DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203469/S-007 & S-008

SUPPLEMENT APPROVAL
REMS APPROVAL

ARIAD Pharmaceuticals
Attention: Andrew Slugg, MS, MBA
Senior Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139-4234

Dear Mr. Slugg:

Please refer to your Supplemental New Drug Application (sNDA) (S-007) dated November 27, 2013, received November 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Iclusig® (ponatinib) 15 mg and 45 mg tablets for oral use.

We acknowledge receipt of your amendments dated November 27; December 3, December 12, and December 18, 2013 (2).

We also refer to your Supplemental New Drug Application (sNDA) (S-008) dated December 5, 2013, received December 6, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Iclusig® (ponatinib) tablets.

We acknowledge receipt of your amendment dated December 17, 2013.

We also refer to our letter dated November 25, 2013, notifying you, under Sections 505(o)(3), 505(o)(4) and 505-1 of the FDCA, of new safety information that we believe should be included in the labeling for Iclusig® (ponatinib) tablets, requiring postmarketing studies and clinical trials and requiring a risk evaluation and mitigation strategy (REMS). The new safety information pertains to the risk of serious adverse reactions of vascular occlusions including loss of vision due to blood clots, and occlusion of mesenteric blood vessels, stroke, myocardial infarction, peripheral vascular disease with ischemic necrosis, and other vascular occlusive events.

Supplemental new drug application S-007 provides for revisions to the labeling for Iclusig® (ponatinib) tablets consistent with our November 25, 2013, Safety Labeling Change Notification Letter.

Supplemental new drug application S-008 provides for the addition of a risk evaluation and mitigation strategy (REMS) for Iclusig® (ponatinib) tablets consistent with our November 25, 2013, letter.

We also acknowledge your initiation of a voluntary suspension of marketing of Iclusig® (ponatinib) on October 31, 2013 in light of postmarketing adverse event reports and follow-up data from clinical trials that indicate an increased frequency of serious vascular occlusive events with Iclusig® (ponatinib) treatment.

As noted in our November 25, 2013 letter, we have determined that revised labeling and a REMS are needed to ensure that the benefits of Iclusig outweigh the risks. Once the REMS is fully operational, your suspension of marketing would no longer be warranted. In order to be fully operational, FDA considers that, at a minimum, the Iclusig REMS website will be active with all required information and functional links.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your December 18, 2013 submission includes final printed labeling (FPL) for your Package Insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter,

with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Refer to the FDA letter dated November 25, 2013, in which you were notified that we have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of vascular occlusion with the use of Iclusig® (ponatinib).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 2113-1 Propose and conduct an enhanced pharmacovigilance study of data from clinical trials and all postmarketing sources to assess risk factors for, management of, and consequences of all vascular occlusive events that are serious or require medical evaluation or treatment, occurring while patients are receiving ponatinib or within 30 days of the last drug dose.

The timetable you submitted on December 18, 2013, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2014
Final Protocol Submission:	06/2014
Study Completion:	03/2017

Final Report Submission:	12/2017

PMR 2113-2 Conduct a prospective, observational study to evaluate the incidence of and risk factors for vascular occlusive events when ponatinib is given with or without anticoagulant or antiplatelet agents. Submit a protocol that includes measures to ensure sufficient long-term follow-up to adequately capture late occurring vascular occlusive events and describe measures that minimize loss to follow-up.

The timetable you submitted on December 18, 2013, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2014
Final Protocol Submission:	10/2014
Study Completion:	10/2018
Final Report Submission:	06/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of vascular occlusion with the use of Iclusig® (ponatinib).

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

PMR 2113-3 Provide long-term follow-up of all patients enrolled in the Phase 1 (AP24534-07-101) and Phase 2 (AP24534-10-201) clinical trials. Assess the long-term safety of ponatinib treatment, including the long-term risk of vascular occlusive events. Include narratives for all cases of vascular occlusion. The final report submission should include text and data sets.

The timetable you submitted on December 18, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission:	03/2017

PMR 2113-4 Submit the final report (using a data cut-off of 30 days following the last dose) for the Phase 3 clinical trial, AP24534-12-301 entitled “Phase 3 Randomized, Open-Label Study of Ponatinib vs Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase” in order to characterize the long-term safety of Iclusig. Include narratives for all cases of vascular occlusion. The final report submission should include text and data sets. Include pharmacokinetic exposure-response and dose-response analyses in final report.

The timetable you submitted on December 18, 2013, states that you will conduct this study according to the following schedule:

	Final Report Submission:	03/2014

PMR 2113-5 Prepare and submit an integrated safety data and summary (final report submission) from all three clinical trials cited in PMRs 2113-3 and 2113-4 (Phase 1, Phase 2, and Phase 3). Include narratives for all cases of vascular occlusion.

The timetable you submitted on December 18, 2013, states that you will conduct this trial according to the following schedule:

	Final Report Submission:	04/2014

PMR 2113-6 Conduct a randomized, multi-arm trial to characterize the safety of a range of ponatinib doses. The trial should be of sufficient size and duration to inform safe use of Iclusig in chronic phase CML. The trial should also assess the efficacy of the doses investigated. Include a plan for adequate PK sampling to provide exposure-toxicity and exposure-response data sufficient to identify appropriate dose ranges (or exposure targets) for patients with T315I mutation and for patients who have progressed after at least two TKIs and are considered to have no alternative therapy available.

The timetable you submitted on December 18, 2013, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	04/2014
Final Protocol Submission:	07/2014
Trial Completion:	12/2018
Final Report Submission:	06/2019

Submit the protocols to your IND 078375, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS, if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. The details of the REMS requirements were outlined in our November 25, 2013 REMS notification letter.

Your proposed REMS, submitted on December 17, 2013, and appended to this letter, is approved.

The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of healthcare providers' understanding of the following:
    a. The indications for Iclusig® (ponatinib) are limited to:
        i. treatment of adult patients with T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
        ii. treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated
    b. The serious risks of vascular occlusion and thromboembolism with Iclusig® (ponatinib) treatment.
    c. The Iclusig® (ponatinib) REMS program and materials

2. Program outreach and communication activities
    a. Distribution of the REMS letters
        i. Total number of recipients included in mass mailing of REMS letters, dates of mailings (United States Postal mail and email).
        ii. Stratify letters sent by: number of letters sent to each prescriber specialty, or professional society, number emailed, or sent via U.S. mail, number undeliverable, and if delivered by email, number of emails opened.
    b. Journal Pieces

i. Date journal pieces appeared in each journal or publication and a copy of the journal piece

c. Professional meetings
   i. Date of professional meeting and materials displayed.
d. Number of unique visits to the Iclusig® (ponatinib) REMS website
e. Number of REMS fact sheets distributed by Ariad representatives during follow-up details/ visits with a healthcare provider.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA 203469 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 203469 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 203469
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 203469
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call CAPT Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

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

/s/

ANN T FARRELL
12/20/2013