrence: (as needed)

R. Angelo De Claro, M.D., _____ Medical Reviewer

Virginia Kwitkowski _____ Medical Team Leader

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/s/

MONSURAT O AKINSANYA
08/14/2012