

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208051Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208051 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Nerlynx Established/Proper Name: neratinib maleate Dosage Form: Tablet		Applicant: Agent for Applicant (if applicable):
RPM: Pamela Balcazar		Division: DOP1
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>7/19/2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): NME
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information were issued 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: Burst
❖ Exclusivity	
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s): AP 7/17/17
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	8/25/16 8/25/16
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 9/16/16 DMEPA: <input type="checkbox"/> None 8/25/16, 2/21/17, 7/7/17 DMPP/PLT (DRISK): <input type="checkbox"/> None 6/23/17 OPDP: <input type="checkbox"/> None 6/23/17 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	9/6/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>11/16/16</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	8/23/16, 8/30/16, 8/31/16, 9/9/16, 9/22/16, 9/26/16, 10/6/16(2), 10/24/16, 10/31/16, 11/3/16, 11/10/16(2), 11/14/16, 11/17/16, 11/22/16, 11/30/16, 12/5/16, 1/30/17, 2/17/17(2), 2/23/17(2), 3/8/17, 4/18/17, 5/11/17(3), 6/7/17, 6/9/17, 6/12/17, 6/13/17, 6/20/17, 6/27/17, 6/28/17, 7/6/17(2)
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 3/21/16
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 8/1/08
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 12/5/16
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 6/20/17
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	May 24, 2017
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/12/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/12/17
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 2- PMR, 3- PMC
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	7/5/17
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See clinical review dated 7/5/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 3/23/17
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/19/17

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/2/17
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested 6/23/17
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/29/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 3/30/17 Included in P/T review, page N/A
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Exec. Summary: 6/21/17 DS: 5/19/17 DP: 5/10/17 Process & Micro: 6/15/17 Biopharm: 3/23/17 Facilities: 6/14/17 Labeling: 5/10/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	6/13/17
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	<input checked="" type="checkbox"/> Done

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/s/

PAMELA I BALCAZAR
07/18/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Wednesday, July 05, 2017 5:54 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Label
Attachments: 3Jul17_FINAL label.docx; 3Jul17_FINAL PLR.docx

Hi Jesse

Here is our final draft of your label. Please review and ensure there are no grammatical errors, typos and link issues. Also please consolidate both documents into one.

Let me know if you have any questions

Thanks

-Pam

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4203
Fax: 301-796-9845
pamela.balcazar@fda.hhs.gov



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/s/

PAMELA I BALCAZAR
07/06/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, July 06, 2017 2:30 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051: PMR/PMC

Dear Jesse,

Please see below final PMRs and PMC wording with agreed upon dates for NDA 208051 NERLYNX®(neratinib). Please provide your response to the information request below by **4PM EST Friday July 7, 2017**

As we continue our review of your Application, our normal policy is to consider post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Final PMR/PMC designation numbers will be assigned later.

PMR #1

PMR Description: Conduct a physiologically-based pharmacokinetic modeling/simulation study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of increased drug exposure and to address the potential for excessive drug toxicity. If the PBPK modeling /simulation is not feasible then a clinical pharmacokinetic trial will be conducted. Submit Final Report, datasets, and labeling.

PMR Schedule
Milestones:

Final Report Submission:

10/2017

PMR# 2

PMR Description: To assess carcinogenic potential conduct a 2-year carcinogenicity study in the rat. Refer to the ICH S1A Guidance for Industry on *The Need for Long Term Rodent Carcinogenicity Studies of*

PMR Schedule Milestones:	Final Protocol Submission:	Submitted/Ongoing
	Study Completion:	<u>02/2017</u>
	Final Report Submission:	<u>12/2017</u>

PMC# 1

PMC Description: Conduct a physiologically-based pharmacokinetic modeling/simulation study or a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Submit Final Report with datasets.

PMC Schedule Milestones:

	Final Report Submission:	<u>10/2017</u>
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PMC #2

PMC Description: Conduct a clinical pharmacokinetic trial to evaluate whether separating the dosing of H₂-receptor antagonists and neratinib can minimize the drug-drug interaction potential. Submit Final Report with Datasets.

PMC Schedule Milestones:

	Final Report Submission:	<u>12/2017</u>
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PMC #3

PMC Description: Submit the overall survival (OS) data and results from Trial 3144A2-3004-WW, ExteNET, "A Randomized, Double-Blind, Placebo-Controlled Trial of Neratinib (HKI-272) After Trastuzumab in Women with Early-Stage HER-2/neu Overexpressed/Amplified Breast Cancer"

PMC Schedule Milestones:

	Trial Completion:	<u>07/2019</u>
	Final Report Submission:	<u>01/2020</u>

Please respond by **4PM EST Friday July 7, 2017** with your agreement to these PMR/PMC by email and officially to your NDA.

Please confirm receipt.

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4203
Fax: 301-796-9845
pamela.balcazar@fda.hhs.gov



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/s/

PAMELA I BALCAZAR
07/06/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Wednesday, June 28, 2017 5:33 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Label
Attachments: 28Jun17_FDA_PPI.docx; 28Jun17_FDA_USPI.docx

Good Afternoon Jesse

The purpose of this email is to provide you with NDA 208051 package insert and PPI with comments from the FDA. When you return the updated label to us please ensure the following:

1. All numbering is updated including tables, figures, headers.
2. Ensure all links are correctly hyperlinked.
3. When responding to our comments or directing any comments to the Agency, please add "TO FDA:" for clarity.
4. Please check for grammatical errors.

We would appreciate updated labels no later than **4PM EST Friday June 30, 2017.**

If you have any questions please let me know.

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4203
Fax: 301-796-9845
pamela.balcazar@fda.hhs.gov



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/s/

PAMELA I BALCAZAR
06/28/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Monday, June 26, 2017 5:16 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Information Request

Good Afternoon Jesse,
The purpose of this email is to relay a clinical information request for NDA 208051:

Given the number of SPI requests for neratinib, we recommend that you open an expanded access protocol for patients with metastatic breast cancer.

We would appreciate a response to this request/advice by **4PM EST Wednesday June 28, 2017.**

Please let me know if you have any questions.

Regards,

Pamela Balcazar, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4203
Fax: 301-796-9845
pamela.balcazar@fda.hhs.gov



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/s/

PAMELA I BALCAZAR
06/27/2017

From: Alebachew, Elleni
To: ["jho@pumabiotechnology.com"](mailto:jho@pumabiotechnology.com)
Cc: ["abentajado@pumabiotechnology.com"](mailto:abentajado@pumabiotechnology.com); ["splant@cato.com"](mailto:splant@cato.com); [Balcazar, Pamela](#)
Subject: NDA 208051- FDA Revised Label -19June17
Date: Monday, June 19, 2017 11:37:00 AM
Attachments: [19Jun17 -draft-labeling_FDA.docx](#)
[image001.png](#)
Importance: High

Hello,

The purpose of this email is to provide you with NDA 208051 package insert with comments from the FDA on behalf of my colleague Pamela Balcazar.

Please respond by **COB tomorrow, Tuesday, June 20, 2017.**

Please confirm receipt.

Regards.

Elleni Alebachew, MS, RAC

Senior Regulatory Health Project Manager

**Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration**

Tel: 301-796-5225

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elleni.alebachew@fda.hhs.gov



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/s/

ELLENI K ALEBACHEW
06/20/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Tuesday, June 13, 2017 5:02 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051: PMR/PMC

Dear Jesse,

Please see below PMRs and PMC wording for NDA 208051 NERLYNX® (neratinib). Please provide your response to the information request below by **4PM EST June 19, 2017.**

As we continue our review of your Application, our normal policy is to consider post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. Most Milestones only require the applicant to provide the month and year for completion of each category.

For milestone calculation purposes only, assume that an approval occurs on the PDUFA date. Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Final PMR/PMC designation numbers will be assigned later.

PMR #1

PMR Description: Conduct a physiologically-based pharmacokinetic modeling/simulation study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of increased drug exposure and to address the potential for excessive drug toxicity. If the PBPK modeling /simulation is not feasible then a clinical pharmacokinetic trial will be conducted. Submit Final Report, datasets, and labeling.

PMR Schedule
Milestones:

Final Report Submission:

MM/DD/YYYY

PMR# 2

PMR Description: To assess carcinogenic potential conduct a 2-year carcinogenicity study in the rat. Refer to the ICH S1A Guidance for Industry on *The Need for Long Term Rodent Carcinogenicity Studies of Pharmaceuticals*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm06>

PMR Schedule Milestones:	Final Protocol Submission:	Submitted/Ongoing
	Study Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

PMC# 1

PMC Description: Conduct a physiologically-based pharmacokinetic modeling/simulation study or a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Submit Final Report with datasets.

PMC Schedule Milestones:		<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

PMC #2

PMC Description: Conduct a clinical pharmacokinetic trial to evaluate whether separating the dosing of H₂ receptor antagonists and neratinib can minimize the drug-drug interaction potential. Submit Final Report with Datasets.

PMC Schedule Milestones:		<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

PMC #3

PMC Description: Submit the overall survival (OS) data and results from Trial 3144A2-3004-WW, ExteNET, "A Randomized, Double-Blind, Placebo-Controlled Trial of Neratinib (HKI-272) After Trastuzumab in Women with Early-Stage HER-2/neu Overexpressed/Amplified Breast Cancer"

PMC Schedule Milestones:	Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

Please review and provide your comments and edits in track changes

Please confirm receipt.

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
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PAMELA I BALCAZAR
06/13/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Monday, June 12, 2017 10:07 AM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Label (additional comments)

Good Morning Jesse

In addition to the comments within the label I sent you on Friday June 9, 2017, we have 1 additional comment that will need your teams attention:

*In section 13.1, the sentence that begins on line 360 and ends on line 362 should be changed from "In a fertility study in rats, neratinib administration up to 12 mg/kg/day (b) (4) caused no effects on mating or the ability of animals to become pregnant." to "In a fertility study in rats, neratinib administration up to 12 mg/kg/day (approximately 0.5 times the maximum recommended dose of 240 mg/day in patients on a mg/m² basis) caused no effects on mating or the ability of animals to become pregnant."
Please make this change before returning your edits and comments.*

Please let me know if you have any questions or comments.

Thanks

Pamela Balcazar, MS
Regulatory Project Manager

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PAMELA I BALCAZAR
06/12/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Friday, June 09, 2017 3:25 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Label
Attachments: 09Jun17_FDA_us-package-insert.docx

Importance: High

Good Afternoon Jesse

The purpose of this email is to provide you with NDA 208051 package insert with comments from the FDA. When you return the updated label to us please ensure the following:

1. All numbering is updated including tables, figures, headers.
2. Ensure all links are correctly hyperlinked.
3. When responding to our comments or directing any comments to the Agency, please add "TO FDA:" for clarity.
4. Please check for grammatical errors.

We would appreciate an updated label no later than **4PM EST Wednesday June 14, 2017.**

If you have any questions please let me know.

Best Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
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PAMELA I BALCAZAR
06/09/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Wednesday, June 07, 2017 4:12 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: RE: NDA 208051 Information Request

Hi Jesse

We found some typo's in the previous email so I am sending an updated information request. The due date stays the same

- Neratinib is predominantly metabolized by the CYP3A enzymes and has indicated pH value dependent solubility. Clinical studies indicated significant exposure changes when concomitant use with strong CYP3A inhibitor, strong CYP 3A inducers and Proton Pump Inhibitors. However, drug interaction studies of concomitant use with moderate CYP3A [inhibitors](#), or moderate CYP3A inducers, or staggering dosing with H2-receptor antagonists have not been conducted, and concomitant use with those drugs may significantly change the neratinib exposure too, which could result in excessive toxicity or loss of neratinib activities. We plan to request that you determine the dosing instructions for these situations. You could choose to conduct physiologically-based pharmacokinetic (PBPK) modeling/simulation studies or clinical pharmacokinetic trials to assess the magnitude of neratinib exposure changes and to determine appropriate dosing recommendations when concomitantly use with moderate CYP3A [inhibitors](#), or moderate CYP3A inducers, or staggering dosing with H2-receptor antagonists. Please let us know whether you choose the PBPK approach or the clinical pharmacokinetic trials for each situation.

Thanks
-Pam

From: Balcazar, Pamela
Sent: Wednesday, June 07, 2017 2:35 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Information Request

Good Afternoon Jesse,

The purpose of this email is to relay a clinical pharmacology information request for NDA 208051.

- Neratinib is predominantly metabolized by the CYP3A enzymes and has indicated pH value dependent solubility. Clinical studies indicated significant exposure changes when concomitant use with strong CYP3A inhibitor, strong CYP 3A inducers and Proton Pump Inhibitors. However, drug interaction studies of concomitant use with moderate CYP3A inducers, or moderate CYP3A inducers, or staggering dosing with H2-receptor antagonists have not been conducted, and concomitant use with those drugs may significantly change the neratinib exposure too, which could result in excessive toxicity or loss of neratinib activities. We plan to request that you determine the dosing instructions for these situations. You could choose to conduct physiologically-based pharmacokinetic (PBPK) modeling/simulation studies or clinical pharmacokinetic trials to assess the magnitude of neratinib exposure changes and to

determine appropriate dosing recommendations when concomitantly use with moderate CYP3A inducers, or moderate CYP3A inducers, or staggering dosing with H2-receptor antagonists. Please let us know whether you choose the PBPK approach or the clinical pharmacokinetic trials for each situation.

We would appreciate a response by **5PM EST Thursday June 8, 2017**. Please let me know if you have any questions.

Thanks

Pamela Balcazar, MS

Regulatory Project Manager

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PAMELA I BALCAZAR
06/07/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, May 04, 2017 3:01 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Clinical IR

Good Afternoon Jesse,
The purpose of this email is to relay a clinical information request for NDA 208051.

Please provide any analyses that you have performed on the Patient Reported Outcome Data (EQ-5D and FACT-B Questionnaires), including completion rates as well as any item level analyses that were performed.

Please provide completion rates in the form of a table as shown below.

	# of Expected Patients		# of patients with FACT-B data (%)		# of patients with EQ-5D data (%)	
	Neratinib	Placebo	Neratinib	Placebo	Neratinib	Placebo
Baseline						
Month 1						
Month 3						
Month 6						
Month 9						
Month 12						

We would appreciate a response by **5PM EST Monday May 8, 2017**. Please let me know if you have any questions.
Thanks

Pamela Balcazar, MS
Sr.Regulatory Project Manager

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PAMELA I BALCAZAR
05/11/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Monday, May 08, 2017 4:41 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Clinical Information Request

Good Afternoon Jesse

The purpose of this email is to relay a clinical information request for NDA 208051.

Please submit updated interim efficacy results from the breast cancer cohort in Study “PUMA-NER-5201: An Open-Label, Phase 2 Study of Neratinib in Patients with Solid Tumors with Somatic HER Mutations or EGFR Gene Amplification”

We would appreciate a response to this information request by **5PM EST Wednesday May 10, 2017**. Please let me know if you have any questions.

Thanks

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
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PAMELA I BALCAZAR
05/11/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, May 11, 2017 11:35 AM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Clinical Information Request

Good Morning Jesse

The purpose of this email is to relay a clinical information request for NDA 208051.

Please submit the topline colestipol data and report for Study PUMA-NER-6201.

We would appreciate a response to this information request by **5PM EST Monday May 15, 2017.**

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
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PAMELA I BALCAZAR
05/11/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Tuesday, April 18, 2017 3:37 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Clinical Information Request

Good Afternoon Jesse

The purpose of this email is to relay a clinical information request for NDA 208051.

Please submit an updated report from Study “PUMA-NER-6201” as well as corresponding datasets. This data should include any results you will present at the Oncologic Drug Advisory Committee on May 24th, 2017.

We would appreciate the *report* by **5PM EST Thursday April 20, 2017** and the *datasets* **as soon as possible**. Please let me know if you have any questions.

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
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PAMELA I BALCAZAR
04/18/2017

Executive CAC

Date of Meeting: March 28, 2017

Committee: Karen Davis Bruno, Ph.D., OND IO Chair
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Member
Ikram Elayan, Ph.D., DPP, Alternate Member
Todd Palmby, Ph.D., DHOT, Pharm Tox Supervisor
Kimberly Ringgold, Ph.D., DHOT, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 208051

Drug Name: Neratinib

Sponsor: Puma Biotechnology, Inc.

Background:

Neratinib is a tyrosine kinase inhibitor that targets ERBB1, ERBB2, and ERBB4. Neratinib was negative in a standard battery of genotoxicity assays. The 2-year oral carcinogenicity study in rats is ongoing. The mouse carcinogenicity study protocol was reviewed by the ECAC on June 9, 2015. The committee recommended a top dose of 50 mg/kg/day for the male mice only based on decreased body weight gain at 125 mg/kg/day. The mid and low doses were based on approximately one-third dose decrements. The committee did not recommend a high dose in females due to inadequate data and suggested that the Applicant could conduct an additional dose range-finding study and resubmit an SPA for concurrence. The Applicant did not conduct another dose range-finding study in females, but based the female high dose on the steady-state AUC₍₀₋₂₄₎ ratio of approximately 17-fold (17,500 ng*hr/mL) in female mice relative to the AUC₍₀₋₂₄₎ of 1060 ng*hr/mL at the maximum clinical dose (240 mg/day) in female patients.

Mouse Carcinogenicity Study:

Neratinib was administered to Tg.rasH2 mice (25/sex/group) at doses of 0 (water & vehicle controls), 8, 20 and 50 mg/kg/day for males and 0 (water & vehicle controls), 20, 50, and 125 mg/kg/day for females given once daily for 6 months. The vehicle was 0.5% polysorbate 80/0.5% MC in purified water. The positive control, N-nitrosomethylurea (NMU), was administered once on Day 1 via IP injection (15/sex/group). Survival was adequate for analysis and there was no difference in survival amongst neratinib-treated mice compared to controls. There were decreased body weights in the 20 and 50 mg/kg/day-treated males and in 125 mg/kg/day-treated females. Clinical signs included decreased activity, hunched posture, thin appearance, tremors, ungroomed fur, changes in respiration (labored, shallow, and/or increased), apparent hypothermia (cold to touch), dehydration, and/or decreased feces. Mild incidences of cellularity or inflammation were observed at 50 mg/kg in males and 125 mg/kg in females. The dose selection in females appears adequate in this study based on sufficient numbers of surviving females in each dose group and observed toxicity.

The positive control, NMU, produced the expected toxicities and neoplasms. Neoplastic findings included splenic hemangiosarcomas and hemangiosarcomas of all sites observed in all treatment groups in male mice including the water and vehicle controls. Statistical analyses of hemangiosarcomas in the spleen and combined from all sites (whole body) showed no statistically significant increase. Under the conditions tested, neratinib is not carcinogenic in CByB6F1/Tg rasH2 transgenic mice following 6-months of oral daily administration.

Executive CAC Recommendations and Conclusions:

Tg RasH2 Mouse:

- The Committee concurred that the study was adequate although the committee did not agree with the basis of dose selection in female mice.
- The Committee concurred that there were no drug-related neoplasms in the 6-month CByB6F1/Tg rasH2 mouse study following daily oral administration of neratinib.

Karen Davis Bruno, Ph.D.

Chair, Executive CAC

cc:\

/Division File, DOP1

/T. Palmby, DHOT

/K. Ringgold, DHOT

/P. Balcazar, DOP1

/S. Leuenroth-Quinn, OND IO

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STEPHANIE J QUINN
03/30/2017

KAREN L DAVIS BRUNO
03/30/2017

From: [Fahnbulleh, Frances](#)
To: MChang@pumabiotechnology.com
Cc: [Balcazar, Pamela](#); [Mark Pilato](#)
Subject: Follow up IR NDA # 208051-neratinib (Nerlynx)
Date: Friday, December 02, 2016 12:52:42 PM

Dear Mr. Chang,

Reference is made to your amendment which proposes to add an additional commercial packaging presentation of 126 tablets per bottle to the NDA. Further reference is made to your email to Pamela Balcazar, dated October 3, 2016, in response to the requested rationale for the 126 count bottle and the question regarding the manufacturing facility packaging. Please see below a follow up request for additional information:

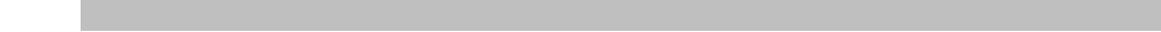
Information Request for Nerlynx (neratinib), NDA 208051

This is a follow up Information Request based on the response you provided to Pamela Balcazar on October 3, 2016.

On October 3, 2016, you provided the following response:

1. What is the rationale to add a 126 tablet bottle.

Response:  (b) (4)


 (b) (4)




We would appreciate a response to this Information Request by **December 15, 2016.**

Respectfully,

Frances Fahnbulleh

Frances Fahnbulleh, RPh, PharmD

Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
CDER/FDA/WO22 , Rm#4404
Ph: 301-796-0942/Fax: 301-796-9832
Email: Frances.Fahnbulleh@fda.hhs.gov

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please notify us immediately by telephone at (301) 796-0942. Thank you.

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FRANCES G FAHNBULLEH
03/08/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, February 23, 2017 9:54 AM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 pharmacometric information request

Good Morning Jesse

The purpose of this email is to relay a pharmacometrics information request for NDA 208051.

Reference is made to the Report “Population Pharmacokinetics Report” in Module 5.3.5.3. Please incorporate any grade and grade 3/4 diarrhea AE into the population PK analysis dataset, and evaluate the effect of diarrhea as a time-varying covariate on neratinib PK. Please provide the datasets/codes and update the popPK report accordingly.

We would appreciate a response to this information request by **4PM EST Friday March 3, 2017.**

If you have any questions please let me know.

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
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pamela.balcazar@fda.hhs.gov



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PAMELA I BALCAZAR
02/23/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, February 23, 2017 3:38 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Clinical Information Request

Good Afternoon Jesse

The purpose of this email is to relay a clinical information request for NDA 208051.

Thank you for your response. In regards to your response to question #4, please also search your safety database (from all Sponsor and Investigator initiated trials other than Study 3004) for patients that meet the following criteria based on laboratory data:

1. AST or ALT > 3 x ULN
2. Serum TBL > 2 x ULN without initial findings of cholestasis (elevated serum ALP)

For each patient identified, please also provide a summary of any relevant clinical information regarding alternate etiologies of increased aminotransferase and total bilirubin, such as disease progression, viral hepatitis, preexisting or acute liver disease, or concomitant medications capable of causing the observed injury.

We would appreciate a response to this information request by **9AM EST Thursday March 2, 2017**. Please let me know if you have any questions.

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
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PAMELA I BALCAZAR
02/23/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, February 16, 2017 5:01 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Clinical Information Request

Hello Jesse

The purpose of this email is to relay a clinical information request for NDA 208051.

Patient number 3144-3004-1329-18168 experienced grade 3 hepatotoxicity that led to drug discontinuation. Lab abnormalities on 3/17/11, six days after initiating neratinib therapy, included ALT > 3 x ULN and TBL > 2 x ULN. There is conflicting information in the patient narrative and datasets regarding when the patient began therapy with tamoxifen and it does not appear that tamoxifen was ever held secondary to hepatotoxicity. In addition, it is not clear why the investigator reported an increase from Grade 2 to Grade 3 hepatotoxicity on 3/24/11 in the absence of new laboratory values or other toxicities on this day.

Please address the following points to the best of your ability:

- 1. Please confirm that the patient began tamoxifen therapy on 6/3/2010 and tamoxifen therapy was continued throughout the duration of the study as documented in the original case report form on pages 314 and 463 (e.g. tamoxifen was not held at any point secondary to hepatotoxicity).***
- 2. Please provide any additional clinical information that may be available to help us understand the increase from grade 2 to grade 3 hepatotoxicity (e.g. were there any other signs of liver toxicity that may not have been reported?)***
- 3. As stated in the protocol (after Amendment 3 in Feb 2010), "liver imaging should be obtained for subjects with any signs or symptoms of hepatotoxicity and/or LFT elevations." Was liver imaging obtained for this patient? If so, please provide the results of this imaging study.***
- 4. Have there been any other potential cases of Hy's Law in the neratinib safety database (all Sponsor and investigator initiated trials)?***

We would appreciate a response to this information request by **9AM EST Thursday February 23, 2017**. Please let me know if you have any questions.

Regards,

Pamela Balcazar, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
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PAMELA I BALCAZAR
02/17/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Friday, February 17, 2017 1:42 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Clinical Pharmacology Information Request

Hello Jesse

The purpose of this email is to relay a clinical pharmacology information request for NDA 208051.

Reference is made to the Clinical Study Report of Study 3144A1-200-WW in module 5.3.4.2. Please submit the raw pharmacokinetic data, with nominal sampling times (time points as stated in the study protocol), and compare the observed Ctrough between the dosing groups.

We would appreciate a response to this information request by 4PM EST Friday February 24, 2017. Please let me know if you have any questions.

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
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/s/

PAMELA I BALCAZAR
02/17/2017

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Monday, January 30, 2017 5:48 PM
To: Jesse Ho (jho@pumabiotechnology.com)
Subject: NDA 208051 Pharm/Tox Information Request

Good Afternoon Mr. Ho,
The purpose of this email is to send you an information request from our Pharm/Tox review team.

The electronic tumor data for the mouse carcinogenicity study were not included in your NDA submission (208051). These data are required for the Agency's independent statistical evaluation of the carcinogenicity of your drug.

We would appreciate a response by **4PM EST Wednesday, February 1, 2017**. If you have any questions, please let me know.

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
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Tel: 240-402-4203
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pamela.balcazar@fda.hhs.gov



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/s/

PAMELA I BALCAZAR
01/30/2017



NDA 208051

MID-CYCLE COMMUNICATION

Puma Biotechnology, Inc.
Attention: Jesse Ho, PharmD, RPh
Senior Associate, Regulatory Affairs
10880 Wilshire Blvd., Suite 2150
Los Angeles, CA 90024

Dear Dr. Ho:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nerlynx™ (neratinib maleate) Tablets, 40 mg.

We also refer to the teleconference between representatives of your firm and the FDA on December 15, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (240) 402-4203.

Sincerely,

{See appended electronic signature page}

Pamela Balcazar, MS
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: December 15, 2016, 2:00-3:00pm

Application Number: 208051

Product Name: Nerlynx™ (neratinib maleate) Tablets, 40 mg

Indication: early stage HER2-overexpressed/amplified breast cancer

Applicant Name: Puma Biotechnology

Meeting Chair: Laleh Amiri-Kordestani, MD

Meeting Recorder: Pamela Balcazar, MS

FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1

Amna Ibrahim, MD, Deputy Director, DOP1

Laleh Amiri-Kordestani, MD, Cross Discipline Team Leader, DOP1

Harpreet Singh, MD, Clinical Reviewer, DOP1

Joyce Cheng, PhD, Biostatistics Reviewer, DBV

Shenghui Tang, PhD, Biostatistics Team Lead, DBV

Walt Cao, PhD, Clinical Pharmacology Reviewer, OCP

Qi Liu, PhD, Clinical pharmacology Team lead, OCP

Nan Zheng, PhD, Pharmacometrics Reviewer, OCP

Jerry Yu, PhD, Pharmacometrics Team Lead, OCP

Pamela Balcazar, MS, Regulatory Health Project Manager, DOP1

APPLICANT ATTENDEES

Alan H. Auerbach, MS Chief Executive Officer & President

Robert Charnas, PhD Sr Vice President, Regulatory Affairs

Mark Pilato Director, Regulatory Sciences CMC

Bilqees Ahktar, MS, MPH Manager, Regulatory Sciences

Jesse Ho, PharmD Senior Associate, Regulatory Sciences

Richard Bryce, MBChB Sr. Vice President, Clinical R&D

Alvin Wong, PharmD Vice President, Clinical Science & Clinical Pharmacology

David Martin Senior Director, Preclinical Research

Susan Moran, MD, MSCE Vice President, Clinical Development

Elizabeth Olek, DO, MPH Sr. Medical Director, Clinical Development

Pamela Wilson Vice President, Clinical Operations

Rolando Ruiz, MD VP, Pharmacovigilance

Bin Yao, MS Sr Vice President, Biostatistics

Dan DiPrimeo, MS Senior Director, Statistical Programming

Yining Ye, PhD
Feng Xu
Susan McCabe

Director, Biostatistics
Director, Biostatistics
Senior Director, Project Management

(b) (4)

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical/Statistics

1. Statistical Analysis Plan Amendments and Study Conduct.
2. Selection of a 2-year iDFS endpoint and magnitude of clinical benefit.
3. Low Event Rate and Early Censoring in the primary analysis.
4. Lack of Benefit in ER negative patients.
5. Missing Data (only 73% reconsented) in Part B 5-year Follow up.
6. Potential bias introduced in the re consent process.
7. Lack of Overall Survival Data.
8. Risk/benefit ratio in terms of toxicity data, with concerns regarding combination of loperamide and neratinib.
9. Lack of supportive efficacy data in the clinical development program (failed trials in metastatic setting).

Clinical Pharmacology

1. Unknown potential PK interaction between loperamide and neratinib in the proposed prophylactic use of loperamide.
2. Dose selection and dose reduction scheme not sufficiently justified due to the uncertainties in the dose proportionality assessment.

Meeting Discussion:

To address clinical pharmacology issue #1 (the effect of prophylactic loperamide use on neratinib exposure), we have two proposals for the sponsor to consider:

1. To conduct a dedicated drug-drug-interaction study in healthy subject; or
2. To collect PK in on-going studies with loperamide prophylaxis and provide detailed loperamide dosing information including duration and amount.

3.0 INFORMATION REQUESTS

No Requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

All major safety concerns can be addressed through review of the submission and the responses to our information requests.

5.0 ADVISORY COMMITTEE MEETING

ODAC is scheduled for May 24, 2017.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting is currently planned for June 20, 2016. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 1, 2017.

We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of the review. You may choose altogether to cancel the Late Cycle Meeting, if you feel it is not needed, given our continued and regular communications. The PDUFA Action Date is July 19, 2017.

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/s/

PAMELA I BALCAZAR
12/16/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Monday, December 05, 2016 1:42 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Cc: Alebachew, Elleni
Subject: NDA 208051 pharmacometric IR

Good Afternoon

The purpose of this meeting is to provide a pharmacometric information request for NDA 208051.

Reference is made to "Population Pharmacometrics Report" in Module 5.3.5.3, submitted on November 21, 2016, in Sequence 0024.

- 1. For ER analysis for ORR in breast cancer patients on neratinib monotherapy, please conduct multivariate logistic regression analysis to adjust for the other potential prognostic factors, such as ECOG, baseline tumor burden and baseline LDH.*
- 2. 24 patients in ereffpk.xpt have adjusted steady state exposure metrics in ereffpk.xpt, but they do not have a matching record in poppk.xpt. Please clarify how the exposure metrics were simulated for these patients.*

We would appreciate a response to this IR by **4PM EST Monday December 12, 2016.**

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4203
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pamela.balcazar@fda.hhs.gov



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/s/

PAMELA I BALCAZAR
12/05/2016

**PeRC Meeting Minutes
November 16, 2016**

PeRC Members Attending:

Lynne Yao
John Alexander
Meshaun Payne
Gettie Audain
Greg Reaman
Donna Snyder
Gil Burkhart
Freda Cooner
Lily Mulageta
Dionna Green
Gerri Baer
Wiley Chambers
Victor Baum
Rosemary Addy
Shrikant Pagay
Adrienne Hornatko-Munoz
Megha Kaushal

Agenda

	NON-RESPONSIVE				
9:00					
9:15					
10:10					
10:20					
10:30					
10:50					
11:00					
11:10					
11:20					
11:40					
	NDA 208051	Nerlynx (neratinib maleate) Full Waiver (with Agreed iPSP)	DOP1	Pamela Balcazar	(b) (4)

6 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

NON-RESPONSIVE

Nerlynx (neratinib maleate) Full Waiver (with Agreed iPSP)

- Proposed Indication: (b) (4)
- *PeRC Recommendations:*
 - The PeRC agrees with the division to grant a full waiver because the studies are highly impracticable or impossible as outlined in the Agreed iPSP.

NON-RESPONSIVE

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/s/

GETTIE AUDAIN
12/02/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Wednesday, November 30, 2016 10:50 AM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 pharmacometric information request

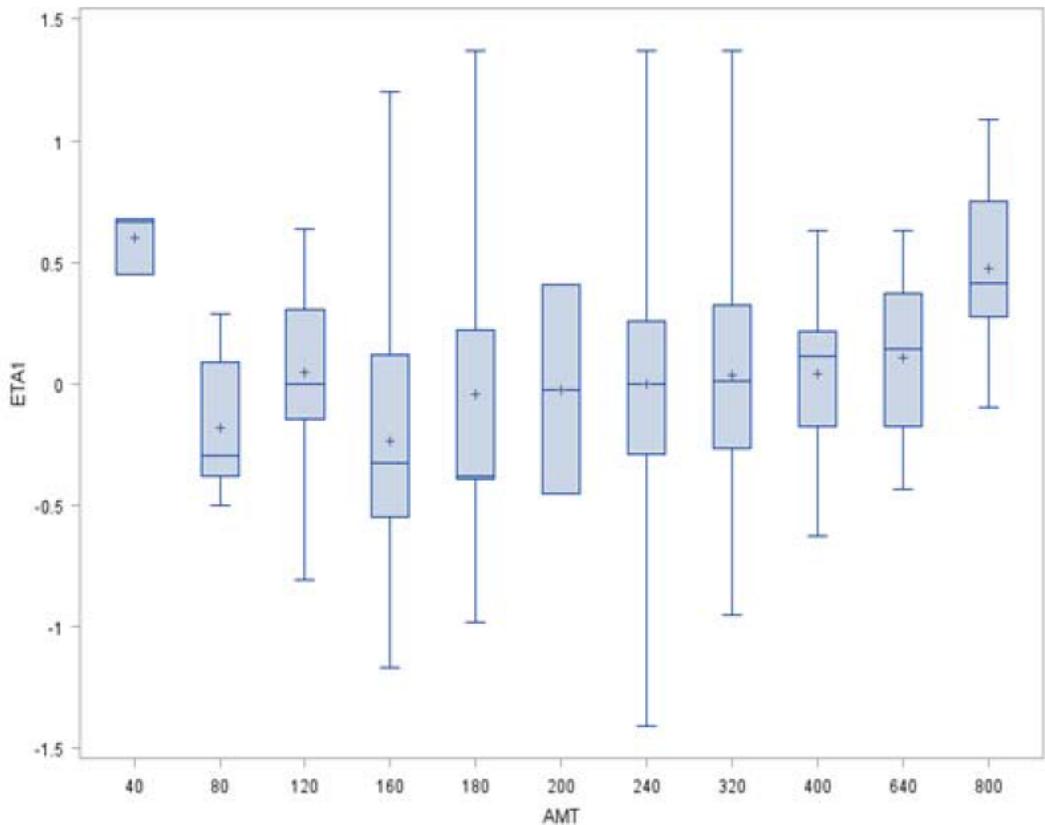
Dear Dr. Chang-Lok

The purpose of this email is to request a response to the following pharmacometric information request.

Reference is made to "Population Pharmacometrics Report" in Module 5.3.5.3, submitted on November 21, 2016, in Sequence 0024.

Please confirm if subjects labeled with concomitant loperamide took the same amount of loperamide throughout the PK sampling period. If not, the amount and time of loperamide administration should be considered as a time-varying covariate in the population PK analysis. Please refer to "Methods and strategies for assessing uncontrolled drug-drug interactions in population pharmacokinetic analyses: results from the International Society of Pharmacometrics (ISOP) Working Group" (J Pharmacokinet Pharmacodyn. 2016 Apr;43(2):123-35) for more information.

- 1. Please clarify the criteria (e.g., BILI, AST, and ASL ranges based on NCI criteria) used to derive HEPTCAT and HEPTCATN in the datasets.*
- 2. Below is a boxplot of individual estimate of ETA1 vs. dose based on the full model (1360.lst). Please provide an explanation to the trend of dose-dependent increase in CL/F above 400 mg dose level, as well as high CL/F values at the 40 mg dose level.*



We would appreciate a response by **4PM EST Wednesday December 7, 2016.**

Regards,

Pamela Balcazar, MS
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4203
Fax: 301-796-9845
pamela.balcazar@fda.hhs.gov



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/s/

PAMELA I BALCAZAR
11/30/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Tuesday, November 22, 2016 10:18 AM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 clinical IR

Good Morning

Our clinical reviewer has the following IR

1. *Patient number 3144-3004-1662-05781 experienced an episode of Grade 4 diarrhea. Based on the CRF (page 653, AE #58) this event occurred on 6/30/11 and resolved on the same day. This event was not marked as serious and there was no reported hospitalization or action taken with neratinib due to this adverse event. Please provide any additional information regarding this case of grade 4 diarrhea that may be available.*

2. *Please submit the final posters/slides for the following abstracts that you will be presenting at the upcoming San Antonio Breast Cancer Symposium:*
 - a. *P2-11-03: Incidence and severity of diarrhea with neratinib + intensive loperamide prophylaxis in patients (pts) with HER2+ early-stage breast cancer (EBC): Interim analysis from the multicenter, open-label, phase II CONTROL trial.*
 - b. *P4-21-10: Characterization of neratinib-induced diarrhea in patients with early-stage HER2+ breast cancer: Analyses from the phase III ExteNET trial.*

We would appreciate a response by **4PM EST Wednesday November 23, 2016.**

Regards

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4203
Fax: 301-796-9845
pamela.balcazar@fda.hhs.gov



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/s/

PAMELA I BALCAZAR
11/22/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, November 17, 2016 2:45 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Stat IR

Good Afternoon Mei Ling,
Our stat reviewer has an additional information request for you

In your modified simulation, we note that you tracked the number of events, stratified HR, and stratified log-rank p-value for each iteration. Please re-run the modified simulation and, in addition to the previously tracked values, also track the 2 year DFS rates for the neratinib and placebo arms and their difference across the 10,000 iterations. Please provide the mean, standard deviation, and range (min and max) for each of the following: 2-year DFS rate for the placebo arm, 2-year DFS rate for the neratinib arm, and the difference between the 2-year DFS rates of neratinib and placebo. Include updated results for the number of events, stratified HR, and stratified log-rank p-value as provided before as well.

We would appreciate a response by **4PM EST Tuesday November 22, 2016.**

Regards,

Pamela Balcazar, MS

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4203
Fax: 301-796-9845
pamela.balcazar@fda.hhs.gov



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PAMELA I BALCAZAR
11/17/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Monday, November 14, 2016 12:55 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 clinical Information request

Good Afternoon Mei Ling

Our clinical reviewer has the following information request for you

1. *There are a number of missing Case Report Forms from study 3144a2-3004-WW in the “Case Report Forms” folder in section 5.3.5.1, including the subjects listed in the table below. There are likely more missing CRFs than are listed below. Please provide any missing CRFs.*

<i>Site ID (as listed in 5.3.5.1)</i>	<i>Site ID (as listed in Datasets)</i>	<i>Subject ID</i>
002	0985	002317
002	0985	002319
003	0986	002302
004	0987	010226
004	0987	010229
004	0987	010233
005	0988	010207
005	0988	010211
005	0988	010215
007	0990	002376
206	1351	004111

2. *Based on the annotated CRF and datasets from study 3144a2-3004-WW, it appears that the information collected regarding concomitant medications included the amount of medication prescribed by the physician but did not include the amount of medication actually taken by the patient. Please confirm that information regarding the amount of medication (e.g. loperamide and other anti-propulsives) actually taken by the patient is not available. If this information was collected and submitted with the NDA, please provide the location where it can be found.*

We would appreciate a response to this request by **4PM EST Wednesday November 16, 2016.**

Regards,
Pamela Balcazar, MS
Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.
White Oak Bldg 22, Room 2133
Silver Spring, MD 20993
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pamela.balcazar@fda.hhs.gov

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PAMELA I BALCAZAR
11/14/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, November 10, 2016 7:03 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Stat information request

Good Evening Mei Ling
Our statistical reviewer has the following:

We identified five patients (see table below) for whom the analysis date in the updated 2-year dataset (ADTTEB1) appears to precede the analysis date in the primary analysis dataset (ADTTE) and in some cases resulted in an event that was previously unreported. Please explain these discrepancies.

<i>USUBJID</i>	<i>TRTP</i>	<i>ADT in ADTTE</i>	<i>AVAL in ADTTE</i>	<i>CNSR in ADTTE</i>	<i>ADT in ADTTEB1</i>	<i>AVAL in ADTTEB1</i>	<i>CNSR in ADTTEB1</i>
<i>3144-3004-1076-00905</i>	<i>Placebo</i>	<i>2011-12-20</i>	<i>24.41068</i>	<i>1</i>	<i>2011-12-16</i>	<i>24.27926</i>	<i>0</i>
<i>3144-3004-1076-15652</i>	<i>Placebo</i>	<i>2012-01-25</i>	<i>12.15606</i>	<i>1</i>	<i>2012-01-16</i>	<i>11.86037</i>	<i>0</i>
<i>3144-3004-1185-17899</i>	<i>Placebo</i>	<i>2013-03-20</i>	<i>23.98357</i>	<i>1</i>	<i>2012-12-20</i>	<i>21.02669</i>	<i>0</i>
<i>3144-3004-1526-05061</i>	<i>Neratinib</i>	<i>2012-01-25</i>	<i>24.93634</i>	<i>1</i>	<i>2011-10-05</i>	<i>21.25667</i>	<i>1</i>
<i>3144-3004-1860-16496</i>	<i>Placebo</i>	<i>2013-03-05</i>	<i>16.52567</i>	<i>0</i>	<i>2012-11-26</i>	<i>13.2731</i>	<i>0</i>

We would appreciate a response to this information request by **4PM EST Thursday November 17, 2016.**

Regards,
Pamela Balcazar, MS
Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.
White Oak Bldg 22, Room 2133
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PAMELA I BALCAZAR
11/10/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, November 10, 2016 7:09 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Clinical Information Request

Good Evening Mei Ling
Our clinical reviewer has the following information request.

In earlier correspondence, you noted that you plan to send updated 5-year DFS datasets to the FDA in December 2016. Please plan to send these by December 1st, 2016.

We would appreciate a response by **4PM EST Monday November 14, 2016** whether your team is in agreement with this timeline.

Regards,
Pamela Balcazar, MS
Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.
White Oak Bldg 22, Room 2133
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PAMELA I BALCAZAR
11/10/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, November 03, 2016 3:16 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Statistical Information Request

Good Afternoon Mei Ling

Reference is made to “Response to 26-Sep-2016 Population Pharmacokinetic Information Request” in Module 1.11.3 (submitted on Oct 31, 2016, in Submission Sequence 0017): Please use the average daily exposure (e.g. simulated $C_{\text{trough,ss}}$, AUC_{ss} , or $C_{\text{max,ss}}$ adjusted by the actual dose intensity from the time of first dose to the time of event), as the exposure metrics in your response to Questions 3 and 4. .

Reference is made to “Analysis Dataset Legacy” in Module 5.3.5 (submitted on Oct 31, 2016, in Submission Sequence 0017): Please clarify the starting dose for SUBJID 5376 in dataset ER3004.xpt.

We would appreciate an update to the response, code, and datasets accordingly by **4PM EST Wednesday November 16, 2016**. Please let me know if you have any questions.

Regards,

Pamela Balcazar, MS

Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.
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PAMELA I BALCAZAR
11/03/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Monday, October 31, 2016 10:40 AM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Information request

Good Morning Mei Ling
Our review team has the following information request.

Please submit a SAS XPT file of QTcl's correction factors of all subjects for Study 3144A1-105-US. Furthermore, provide the name of the ECG central lab, the method used to measure ECG intervals (manual, semi-automatic, or automatic), and what ECG readers were blinded to.

We would appreciate a response to this request by **4PM EST Thursday November 3, 2016**.

Regards,
Pamela Balcazar, MS
Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.
White Oak Bldg 22, Room 2133
Silver Spring, MD 20993
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/s/

PAMELA I BALCAZAR
10/31/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Monday, October 24, 2016 1:12 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Stat Information Request

Good Afternoon Mei Ling
Our stat reviewer has the following information request.

In Section 3.1 of the SDTM overview, you indicate that the SDTM datasets were not used as sources for the analysis datasets in part B and further state, "The analysis datasets for part B are derived directly from the raw datasets without representation in the ADaM dataset. This was done to preserve the blinding for OS." Please instruct on how to access the raw datasets from which the analysis datasets for part B were derived. If this information is not currently included in the submission, please submit the indicated raw datasets and SAS programs used to derive the corresponding analysis datasets (ADTTEB1 and ADTTEB2) with documentation.

We would appreciate a response by **3PM EST Friday October 28, 2016.**

Regards,
Pamela Balcazar, MS
Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.
White Oak Bldg 22, Room 2133
Silver Spring, MD 20993
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PAMELA I BALCAZAR
10/24/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Wednesday, October 05, 2016 4:25 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Clinical IR

Good Afternoon Mei Ling

Our clinical reviewer has the following information request.

We wanted to bring to your attention missing data within the Adverse Events Domain of Tabulation Data from Study 3144A2-3004-WW. The Standard Toxicity Grade (AETOXGR) is missing for 80 records. 76 of 80 missing records are from one site (1804); the remaining 4 are from a second site (2086). If available, please provide the CTC grade for the missing records.

We would appreciate a response to this information request by **4PM EST Wednesday October 19, 2016.**

Thanks,
Pamela Balcazar, MS
Regulatory Health Project Manager
Division of Oncology Products 1, OHOP
White Oak Bldg 22, 2nd floor, Room 2133
(240) 402-4203 (office)
(301) 796-9845 (fax)
pamela.balcazar@fda.hhs.gov

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/s/

PAMELA I BALCAZAR
10/06/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, October 06, 2016 3:33 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Clinical IR

Good Afternoon Mei Ling

Our clinical reviewer has the following information request.

In response to our previous information request, you reported that you plan to submit your updated 5-year iDFS results in May of 2017.

Please confirm that based on when you stopped enrolling patients, it is expected that all enrolled patients will have completed 5 years of follow up by this month, October 2016. If that is the case, please provide a summary of your updated 5-year iDFS results within the year 2016. We would also like for you to provide datasets for these results.

Please explain the rationale behind the 7-month delay between availability up updated 5-year iDFS results and providing them to the Agency.

We would appreciate a response to this information request by **4PM EST Wednesday October 12, 2016.**

Regards,

Pamela Balcazar, MS

Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.
White Oak Bldg 22, Room 2133
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/s/

PAMELA I BALCAZAR
10/06/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Monday, September 26, 2016 9:12 AM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Information request

Good Morning Mei Ling,

Please disregard previous information request email that was sent and reference this one. I have corrected the response date on this one.

Our Pharmacometrics Team has the following information request for your NDA.

Reference is made to the Report "Population Pharmacokinetics Report" in Module 5.3.5.3:

1. *Add Studies A1-105, A1-107, A1-1116, A1-1117, A1-1127, 10-005, A1-200, and NER-4201 to the population PK analysis dataset. Further evaluate the effect of race, renal function measures and category, hepatic function measures and category, healthy vs patient, cancer type, loperamide use(or other anti-diarrheal drug use) and other concomitant medication on neratinib PK. Update the popPK report accordingly.*
2. *In Study ExteNET/3004, conduct graphical analysis (K-M analysis) on iDFS in subgroups with or without dose reduction. Evaluate the relationship (logistic regression) between safety endpoints and the average daily dose up to the time of events of interest. Submit the results with code and final analysis datasets. In addition, include the time of event for each individual for each type of endpoint in the datasets.*
3. *Conduct ER analysis (logistic regression) on efficacy with data from breast cancer patients on neratinib monotherapy in Studies A1-102, A1-104, A1-2206, A1-201, and A2-3033. Use the average daily exposure up to the time of event (i.e., time of the assessment of response) as the exposure metrics. Submit the results with code and final analysis datasets. In addition, include the time of event for each individual in the datasets.*
4. *Conduct ER analysis (logistic regression) for safety with data from patients on neratinib monotherapy in Studies A1-102, A1-104, A1-2206, A1-201, and A2-3033. Conduct ER analysis using the following safety endpoints: Grade 1 diarrhea, Grade 2 diarrhea, Grade 3 and above diarrhea, Grade 3 and above fatigue, elevated liver enzyme levels, and rash. Use the average daily exposure up to the time of event as the exposure metrics. Submit the results with code and final analysis datasets. In addition, include the time of event for each individual for each type of safety event in the datasets.*

We would appreciate a response by **4PM EST Monday October 31, 2016**. If you have any questions please let me know.

Regards,

Pamela Balcazar, MS

Regulatory Health Project Manager

Food and Drug Administration (FDA)

Office of Hematology and Oncology Products – DOP1

10903 New Hampshire Ave.

White Oak Bldg 22, Room 2133
Silver Spring, MD 20993
(240) 402-4203 (office)
(301) 796-9845 (fax)
pamela.balcazar@fda.hhs.gov

***FDA requires the use of secure email for all communications that may include proprietary information.
To establish, please contact secureemail@fda.hhs.gov*

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/s/

PAMELA I BALCAZAR
09/26/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Thursday, September 22, 2016 10:09 AM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051

Hi Mei Ling

Our clinical reviewers have the following information request for you.

1. *In your application orientation meeting, you discussed the potential cross talk between ER-HER2 in ER+, ERBB2 mutant tumors, and cited preliminary data from Study 5201. Please provide with us an updated study report of Study 5201, including any patient narratives you may have.*
2. *Please confirm when you plan to submit the updated 5-year iDFS results.*

We would appreciate a response by **4PM EST August 27, 2016**. If you have any questions please let me know.

Regards,

Pamela Balcazar, MS

Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.
White Oak Bldg 22, Room 2133
Silver Spring, MD 20993
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/s/

PAMELA I BALCAZAR
09/22/2016



NDA 208051

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Puma Biotechnology, Inc.
Attention: Mei Ling Chang-Lok, PhD
Sr. Director, Global Regulatory Lead
10880 Wilshire Blvd., Suite 2150
Los Angeles, CA 90024

Dear Dr. Chang-Lok:

Please refer to your New Drug Application (NDA) dated July 19, 2016, received July 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Nerlynx™ (neratinib maleate) Tablets, 40 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 19, 2017. This application is also subject to the provisions of “The Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 26, 2017. In addition, the planned date for our internal mid-cycle review meeting is December 13, 2016. We are currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. Revise the horizontal lines in the Highlight section as the horizontal lines in the headings don’t extend over the width to the left side of the columns.
2. Revise the type of font to be consistent throughout the label.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 5, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Pamela Balcazar, Regulatory Project Manager, at (240) 402-4203.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GEOFFREY S KIM
09/16/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Tuesday, September 06, 2016 2:09 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 Clinical IR

Good Afternoon Mei Ling
Our clinical reviewer has the following request for you.

We are having difficulty manipulating the site-listings.pdf which is located in Module 5.3.5.4 bimo-BIMO, in the folder “List Description Investigator Site” The file is entitled “Site Listings” .

Please resubmit this file so that it can be manipulated in Adobe. Alternatively, please re-submit this information in multiple, separate files, none of which exceed 10 MB.

We would appreciate a response by **4PM EST Thursday September 8, 2016.**

If you have any questions please let me know.

Regards,
Pamela Balcazar, MS
Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.
White Oak Bldg 22, Room 2133
Silver Spring, MD 20993
(240) 402-4203 (office)
(301) 796-9845 (fax)
pamela.balcazar@fda.hhs.gov

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/s/

PAMELA I BALCAZAR
09/09/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Wednesday, August 31, 2016 12:52 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 clinical IR

Good Afternoon Mei Ling

We have the following information request

- 1. Please confirm who determined the primary efficacy endpoint of iDFS? Was it just the site clinical investigator or was there also an independent central review?**
- 2. If there was a central review vendor, please clarify whose results are presented in APPENDIX 16.2.6. from CSR 3144A2-3004-WW DATED 12-APR-16? The clinical investigator or IRC?**
- 3. Please confirm data cut off for the data listings in study 3144A2-3004-WW.**
- 4. For Site 1804, Dr. Robert Nicolas of Fairfax, VA, there is no data in the application for DFS. Can you confirm that there were no efficacy endpoints reported for this site?**

We would appreciate a response to this information by **4PM EST Thursday September 1, 2016.**

Regards,

Pamela Balcazar, MS

Regulatory Health Project Manager

Food and Drug Administration (FDA)

Office of Hematology and Oncology Products – DOP1

10903 New Hampshire Ave.

White Oak Bldg 22, Room 2133

Silver Spring, MD 20993

(240) 402-4203 (office)

(301) 796-9845 (fax)

pamela.balcazar@fda.hhs.gov

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/s/

PAMELA I BALCAZAR
08/31/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Tuesday, August 30, 2016 2:49 PM
To: Mei Ling Chang (MChang@pumabiotechnology.com)
Subject: NDA 208051 information request

Good Afternoon Mei-Ling

Hope you all had a good trip back to California. We have the following information requests for your team.

Clinical

1. For the 3004 ADaM – interim 5-year data, please submit CRF's for patients who were re-consented for 5-year DFS and OS follow up. (Parts B and C)
2. Please submit any monitoring guides or policies and procedures which were implemented in the collection of data for Parts B and C.

Biostatistics

1. Please submit stand-alone/executable programs (with documentation) for the simulation study you conducted as a sensitivity analysis to address early neratinib drop-outs.
2. We were unable to locate any IDMC meeting minutes in the submission. If they were submitted, please help direct us to their location, and if not, please provide this information.

We would appreciate a response to these IR's by **4PM EST Tuesday September 6, 2016.**

Please let me know if you have any questions.

Regards,

Pamela Balcazar, MS

Regulatory Health Project Manager

Food and Drug Administration (FDA)

Office of Hematology and Oncology Products – DOP1

10903 New Hampshire Ave.

White Oak Bldg 22, Room 2133

Silver Spring, MD 20993

(240) 402-4203 (office)

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pamela.balcazar@fda.hhs.gov

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/s/

PAMELA I BALCAZAR
08/30/2016



NDA 208051

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Puma Biotechnology, Inc.
10880 Wilshire Blvd.
Suite 2150
Los Angeles, CA 90024

ATTENTION: Mei Ling Chang-Lok, Ph.D.
Sr. Director, Global Regulatory Lead

Dear Dr. Chang-Lok:

Please refer to your New Drug Application (NDA) dated and received July 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neratinib Tablets, 40 mg.

We also refer to your correspondence, dated and received July 19, 2016, requesting review of your proposed proprietary name, Nerlynx.

We have completed our review of the proposed proprietary name, Nerlynx and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 19, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Pamela Balcazar, Regulatory Project Manager in the Office of New Drugs at (240) 402-4203.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/25/2016

Balcazar, Pamela

From: Balcazar, Pamela
Sent: Tuesday, August 23, 2016 11:48 AM
To: 'Mei Ling Chang'
Subject: RE: NDA 208051 information request

Hi Mei Ling

Just the EXTENET 3004 study.

Thanks,
Pamela Balcazar | DOP1 | WO 22, RM 2133
pamela.balcazar@fda.hhs.gov

From: Mei Ling Chang [<mailto:MChang@pumabiotechnology.com>]
Sent: Tuesday, August 23, 2016 11:42 AM
To: Balcazar, Pamela
Subject: RE: NDA 208051 information request

Dear Pamela,

Just to clarify, would you like a table including just the EXTENET (3004) and 6201 studies or should this table include other studies?

Thank you,

Mei Ling

From: Balcazar, Pamela [<mailto:Pamela.Balcazar@fda.hhs.gov>]
Sent: Tuesday, August 23, 2016 8:38 AM
To: Mei Ling Chang
Subject: NDA 208051 information request

Hi Mei Ling

Can you provide us with a table that includes all original site numbers, the SITEID (derived Study Site Identifier used in datasets) and the investigators name?

We need this information by **4PM EST Thursday August 25, 2016**. Please let me know if you have any questions.

Regards,
Pamela Balcazar, MS
Regulatory Health Project Manager
Food and Drug Administration (FDA)
Office of Hematology and Oncology Products – DOP1
10903 New Hampshire Ave.

White Oak Bldg 22, Room 2133
Silver Spring, MD 20993
(240) 402-4203 (office)
(301) 796-9845 (fax)
pamela.balcazar@fda.hhs.gov

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/s/

PAMELA I BALCAZAR
08/23/2016



IND 066783

MEETING MINUTES

Puma Biotechnology, Inc.
Attention: Mei Ling Chang-Lok, Ph.D.
Senior Director, Global Regulatory Lead
10880 Wilshire Blvd Suite 2150
Los Angeles, CA 90024

Dear Dr. Chang-Lok:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Neratinib (PB-272).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Pamela Balcazar, Regulatory Project Manager, at (240) 402-4203.

Sincerely,

{See appended electronic signature page}

Pamela Balcazar, MS
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology
Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Clinical Team Lead
Division of Oncology Products
Office of Hematology and Oncology
Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: March 21, 2016, 2-3 pm
Meeting Location: White Oak Building 22, Conference Room: 1419
Application Number: IND 066783
Product Name: Neratinib (PB-272)
Indication: early-stage HER2-overexpressed/amplified breast cancer
Sponsor/Applicant Name: Puma Biotechnology

Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Pamela Balcazar, MS

FDA ATTENDEES

Geoffrey Kim, MD	Director, DOP1
Laleh Amiri-Kordestani, MD	Clinical Team Lead (Acting), DOP1
Amanda Walker, MD	Clinical Reviewer, DOP1
Julia Beaver, MD	Clinical Reviewer, DOP1
Michael Brave, MD	Clinical Reviewer, DOP1
Sara Horton, MD	Clinical Reviewer, DOP1
Tatiana Prowell, MD	Clinical Reviewer, DOP1
Nancy Scher, MD	Clinical Reviewer, DOP1
Suparana Wedam, MD	Clinical Reviewer, DOP1
Chana Weinstock, MD	Clinical Reviewer, DOP1
Todd Palmby, PhD	Pharm/Tox Team Lead, DHOT
Haw-Jyh Chiu, PhD	Pharm/Tox Reviewer, DHOT
Pengfei Song, PhD	Clinical Pharmacology Reviewer, OCP
Jeanne Fourie-Zirkelbach, PhD	Clinical Pharmacology Reviewer, DCPV
Shenghui Tang, PhD	Statistics Team Lead, DBV
Erik Bloomquist, PhD	Statistics Reviewer, DBV
Alice Kacuba, RN	Chief, Project Management, DOP1
Pamela Balcazar, MS	Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES

Alan H. Auerbach, MS	Chief Executive Officer & President
Richard P. Bryce, MBChB	Sr. Vice President, Clinical R&D
Mei Ling Chang-Lok, PhD	Sr. Director, Global Regulatory Lead
Erin E. Jones, MS	Vice President, Global Regulatory Affairs
Susan Moran, MD, MSCE	Sr. Medical Director, Clinical R&D
Alvin Wong, PharmD	Vice President, Clinical Science & Clinical Pharmacology
Bin Yao, MS	Vice President, Biostatistics

1.0 BACKGROUND

Puma Biotechnology, Inc. is currently developing neratinib (PB-272, HKI-272) tablets under IND 066783. Neratinib is an irreversible tyrosine kinase inhibitor that blocks EGFR, HER2 and HER4. The purpose of this Type B meeting is to review and reach agreement with the Agency on the format and content of Puma's planned NDA. Puma is preparing an NDA based on the results of Study 3144A2-3004-WW ("Study 3004") for the marketing of neratinib with the following indication:

Extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy.

Puma intends to support the NDA submission with results from Study 3004, a Phase 3, randomized, placebo-controlled study in 2,840 patients comparing neratinib with placebo after adjuvant treatment with trastuzumab-based therapy in women with early-stage HER2-positive breast cancer. Study 3004 demonstrated that neratinib administered for 12 months improves the absolute DFS at two years from 91.6% to 93.9% (HR 0.67; 95% CI 0.50-0.91; 1 sided $p = 0.005$). Efficacy results from Study 3004 are shown in the table below.

Table 1: Efficacy Endpoint Analyses (Intention-to-Treat Population)

Variable	Estimated event-free survival rate at 2 years*		Hazard ratio (95 percent confidence interval)†	One-sided P Value‡
	Neratinib (N = 1420)	Placebo (N = 1420)		
	percent	percent		
Invasive disease-free survival	93.9	91.6	0.67 (0.50, 0.91)	0.005
Disease-free survival including ductal carcinoma <i>in situ</i>	93.9	91.0	0.63 (0.46, 0.84)	<0.001
Distant disease-free survival	95.1	93.7	0.75 (0.53, 1.04)	0.044
Time to distant recurrence	95.4	93.9	0.71 (0.50, 1.00)	0.027
CNS recurrence	0.91	1.25	–	0.218

CNS = central nervous system.

* Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.

† Stratified Cox proportional hazards model

‡ Stratified 1-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

Puma plans to submit the NDA to the Agency at the end of Q2 2016. However, as summarized below there are several statistical issues related to the design and conduct of Study 3004.

Study 3004 began enrollment in April 2009 under Wyeth. The primary objective was to compare invasive disease free survival (iDFS) of women with stage I-III, node positive or negative, HER2 overexpressed/amplified breast cancer after standard locoregional and systemic treatment including 12 months of trastuzumab followed by extended adjuvant treatment with either neratinib or placebo for one year. Patients were initially allowed to enroll up to two years after completion of neoadjuvant trastuzumab.

After study commencement, the BCIRG 006 adjuvant trastuzumab study reported a 93%, 5-year DFS rate for node-negative patients treated with AC-TH, indicating that the risk of tumor recurrence may be lower than expected when the trial was originally designed. As a result, the study was amended in February 2010 to only enroll patients with a higher risk of recurrence, defined as node positive disease and trastuzumab completion ≤ 1 year prior to randomization. The primary endpoint was altered to iDFS in the amended ITT population. In October 2011, two key changes were made by Pfizer (who acquired Wyeth in 2009) – 1) cessation of enrollment and 2) shortening follow-up to two years from study randomization.

Study 3004 was continued under this design until January 2014 at which time Puma (who licensed neratinib from Pfizer in 2011) implemented a global amendment (Global amendment 13) that restored the study to its primary intention, ie, to obtain iDFS and OS data for all randomized subjects with the primary analysis being conducted at 2 years of follow-up. At this point, patients were re-enrolled on the study in order to obtain additional follow-up data for 5-years post-randomization.

Another statistical concern with the study was that the number of patients followed for 24 months was relatively low in each arm, 662 (47%) patients in the neratinib arm and 704 (50%) patients in the placebo arm. In previous communications with the Sponsor, FDA asked for information regarding the significant number of early drop outs in Study 3004. The Sponsor clarified that the early drop-outs in the neratinib arm were primarily due to toxicities experienced by patients either as a direct reason (“adverse event”) or a related but indirect reason (“subject request”). A total of 355 patients in the neratinib arm discontinued treatment due to an AE and 123 subjects discontinued at their request. In total, this represents approximately 37% of the patients who received neratinib.

The most common adverse events in Study 3004 were GI toxicities, specifically diarrhea, nausea, vomiting, and abdominal pain. The most frequently reported Grade 3 or 4 TEAEs and the most frequent TEAEs leading to study drug discontinuation were diarrhea and, to a lesser extent, vomiting. In the 1,408 patients who received neratinib in Study 3004, 39.8% and 1.4% experienced Grade 3 and 4 diarrhea, respectively. Other commonly reported TEAEs include fatigue, dermatologic toxicities, and intermittent increases in liver enzymes; less than 2% of these events were severe or required treatment discontinuation and $<0.5\%$ were considered serious.

The Sponsor is currently investigating the use of prophylactic loperamide with the use of neratinib in the extended adjuvant setting. Of the 159 patients who have received prophylactic loperamide across the development program, the rate of Grade 3 diarrhea was improved to (b) (4)%. The implementation of loperamide prophylaxis also appears to decrease the number of drug discontinuations, dose reductions, and treatment interruptions.

FDA sent Preliminary Comments to Puma Biotechnologies on March 08, 2016.

2. DISCUSSION

Question 1: Protocol 3144A2-3004-WW is a Phase III randomized, double-blind, placebo-controlled trial of neratinib (HKI-272) after trastuzumab based therapy in women with early-stage HER-2/neu overexpressed/amplified breast cancer with the primary endpoint of invasive disease-free survival (DFS). The primary data to support efficacy and safety for the indication will be derived from the primary analysis of Study 3144A2-3004-WW (“3004”). In addition, 30 interim and final clinical study reports (CSRs) from trials of neratinib in various indications (early Breast Cancer, Metastatic Breast Cancer and other solid tumors with mutations) will be included in the NDA to support the pivotal 3004 study. A total of 1408 patients were exposed to neratinib in the pivotal trial and a total of 3252 patients were exposed during the development program.

Does the Division agree that the efficacy and safety results from the single pivotal study, 3144A2-3004-WW (“3004”), along with the efficacy and safety data from supportive studies provide sufficient clinical experience to characterize the benefits and risks of neratinib, and support the basis of an NDA for approval in the proposed indication?

FDA Response dated March 08, 2016: No. We do not encourage an NDA submission based on the efficacy and safety results of Study 3144A2-3004-WW that you have provided in your briefing package. Your study has several issues that will likely make the interpretation of the results problematic. For one, the number of dropouts can impact the interpretation of the final results due to a small overall number of DFS events and brings into question whether this trial constitutes an adequate and well-controlled trial. Two, the protocol change to an increased risk population (global amendment 3) precludes the interpretation of ITT population as all-comers. Three, the use of a time-driven primary analysis instead of an event-driven analysis can artificially censor individuals with known DFS times. Four, the group of individuals reenrolled for the 5-year follow-up may or may not be representative of the full ITT population. And five, the Agency has not utilized a 2-year DFS as the primary analysis for an adjuvant study in breast cancer to support marketing approval of an NDA.

If the application is submitted, an Oncologic Drugs Advisory Committee discussion will be required.

Meeting Discussion: We acknowledge sponsor’s responses. FDA reiterated the concerns about the study results however these statistical and clinical issues are not refuse to file issues.

Question 2: Puma submitted version 1.1 of the 3144A2-3004 WW Statistical Analysis Plan (SAP) on July 01, 2015 to incorporate changes requested by the Agency. Does the Division have further comments on version 1.1 of the SAP?

FDA Response dated March 08, 2016: Please see response to Q1. FDA reiterates its previous comment from March 11, 2015: “We noticed that you proposed a sensitivity analysis of DFS, in which patients with DFS events right after two or more missing physical exams will be censored at the last physical exam. Instead of making this a sensitivity analysis, you should use this censoring rule for the primary analysis.”

Meeting Discussion: No discussion

Question 3: Puma proposes to submit a safety update 120-days after the original NDA is submitted inclusive of the following information:

1. Patients enrolled in the pivotal study, 3004, are no longer on treatment and the update will therefore consist of any incremental safety data entered into the clinical database between the data cutoff of July 2014 and database lock in December 2014. An updated SAE listing including any neratinib related SAEs reported by enrolled patients since December 2014 will be provided from the safety database.
2. Updated cumulative safety data from the ongoing PUMA-NER-6201, an open-label study to characterize the incidence and severity of diarrhea in patients with early-stage HER2+ breast cancer (analogous to the 3004 population) treated with neratinib for one year and intensive loperamide prophylaxis given for the first two cycles of treatment.
3. Pooled cumulative diarrhea analyses from the 4 ongoing studies where prophylactic use of antidiarrheal medication is mandatory will be provided. These studies include studies of neratinib monotherapy (PUMA-NER-6201 and PUMA-NER 5201) and studies of neratinib in combination with temsirolimus (PUMA-NER-4201 and Study 10-005).

Revised safety data from ongoing clinical studies will be reflected in both updated Clinical Summary of Safety and labeling. Does the Agency agree that this plan is acceptable?

FDA Response dated March 08, 2016: Yes. See response to Q1.

Meeting Discussion: No discussion

Question 4: Based on the safety data of the pivotal Phase III study 3144A2-3004-WW (randomized, double blind, placebo-controlled trial), PUMA does not believe that REMS is warranted. The Sponsor proposes to utilize routine post marketing

pharmacovigilance and labeling to manage the identified and potential risks for neratinib.

Does the Agency agree that neratinib in extended HER2 amplified adjuvant breast cancer, with a routine post marketing pharmacovigilance process in place, adequately assesses potential patient risks for this patient population and an additional REMS program is not required?

FDA Response dated March 08, 2016: See response to Q1. This would be a review issue.

Meeting Discussion: No discussion

Question 5: No diarrhea prophylactic measures to prevent neratinib related diarrhea were undertaken in pivotal study 3144A2-3004-WW, where diarrhea was treated after it occurred. In efforts to potentially prevent and reduce the incidence of neratinib related Grade 3 and higher diarrhea, ongoing clinical studies (PUMA-NER 6201, PUMA-NER-4201, PUMA-NER 5201 and Study 10-005) have shown that loperamide administered prophylactically substantially reduces the frequency and severity of Grade 3 and higher diarrhea.

In an effort to guide physician's treatment, Puma plans to include the results from Study 6201, a Phase II trial of neratinib monotherapy for one year as extended adjuvant treatment in patients with HER2 positive early stage breast cancer in patients who have previously received adjuvant trastuzumab in which patients received loperamide prophylaxis for the first two cycles, in the label. Does the Agency agree with our plan to include loperamide prophylaxis instructions in the draft labeling?

FDA Response dated March 08, 2016: See Response to Q1. Labeling is not discussed prior to NDA review. This would be a review issue. We are concerned that even with loperamide prophylaxis there was still an observed incidence of Grade 3 diarrhea of (b) (4) %.

Meeting Discussion: FDA recommends submitting the data from study 6201 with the sponsor's potential NDA submission for review.

Question 6: As discussed in the 25 November 2014 Type-C meeting with the Agency, the neratinib NDA for adjuvant breast cancer will be supported by a carcinogenicity program comprised of 6-month RasH2 transgenic mouse carcinogenicity and a 2 year Sprague Dawley rat carcinogenicity study. Provided in this briefing document, are the results of the 6-month transgenic mouse carcinogenicity study. In response to global health authority input, Puma has amended the rat carcinogenicity study to include a 1 year interim data analysis, which will be available at the time of the NDA submission. The 1 year interim data analysis replaces the 39 week interim data analysis that was in the prior version of the rat carcinogenicity protocol. In consideration that neratinib has been characterized in a full battery of Segment I, II and III developmental and

reproductive toxicity studies, 9-month dog and 6-month rat chronic toxicity studies, as well as the standard battery of genotoxicity studies, and results have shown no significant safety signals, Puma proposes to submit the final 6-month transgenic carcinogenicity report and a one year interim report of the 2-year rat carcinogenicity in the original NDA submission and provide the final 2-year rat carcinogenicity study report as a post-marketing commitment.

Does the Agency agree that the final 6-month rasH2 Tg mouse carcinogenicity report and a 1-yr interim report for the Sprague-Dawley rat carcinogenicity study are adequate preclinical safety data to support a complete review of the original NDA submission?

FDA Response dated March 08, 2016: No. We reiterate that final study reports for both the 6-month rasH2 Tg mouse and 2-year rat carcinogenicity studies should be included in an NDA submission to support the proposed indication, which is consistent with the ICH M3(R2) guidance.

Meeting Discussion: FDA recommends that the sponsor submit a type A meeting request and include the 1 year interim report for the rat carcinogenicity study and the final report for the 6-month transgenic mouse carcinogenicity study when available. After reviewing this meeting package, FDA will determine if the lack of a final report for the 2 year study will be a filing issue.

Question 7: Does the Agency agree that the overall proposed table of contents and organization of the new drug marketing application to be submitted electronically in eCTD format are acceptable?

FDA Response dated March 08, 2016: Please refer to our Type C WRO meeting dated October 27, 2015 regarding the table of contents and organization. Please see Response to Question 1.

Meeting Discussion: No discussion

Additional FDA Comment dated March 08, 2016:

We refer you to previous clarifications requested by FDA (SDN 890) regarding proposed Clinical Pharmacology Program for the initial NDA submission. With respect to the pop PK analysis for the original NDA submission:

- Please provide justification for excluding PK data from other studies (e.g., study 3144A1-102-US and study 3144A1-104-JA) in your planned population PK analysis.
- Clarify if exposure-response analyses for efficacy and safety are planned for study 3144A2-3004-WW.

The meeting package did not contain enough information to determine whether an adequate PK bridge was established between the clinical trial formulations (capsule/tablet) and the (b) (4) mg tablet commercial formulation. Please clarify which formulation of your drug was used in trial 3144A2-3004-WW.

Meeting Discussion: No discussion

3. OTHER

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

All applications are expected to be complete upon submission. Please see Question 1 and 2 above, along with respective FDA responses. After the submission of the Type A Meeting Request to provide for and discuss the results of final study reports for both the 6-month rasH2 Tg mouse and the interim 1-year update on the 2-year rat carcinogenicity studies, FDA and the Sponsor will then document discussion of any late submissions.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidance.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments,

and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

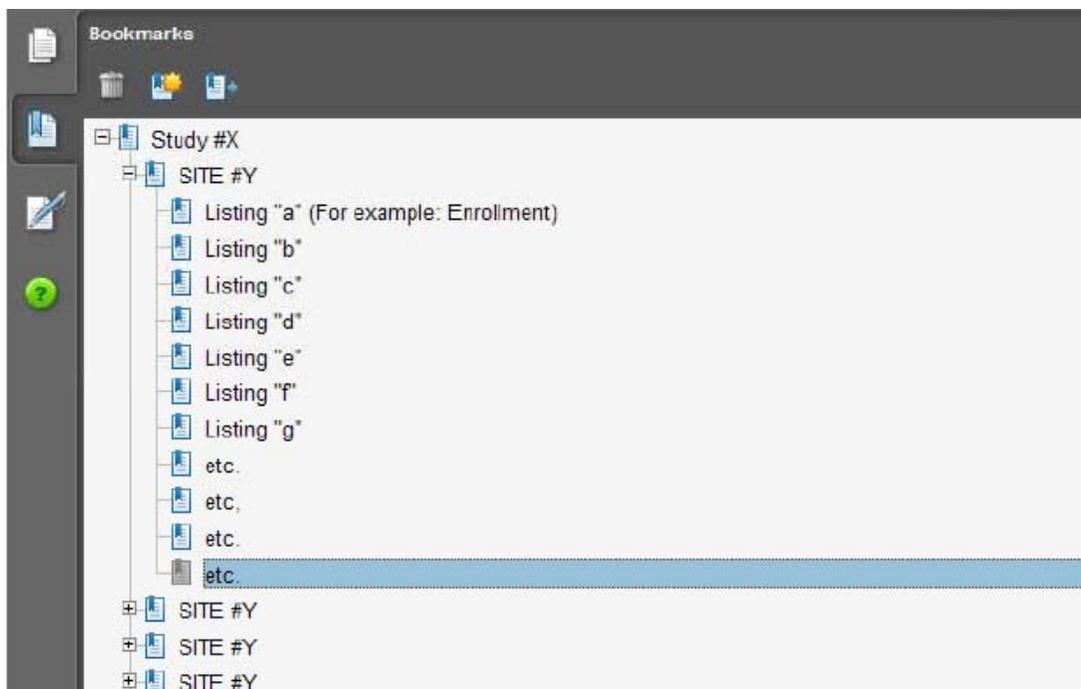
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

6.0 Sponsor Comments Submitted on March 18, 2016

APPEARS THIS WAY ON ORIGINAL



IND 066783

MEETING PRELIMINARY COMMENTS

Puma Biotechnology, Inc.
Attention: Mei Ling Chang-Lok, Ph.D.
Senior Director, Global Regulatory Lead
10880 Wilshire Blvd
Suite 2150
Los Angeles, CA 90024

Dear Dr. Chang-Lok:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Neratinib (PB-272).

We also refer to your January 15, 2016, correspondence, received January 15, 2016, requesting a meeting to discuss and reach agreement on Puma's planned NDA. Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-4203.

Sincerely,

{See appended electronic signature page}

{See appended electronic signature page}

Pamela Balcazar, MS
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology
Products
Center for Drug Evaluation and Research

Laleh Amiri-Kordestani, MD
Clinical Team Lead
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Center for Drug Evaluation and Research

Enclosure:
Preliminary Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: March 21, 2016, 2-3 pm
Meeting Location: White Oak Building 22, Conference Room: 1419

Application Number: IND 066783
Product Name: Neratinib (PB-272)
Indication: early-stage HER2-overexpressed/amplified breast cancer
Sponsor/Applicant Name: Puma Biotechnology

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 21, 2016, at 2-3pm, at FDA White Oak between Sponsor and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Puma Biotechnology, Inc. is currently developing neratinib (PB-272, HKI-272) tablets under IND 066783. Neratinib is an irreversible tyrosine kinase inhibitor that blocks EGFR, HER2 and HER4. The purpose of this Type B meeting is to review and reach agreement with the Agency on the format and content of Puma's planned NDA. Puma is preparing an NDA based on the results of Study 3144A2-3004-WW ("Study 3004") for the marketing of neratinib with the following indication:

Extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy.

Puma intends to support the NDA submission with results from Study 3004, a Phase 3, randomized, placebo-controlled study in 2,840 patients comparing neratinib with placebo after adjuvant treatment with trastuzumab-based therapy in women with early-stage HER2-positive breast cancer. Study 3004 demonstrated that neratinib administered for 12 months improves the absolute DFS at two years from 91.6% to 93.9% (HR 0.67; 95% CI 0.50-0.91; 1 sided p = 0.005). Efficacy results from Study 3004 are shown in Table 1 below.

Table 1: Efficacy Endpoint Analyses (Intention-to-Treat Population)

Variable	Estimated event-free survival rate at 2 years*		Hazard ratio (95 percent confidence interval)†	One-sided P Value‡
	Neratinib (N = 1420)	Placebo (N = 1420)		
	percent	percent		
Invasive disease-free survival	93.9	91.6	0.67 (0.50, 0.91)	0.005
Disease-free survival including ductal carcinoma <i>in situ</i>	93.9	91.0	0.63 (0.46, 0.84)	<0.001
Distant disease-free survival	95.1	93.7	0.75 (0.53, 1.04)	0.044
Time to distant recurrence	95.4	93.9	0.71 (0.50, 1.00)	0.027
CNS recurrence	0.91	1.25	–	0.218

CNS = central nervous system.

* Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.

† Stratified Cox proportional hazards model

‡ Stratified 1-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

Puma plans to submit the NDA to the Agency at the end of Q2 2016. However, as summarized below there are several statistical issues related to the design and conduct of Study 3004.

Study 3004 began enrollment in April 2009 under Wyeth. The primary objective was to compare invasive disease free survival (iDFS) of women with stage I-III, node positive or negative, HER2 overexpressed/amplified breast cancer after standard locoregional and systemic treatment including 12 months of trastuzumab followed by extended adjuvant treatment with either neratinib or placebo for one year. Patients were initially allowed to enroll up to two years after completion of neoadjuvant trastuzumab.

After study commencement, the BCIRG 006 adjuvant trastuzumab study reported a 93% 5-year DFS rate for node-negative patients treated with AC-TH, indicating that the risk of tumor recurrence may be lower than expected when the trial was originally designed. As a result, the study was amended in February 2010 to only enroll patients with a higher risk of recurrence, defined as node positive disease and trastuzumab completion ≤1 year prior to randomization. The primary endpoint was altered to iDFS in the amended ITT population. In October 2011, two key changes were made by Pfizer (who acquired Wyeth in 2009) – 1) cessation of enrollment and 2) shortening follow-up to two years from study randomization.

Study 3004 was continued under this design until January 2014 at which time Puma (who licensed neratinib from Pfizer in 2011) implemented a global amendment (Global amendment 13) that restored the study to its primary intention, ie, to obtain iDFS and OS data for all randomized subjects with the primary analysis being conducted at 2 years of follow-up. At this

point, patients were re-enrolled on the study in order to obtain additional follow-up data for 5-years post-randomization.

Another statistical concern with the study was that the number of patients followed for 24 months was relatively low in each arm, 662 (47%) patients in the neratinib arm and 704 (50%) patients in the placebo arm. In previous communications with the Sponsor, FDA asked for information regarding the significant number of early drop outs in Study 3004. The Sponsor clarified that the early drop-outs in the neratinib arm were primarily due to toxicities experienced by patients either as a direct reason (“adverse event”) or a related but indirect reason (“subject request”). A total of 355 patients in the neratinib arm discontinued treatment due to an AE and 123 subjects discontinued at their request. In total, this represents approximately 37% of the patients who received neratinib.

Sponsor Comment:

Please see Question 1 response below. As noted in the 8 March 2016 request for information, per protocol, patients who discontinued treatment with neratinib or placebo were to be continued on study and followed for iDFS.

The most common adverse events in Study 3004 were GI toxicities, specifically diarrhea, nausea, vomiting, and abdominal pain. The most frequently reported Grade 3 or 4 TEAEs and the most frequent TEAEs leading to study drug discontinuation were diarrhea and, to a lesser extent, vomiting. In the 1,408 patients who received neratinib in Study 3004, 39.8% and 1.4% experienced grade 3 and 4 diarrhea, respectively. Other commonly reported TEAEs include fatigue, dermatologic toxicities, and intermittent increases in liver enzymes; less than 2% of these events were severe or required treatment discontinuation and <0.5% were considered serious.

Sponsor Comment:

Puma would like to clarify that there was 1 patient (0.1%) with grade 4 diarrhea in the neratinib arm.

The Sponsor is currently investigating the use of prophylactic loperamide with the use of neratinib in the extended adjuvant setting. Of the 159 patients who have received prophylactic loperamide across the development program, the rate of Grade 3 diarrhea was improved to (b) (4)%. The implementation of loperamide prophylaxis also appears to decrease the number of drug discontinuations, dose reductions, and treatment interruptions.

Sponsor Comment:

Puma would like to clarify that the Grade 3 diarrhea across development program was short lived with an average duration of 1-2 days.

2.0 DISCUSSION

2.1 Clinical/ Statistics

Question 1: Protocol 3144A2-3004-WW is a Phase III randomized, double-blind, placebo-controlled trial of neratinib (HKI-272) after trastuzumab based therapy in women with early-stage HER-2/neu overexpressed/amplified breast cancer with the primary endpoint of invasive disease-free survival (DFS). The primary data to support efficacy and safety for the indication will be derived from the primary analysis of Study 3144A2-3004-WW (“3004”). In addition, 30 interim and final clinical study reports (CSRs) from trials of neratinib in various indications (early Breast Cancer, Metastatic Breast Cancer and other solid tumors with mutations) will be included in the NDA to support the pivotal 3004 study. A total of 1408 patients were exposed to neratinib in the pivotal trial and a total of 3252 patients were exposed during the development program.

Does the Division agree that the efficacy and safety results from the single pivotal study, 3144A2-3004-WW (“3004”), along with the efficacy and safety data from supportive studies provide sufficient clinical experience to characterize the benefits and risks of neratinib, and support the basis of an NDA for approval in the proposed indication?

FDA Response: No. We do not encourage an NDA submission based on the efficacy and safety results of Study 3144A2-3004-WW that you have provided in your briefing package. Your study has several issues that will likely make the interpretation of the results problematic.

- 1. For one, the number of dropouts can impact the interpretation of the final results due to a small overall number of DFS events and brings into question whether this trial constitutes an adequate and well-controlled trial.**

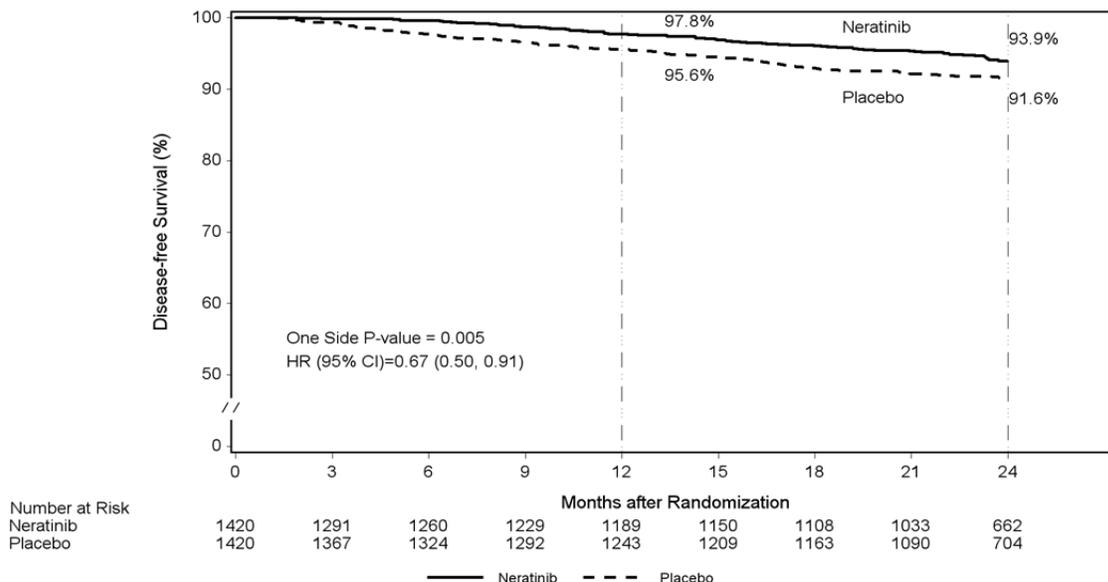
Sponsor Response:

We would like to provide some clarification of the data that was provided in Puma’s February 16th Briefing Document and the data that was provided in Puma’s March 8th response to request for information. Table 2 of the briefing document tabulated end of treatment reasons against the distribution of iDFS time (in 3 month increments) for censored patients. The column totals indicated the number of patients who were censored (dropped out) at any given time interval. As FDA correctly points out above, and is shown in Table 2 of the Briefing Document, 355 patients in the neratinib arm came off treatment due to an AE and 123 subjects in the neratinib arm discontinued treatment with neratinib due to subject request. However, these patients did not all drop out of the study after treatment discontinuation; as is noted in the 8 March 2016 request for information, per protocol, patients who discontinued treatment with neratinib or placebo were to be continued on study and followed for iDFS. The number of patients who dropped out early (0-3 months) was 127 patients, as indicated by the column total. The majority of the 127 patients who ended treatment (and follow-up) did so due to either adverse events (73) or subject request (39). Of the total 355 patients who discontinued treatment due to adverse event and the total 123 patients who ended treatment due to subject request, 65 and 20, respectively, were followed on study and censored between 21-24 months and 139 and 37, respectively, completed 24 month follow-up, as is shown in Table 2 of the Briefing Document.

Please note that in Table 4 of the February 16th Briefing Document and Table 1 in the March 8th request for information, which tabulate the end of study reasons against the distribution of iDFS time (in 3 month increments), there were 243 (17%) patients ending study due to “subject request” or “other” (27 of whom actually completed 24 month follow-up). As was shown in Figure 2 in the March 8th request for information, the End of Study CRF did not include an option for the end of study reason being an adverse event. Therefore, we believe that the two categories of “subject request” or “other” would approximate the patients ending study related to adverse events. As we also described in the Briefing Document, additional data collected in part B of the protocol (from sites who had not obtained IRB approval in time for the Part A analysis) has helped restore more follow-up data in the first 24 months of the trial.

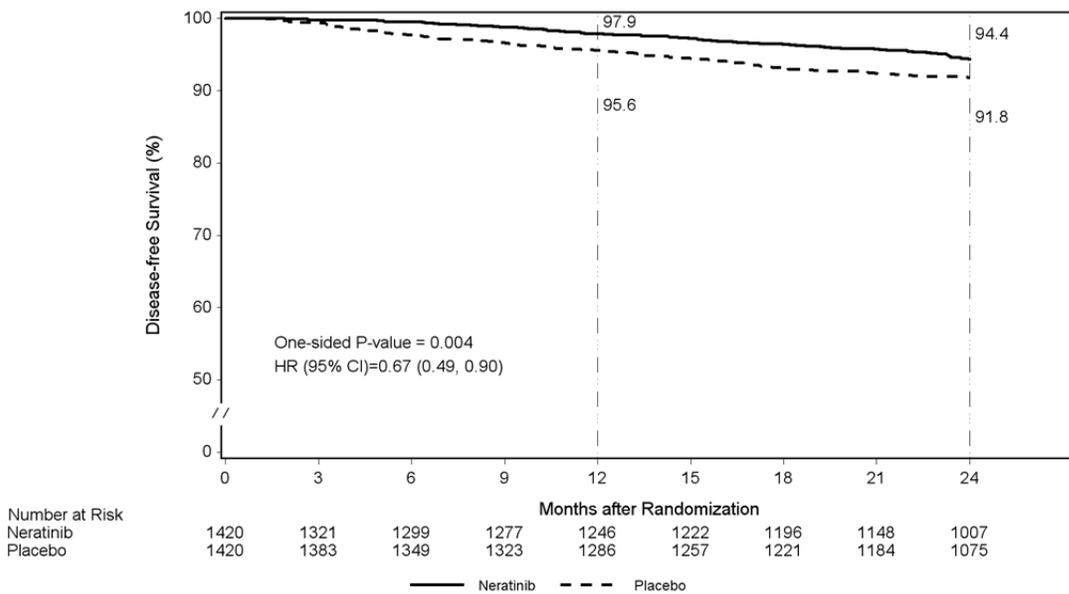
As noted by the FDA, the number of patients followed up for 24 months was relatively low in each arm, 662 (47%) patients in the neratinib arm and 704 (50%) patients in the placebo arm. As is noted in Figure 1 below, a large amount of censoring occurred between months 21 and 24; this was an artifact of the protocol-defined visit window. Per protocol, patient visits for months 12 through 24 were to occur every 4 months with a +/- 28 day window; therefore, patients with visits between 21 – 23 months might not have returned for the 24 month visit. As can be seen in the Kaplan-Meier curve in Figure 1, 1033 (73%) patients in the neratinib arm and 1090 (77%) patients in the placebo arm were followed up to 21 months. An analysis of data up to 20 months (the second to last scheduled assessment in part A of the protocol) yielded a hazard ratio of 0.59 (0.42, 0.81), which is consistent with the results of the primary analysis.

Figure 1: Kaplan-Meier Plot of iDFS



As we described in our Briefing Document, an updated 2 year iDFS analysis was conducted when additional data collected in Part B of the protocol was included in an exploratory analysis (3 year analysis) that was presented at the San Antonio Breast Cancer Symposium in December 2015. (Figure 2) This updated analysis now includes 24 month follow-up data for 1007 (71%) neratinib and 1075 (76%) placebo patients; the hazard ratio and absolute DFS improvement are in-line with the results from the primary analysis. Figure 2 shows the updated iDFS analysis with additional data from part B when applying the FDA censoring rule.

Figure 2: KM Curves of the updated iDFS analysis with additional data from part B applying FDA censoring rule, ITT Population**



**Events were within 24 months + 28 days and patients were censored using FDAs censoring rule and taking into account of all available data collected in part B of the protocol.

The key purpose of Amendment #13 was to restore the ExteNET protocol to its original objectives by obtaining long-term iDFS follow-up data for Part B and survival for Part C. The December 2015 analysis included data from sites that had agreed to Amendment 13 of the protocol but had not received approvals from their IRBs in time for the primary analysis in July 2014. Since that time Puma has received additional data from sites that had agreed to Amendment 13 but had not received approval from their IRBs in time for the exploratory analysis in December 2015. As of 11 Mar 2016, an additional 137 patients (both neratinib and placebo arms) have been re-enrolled. The additional follow-up data from these patients will increase the number of patients at risk in the first 24 months of the study and therefore support the integrity and validity of the primary 2-year analysis. Puma plans to provide this updated analysis with the additional patients from Part B

upon submission to the NDA in June 2016, at which point Puma projects at least 2,200 patients data will be re-enrolled.

We examined carefully the potential impact of early (< 3 months follow up) censoring on the primary conclusion of the study. The analysis showed that, with respect to prognostics factors known to contribute to disease outcome, patients who came off study early did not differ from patients who were followed longer. This was shown in Table 7 of the February 16th Briefing Document.

In addition, sensitivity analyses were performed using imputation to assign placebo patient data to neratinib patients who dropped out early (no imputation was done for the placebo patients who dropped out early). Resampling was performed by matching patients on stratification factors and DFS time at drop out. Four early drop-out scenarios were considered in 3-month increments from month 3 to month 12. For each scenario, 10,000 simulations were performed. The results are summarized in Table 2 and support the robustness of the primary analysis.

Table 2: Simulation Results

Cut-off Month	Mean (SD) Hazard Ratio	Mean (range) Additional Events	Percent 1-sided P-value ≤ 0.025
3	0.685 (0.020)	9 (0-21)	99.9%
6	0.687 (0.022)	11 (2-26)	99.7%
9	0.689 (0.022)	12 (1-29)	99.5%
12	0.691 (0.023)	14 (2-27)	99.0%

2. The protocol change to an increased risk population (global amendment 3) precludes the interpretation of ITT population as all-comers.

Sponsor Response:

We benchmarked the key patient characteristics of our study population with the landmark studies of trastuzumab in the adjuvant setting. The summary is provided in Table 3. We note that the percent of node negative patients in ExteNET is in line with the percent of node negative patients in the adjuvant trials of trastuzumab.

Table 3: Node Status of Adjuvant Breast Cancer Studies

	ExteNET (N=2840)	B31/N9831 (N=3351)	HERA (N=3387)	BCIRG 006 (N=3222)
Node Status				
Negative	24%	6%	32%	29%
1-3 nodes	47%	53%	29%	38%
4 or more nodes	30%	41%	28%	33%
Not assessed (neoadj)	-	<1%	11%	-

A predefined population of interest was the aITT population (Amendment #3) which represented a high risk population defined as women with node positive breast cancer and/or residual disease after neoadjuvant chemotherapy who completed adjuvant trastuzumab within a year of study randomization. This was the target population of the protocol after amendment 3 and a pre-specified analysis population in the SAP. While the primary analysis in the ITT population (node negative and node positive) was pre-specified prior to unblinding and has scientific validity, Puma is open to a discussion on (b) (4) due to FDA's concern on the generalizability of the results from the ITT population.

Analyses of the primary iDFS endpoint in the aITT population (using FDA's censoring rule, see responses to question 2) are summarized in Figure 3. There were 137 iDFS events (53 in neratinib, 84 in placebo). These results are consistent with the findings in the ITT population. In addition, updated aITT results (using FDA's censoring rule) including data collected in part B up to December 2015 are also shown in Figure 4. There were 144 iDFS events (56 in neratinib, 88 in placebo). As described earlier and similar to the ITT population, more complete follow-up data were available in the updated 2-year analyses in the aITT population. At month 24, 72% of the neratinib patients and 74% of the placebo patients had complete follow-up.

Additional subgroup analyses within the aITT population, using FDA's censoring rule, are provided in Appendix 1.

Figure 3. 2-Year Kaplan-Meier Plot of Disease-free Survival – FDA Censoring rule, aITT Population

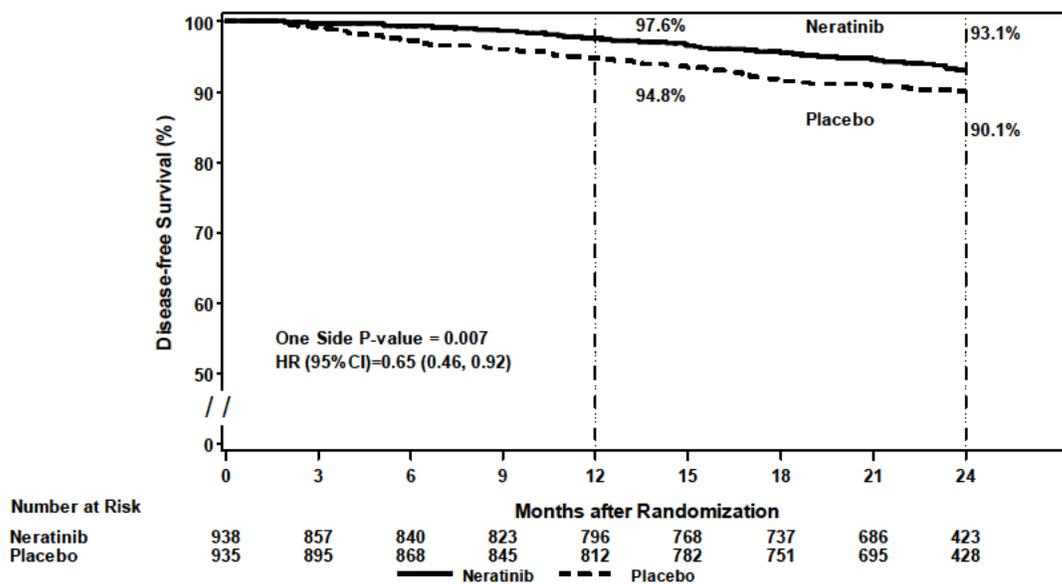
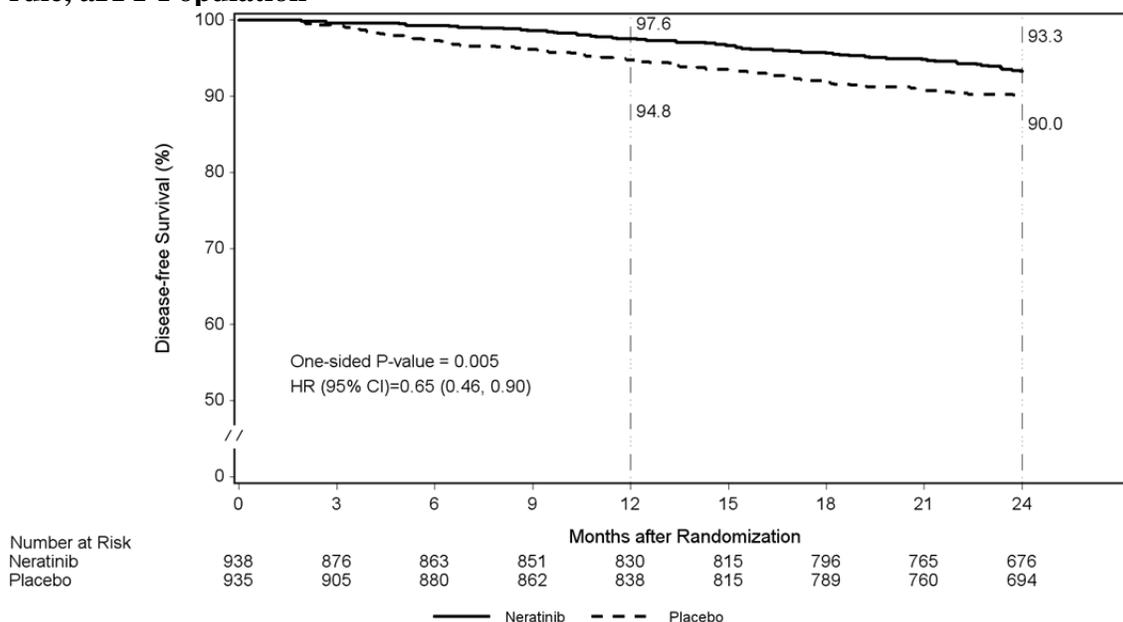


Figure 4. Updated 2-Year Kaplan-Meier Plot of Disease-free Survival – FDA Censoring rule, aITT Population



Also, as mentioned above in Question 1, since completing the exploratory analysis in December 2015, Puma is continuing to receive additional data from sites that had agreed to Amendment 13 but had not received approval from their IRBs in time for the exploratory analysis in December 2015. The additional follow-up data from these patients will increase the number of patients at risk in the first 24 months of the study and therefore support the integrity and validity of the primary 2-year analysis. Puma will provide this updated analysis with the additional patients from Part B upon submission to the NDA in June 2016.

3. The use of a time-driven primary analysis instead of an event-driven analysis can artificially censor individuals with known DFS times.

Sponsor Response:

The time-driven analysis at 2 years was pre-specified in the SAP for the primary analysis in the Part A portion of the protocol. While adequate statistical power was not assured at the time of the time-driven primary analysis, the pre-specification of the analysis prior to unblinding would ensure scientifically valid inference. We appreciate the agency’s concern that known DFS events might be artificially censored. In our analyses, 8 DFS events were censored (3 in neratinib, 5 in placebo). Censoring of these events helped reduce potential bias as uniform follow-up beyond 2 years were not mandated in the part A.

The following analyses show the results using time driven (as defined by the truncation rule in Puma’s SAP) or event driven (when all events in part A are included) approaches.

All analyses use FDA's censoring rule which will be the primary analysis approach as explained in response to Question 2.

- 1) ITT population applying the FDA censoring rule (time driven)
 - Hazard ratio=0.66 (0.49, 0.90), 1-sided P=0.004
 - 2-year iDFS rates 94.2% vs 91.9%
 - iDFS events 67 vs 106
- 2) ITT population applying FDA's censoring approach (event driven)
 - Hazard ratio=0.65 (0.48, 0.87), 1-sided P=0.002
 - 2-year iDFS rates 94.2% vs 91.9%
 - iDFS events 69 vs 110
- 3) aITT population applying the FDA censoring rule (time driven)
 - Hazard ratio=0.65 (0.46, 0.92), 1-sided P=0.007
 - 2-year iDFS rates 93.1% vs 90.1%
 - iDFS events 53 vs 84

- 4) aITT population applying FDA's censoring approach (event-driven))
 - Hazard ratio=0.64 (0.45, 0.89), 1-sided P=0.004
 - 2-year iDFS rates 93.2% vs 90.2%
 - iDFS events 54 vs 87

4. The group of individuals reenrolled for the 5-year follow-up may or may not be representative of the full ITT population.

Sponsor Response:

Demographics for the patients enrolled in Part A (2 year follow up) and Part B (> 2 year follow up) are presented in [Appendix 2 \(Tables 4-6\)](#).

We understand the FDA's concern regarding the representativeness of the re-enrolled patients. An analysis was conducted to compare baseline demographic and disease characteristics for the patients in the ITT population to those with > 24 months of DFS follow up primarily from Part B of the protocol (5 year follow up). The analysis shows that the baseline demographic and disease characteristics of the patients with greater than 24 months of follow up appear to be similar to those enrolled in Part A.

The key purpose of Amendment #13 was to restore the ExteNET protocol to its original objectives by obtaining long-term iDFS follow-up data for Part B and survival for Part C. The December 2015 analysis included data from sites that had agreed to Amendment 13 of the protocol but had not received approvals from their IRBs in time for the primary analysis in July 2014. Since that time Puma has received additional data from sites that had agreed to Amendment 13 but had not received approval from their IRBs in time for the exploratory analysis in December

2015. Puma plans to provide this updated analysis with the additional patients from Part B upon submission to the NDA in June 2016, at which point Puma projects at least 2,200 patients data will be re-enrolled.

5. The Agency has not utilized a 2-year DFS as the primary analysis for an adjuvant study in breast cancer to support marketing approval of an NDA.

Sponsor Response:

Puma is aware of precedent with letrozole based on the MA.17 trial, and anastrozole based on the ATAC trial, where accelerated approvals were granted based on DFS with median follow-up less than 3-yrs in adjuvant breast cancer, and appreciate there are significant differences between these applications and neratinib's ExteNET proposal.



If the application is submitted, an Oncologic Drugs Advisory Committee discussion will be required.

Question 2: Puma submitted version 1.1 of the 3144A2-3004 WW Statistical Analysis Plan (SAP) on July 01, 2015 to incorporate changes requested by the Agency. Does the Division have further comments on version 1.1 of the SAP?

FDA Response: Please see response to Q1. FDA reiterates its previous comment from March 11, 2015: “we noticed that you proposed a sensitivity analysis of DFS, in which patients with DFS events right after two or more missing physical exams will be censored at the last physical exam. Instead of making this a sensitivity analysis, you should use this censoring rule for the primary analysis.”

Sponsor Response:

We agree to revise the SAP to make this a primary analysis approach. This change, while post unblinding, does not alter the conclusion of the primary analysis. The results are provided below for ease of reference. These analyses, while comparing different censoring rules, all used the time-driven approach as specified in the SAP.

- 1) ITT population applying the SAP censoring approach
 - Hazard ratio=0.67 (0.50, 0.91), 1-sided P=0.005
 - 2-year iDFS rates 93.9% vs 91.6%
 - iDFS events 70 vs 109

- 2) ITT population applying FDA's censoring rule
 - Hazard ratio=0.66 (0.49, 0.90), 1-sided P=0.004
 - 2-year iDFS rates 94.2% vs 91.9%

- iDFS events 67 vs 106
- 3) aITT population applying the SAP censoring rule
- Hazard ratio=0.66 (0.47,0.92), 1-sided P=0.007
 - 2-year iDFS rates 92.9% vs 89.8%
 - iDFS events 55 vs 87
- 4) aITT population applying FDA's censoring rule
- Hazard ratio=0.65 (0.46, 0.92), 1-sided P=0.007
 - 2-year iDFS rates 93.1% vs 90.1%
 - iDFS events 53 vs 84

2.2. Safety

Question 3: Puma proposes to submit a safety update 120-days after the original NDA is submitted inclusive of the following information:

1. Patients enrolled in the pivotal study, 3004, are no longer on treatment and the update will therefore consist of any incremental safety data entered into the clinical database between the data cutoff of July 2014 and database lock in December 2014. An updated SAE listing including any neratinib related SAEs reported by enrolled patients since December 2014 will be provided from the safety database.
2. Updated cumulative safety data from the ongoing PUMA-NER-6201, an open-label study to characterize the incidence and severity of diarrhea in patients with early-stage HER2+ breast cancer (analogous to the 3004 population) treated with neratinib for one year and intensive loperamide prophylaxis given for the first two cycles of treatment.
3. Pooled cumulative diarrhea analyses from the 4 ongoing studies where prophylactic use of antidiarrheal medication is mandatory will be provided. These studies include studies of neratinib monotherapy (PUMA-NER-6201 and PUMA-NER 5201) and studies of neratinib in combination with temsirolimus (PUMA-NER-4201 and Study 10-005).

Revised safety data from ongoing clinical studies will be reflected in both updated Clinical Summary of Safety and labeling. Does the Agency agree that this plan is acceptable?

FDA Response: Yes. See response to Q1.

Sponsor Response: Thank you; no further discussion needed.

Question 4: Based on the safety data of the pivotal Phase III study 3144A2-3004-WW

(randomized, double blind, placebo-controlled trial), PUMA does not believe that REMS is warranted. The Sponsor proposes to utilize routine post marketing pharmacovigilance and labeling to manage the identified and potential risks for neratinib.

Does the Agency agree that neratinib in extended HER2 amplified adjuvant breast cancer, with a routine post marketing pharmacovigilance process in place, adequately assesses potential patient risks for this patient population and an additional REMS program is not required?

EDA Response: See response to Q1. This would be a review issue.

Sponsor Response: Thank you; no further discussion needed.

Question 5: No diarrhea prophylactic measures to prevent neratinib related diarrhea were undertaken in pivotal study 3144A2-3004-WW, where diarrhea was treated after it occurred. In efforts to potentially prevent and reduce the incidence of neratinib related grade 3 and higher diarrhea, ongoing clinical studies (PUMA-NER 6201, PUMA-NER-4201, PUMA-NER 5201 and Study 10-005) have shown that loperamide administered prophylactically substantially reduces the frequency and severity of grade 3 and higher diarrhea.

In an effort to guide physician's treatment, Puma plans to include the results from Study 6201, a Phase II trial of neratinib monotherapy for one year as extended adjuvant treatment in patients with HER2 positive early stage breast cancer in patients who have previously received adjuvant trastuzumab in which patients received loperamide prophylaxis for the first two cycles, in the label. Does the Agency agree with our plan to include loperamide prophylaxis instructions in the draft labeling?

EDA Response: See response to Q1. Labeling is not discussed prior to NDA review. This would be a review issue. We are concerned that even with loperamide prophylaxis there was still an observed incidence of grade 3 diarrhea of (b) (4) %.

Sponsor Response: Thank you; no further discussion is needed regarding labeling. However, we wish to draw your attention to Figure 5 which shows the worst grade treatment-emergent diarrhea in weeks 1-4 and then by treatment month for Study 6201. (b) (4)

(b) (4)

(b) (4)

Figure 5: Study 6201, Worst Treatment-emergent Diarrhea by Treatment Week and Month

(b) (4)

2.3. Non-Clinical

Question 6: As discussed in the 25 November 2014 Type-C meeting with the Agency, the neratinib NDA for adjuvant breast cancer will be supported by a carcinogenicity program comprised of 6-month RasH2 transgenic mouse carcinogenicity and a 2 year Sprague Dawley rat carcinogenicity study. Provided in this briefing document, are the results of the 6-month transgenic mouse carcinogenicity study. In response to global health authority input, Puma has amended the rat carcinogenicity study to include a 1 year interim data analysis, which will be available at the time of the NDA submission. The 1 year interim data analysis replaces the 39 week interim data analysis that was in the prior version of the rat carcinogenicity protocol. In consideration that neratinib has been characterized in a full battery of Segment I, II and III developmental and reproductive toxicity studies, 9-month dog and 6-month rat chronic toxicity studies, as well as the standard battery of genotoxicity studies, and results have shown no significant safety signals, Puma proposes to submit the final 6-month transgenic carcinogenicity report and a 1-yr interim report of the 2-year rat carcinogenicity in the original NDA submission and provide the final 2-year rat carcinogenicity study report as a post-marketing commitment.

Does the Agency agree that the final 6-month rasH2 Tg mouse carcinogenicity report

and a 1-yr interim report for the Sprague-Dawley rat carcinogenicity study are adequate preclinical safety data to support a complete review of the original NDA submission?

FDA Response: No. We reiterate that final study reports for both the 6-month rasH2 Tg mouse and 2-year rat carcinogenicity studies should be included in an NDA submission to support the proposed indication, which is consistent with the ICH M3(R2) guidance.

Sponsor Response:

Puma references the FDA's November 2014 and April 2015 feedback:

November 11, 2014 Non-clinical Meeting

The sponsor proposes the following specific clinical indication: Extended adjuvant treatment of patients with early stage (b) (4) HER2-overexpressed/amplified (b) (4) breast cancer who have received prior adjuvant trastuzumab therapy.

The proposed clinical indication (b) (4)

(b) (4)

...feedback on the required nonclinical studies to support an NDA for the adjuvant treatment of patients with early stage (b) (4) HER2+ breast cancer with prior adjuvant trastuzumab therapy.

April 24, 2015 Type-C Meeting

FDA stated that to support an NDA for the proposed indication (adjuvant treatment of patients with early stage (b) (4) HER2+ breast cancer), final study reports from rodent carcinogenicity studies, including a 2-year rat study, should be provided at the time of NDA submission...studies are needed to support the risk: benefit for neratinib in this patient population.

As noted above in Question 1, Puma is open to changing the proposed indication to the (b) (4)

(b) (4)

In appreciating ICH M3R2 references ICH S1A where "For pharmaceuticals developed to treat certain serious diseases for adults or pediatric patients, carcinogenicity testing, if recommended, can be concluded post-approval" and "When such pharmaceuticals are intended for adjuvant therapy in tumour free patients or for prolonged use in noncancer indications, carcinogenicity studies are usually needed." As this population is considered to have disease that is of

higher risk of recurrence and this population is not cancer free since they are either node positive or have residual disease after neoadjuvant therapy, would the Agency be open to a discussion regarding accepting the 6 month Tg mouse carcinogenicity data and 1-year rat carcinogenicity data in the NDA and provide the rat 2-year carcinogenicity in the post filing or post marketing setting?

2.4. Regulatory

Question 7: Does the Agency agree that the overall proposed table of contents and organization of the new drug marketing application to be submitted electronically in eCTD format are acceptable?

FDA Response: Please refer to our Type C WRO meeting dated 10/27/15 regarding the table of contents and organization. Please see response to question 1.

Sponsor Response: Thank you; no further discussion needed.

Additional Comment:

We refer you to previous clarifications requested by FDA (SDN 890) regarding proposed Clinical Pharmacology Program for the initial NDA submission. With respect to the pop PK analysis for the original NDA submission:

- Please provide justification for excluding PK data from other studies (e.g., study 3144A1-102-US and study 3144A1-104-JA) in your planned population PK analysis.
- Clarify if exposure-response analyses for efficacy and safety are planned for study 3144A2-3004-WW.

The meeting package did not contain enough information to determine whether an adequate PK bridge was established between the clinical trial formulations (capsule/tablet) and the (b) (4) mg tablet commercial formulation. Please clarify which formulation of your drug was used in trial 3144A2-3004-WW.

Sponsor Response: Trial 3144A2-3004-WW used the 40-mg film coated tablet (6 tablets per day) that will be the proposed commercial formulation. (b) (4)

3.0 OTHER

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 25, 2016 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management

actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidance.

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that was signed
electronically and this page is the manifestation of the
electronic
signature.**

/s/

PAMELA I BALCAZAR
03/07/2016

LALEH AMIRI KORDESTANI
03/07/2016

APPENDIX 1.

Table 1: Subgroup Analysis of Disease-free Survival - FDA Censoring Rule, Hormone Receptor-positive Patients for the aITT Population

	Neratinib (N=547)	Placebo (N=545)
Patients With Events - n (%)	25 (4.6)	51 (9.4)
Local/Regional Invasive Recurrence	2 (0.4)	12 (2.2)
Invasive Ipsilateral Breast Tumor Recurrence	1 (0.2)	2 (0.4)
Invasive Contralateral Breast Cancer	1 (0.2)	2 (0.4)
Distant Recurrence	20 (3.7)	34 (6.2)
Death From Any Cause	1 (0.2)	1 (0.2)
Patients Censored - n (%)	522 (95.4)	494 (90.6)
Kaplan-Meier Estimate (%)		
12 Month (95% CI)	98.0 (96.2, 98.9)	95.5 (93.4, 97.0)
24 Month (95% CI)	94.5 (91.9, 96.2)	89.6 (86.5, 92.0)
Stratified Log-rank Test P-value (one-sided) ^a		0.002
Unstratified Log-rank Test P-value (one-sided)		0.002
Stratified Cox Proportional Hazards Model ^a		
Hazard Ratio (95% CI) ^b		0.51 (0.31, 0.81)
Unstratified Cox Proportional Hazards Model		
Hazard Ratio (95% CI) ^b		0.50 (0.31, 0.80)

Page 1 of 1

Disease-free survival time is defined as the time from date of randomization until the first disease recurrence of the following events: invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence and death from any cause.

^a The Log-rank test and Cox model are stratified by randomization stratification factors: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4) and ER/PgR status (positive or negative).

^b The Hazard ratio is presented as neratinib vs. placebo.

Figure 1: Kaplan-Meier Plot of Disease-free Survival - FDA Censoring Rule, Hormone Receptor-positive Patients for the aITT Population

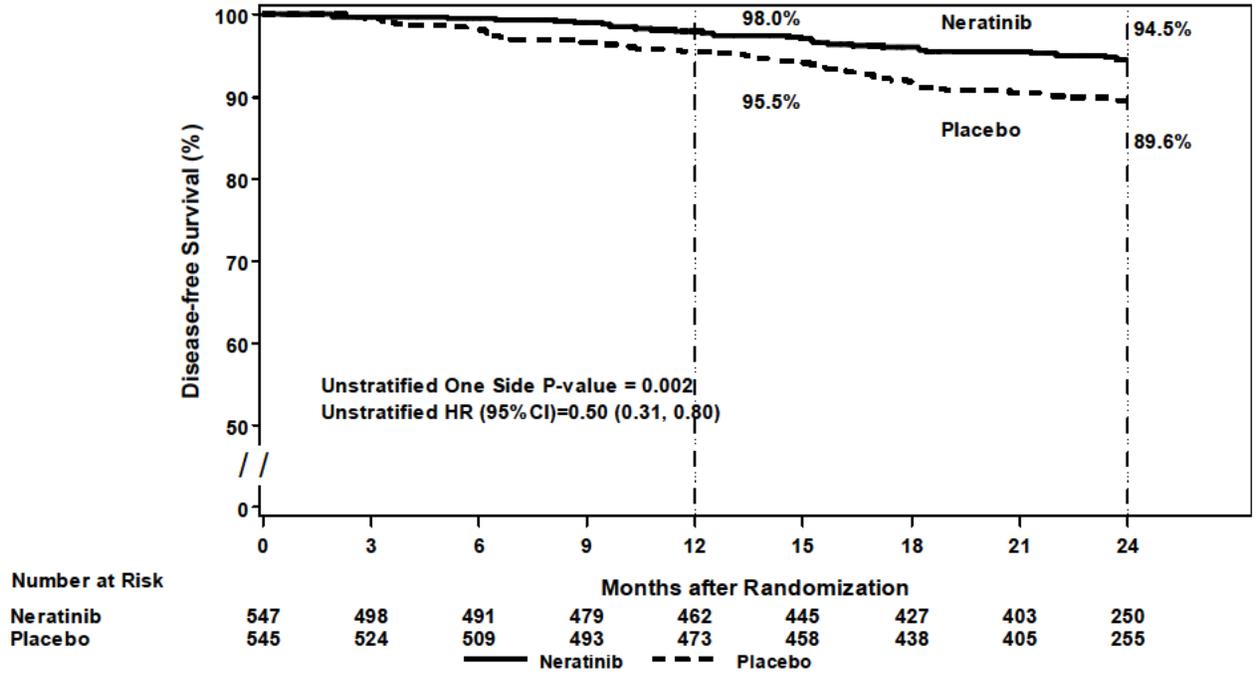


Table 2: Subgroup Analysis of Disease-free Survival - FDA Censoring Rule, Hormone Receptor-negative Patients for the aITT Population

	Neratinib (N=391)	Placebo (N=390)
Patients With Events - n (%)	28 (7.2)	33 (8.5)
Local/Regional Invasive Recurrence	2 (0.5)	7 (1.8)
Invasive Ipsilateral Breast Tumor Recurrence	1 (0.3)	2 (0.5)
Invasive Contralateral Breast Cancer	0 (0)	2 (0.5)
Distant Recurrence	24 (6.1)	22 (5.6)
Death From Any Cause	1 (0.3)	0 (0)
Patients Censored - n (%)	363 (92.8)	357 (91.5)
Kaplan-Meier Estimate (%)		
12 Month (95% CI)	97.2 (94.8, 98.5)	93.8 (90.9, 95.9)
24 Month (95% CI)	91.3 (87.6, 93.9)	90.9 (87.4, 93.4)
Stratified Log-rank Test P-value (one-sided) ^a		0.310
Unstratified Log-rank Test P-value (one-sided)		0.297
Stratified Cox Proportional Hazards Model ^a		
Hazard Ratio (95% CI) ^b		0.88 (0.53, 1.46)
Unstratified Cox Proportional Hazards Model		
Hazard Ratio (95% CI) ^b		0.87 (0.52, 1.44)

Page 1 of 1

Disease-free survival time is defined as the time from date of randomization until the first disease recurrence of the following events: invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence and death from any cause.

^aThe Log-rank test and Cox model are stratified by randomization stratification factors: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4) and ER/PgR status (positive or negative).

^bThe Hazard ratio is presented as neratinib vs. placebo.

Figure 2: Kaplan-Meier Plot of Disease-free Survival - FDA Censoring Rule, Hormone Receptor-negative Patients for the aITT Population

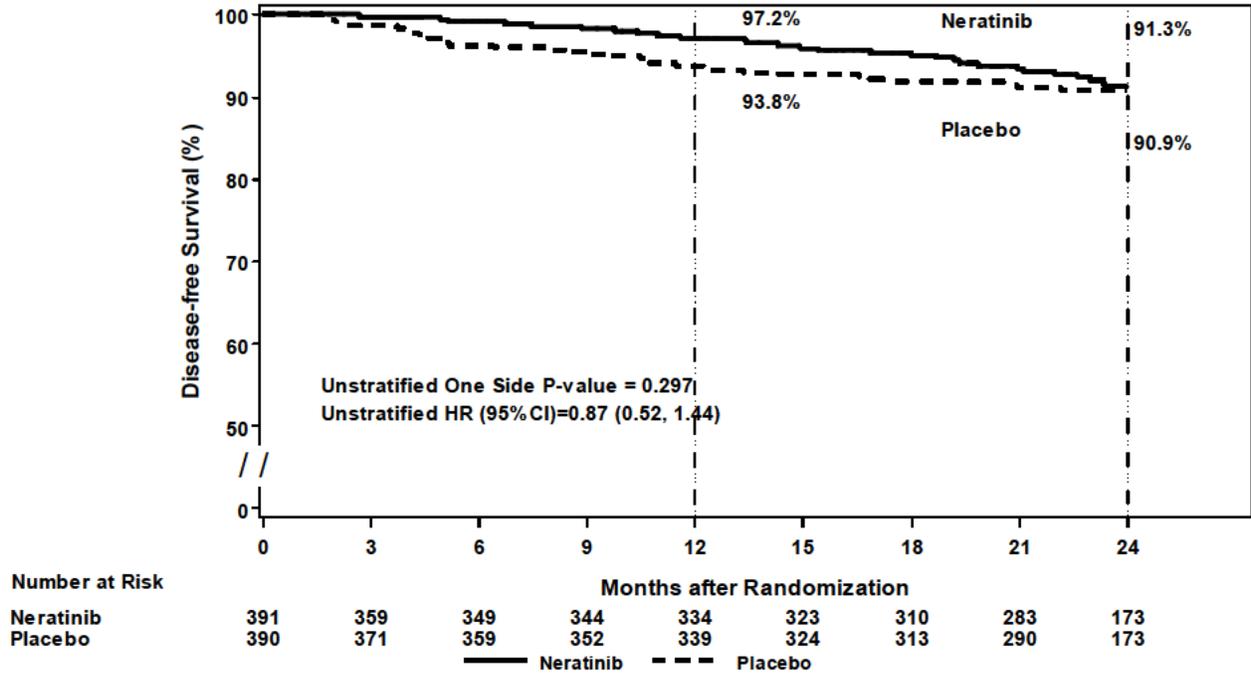


Table 3: Primary Analysis of Disease-free Survival - FDA Censoring Rule, Centrally-confirmed ERBB2-positive Population for the aITT Population

	Neratinib (N=473)	Placebo (N=457)
Patients With Events - n (%)	22 (4.7)	50 (10.9)
Local/Regional Invasive Recurrence	3 (0.6)	13 (2.8)
Invasive Ipsilateral Breast Tumor Recurrence	1 (0.2)	2 (0.4)
Invasive Contralateral Breast Cancer	0 (0)	3 (0.7)
Distant Recurrence	17 (3.6)	31 (6.8)
Death From Any Cause	1 (0.2)	1 (0.2)
Patients Censored - n (%)	451 (95.3)	407 (89.1)
Kaplan-Meier Estimate (%)		
12 Month (95% CI)	98.2 (96.4, 99.1)	93.7 (91.0, 95.6)
24 Month (95% CI)	94.7 (92.0, 96.5)	88.2 (84.7, 90.9)
Stratified Log-rank Test P-value (one-sided) ^a		<.001
Unstratified Log-rank Test P-value (one-sided)		<.001
Stratified Cox Proportional Hazards Model ^a		
Hazard Ratio (95% CI) ^b		0.42 (0.25, 0.68)
Unstratified Cox Proportional Hazards Model		
Hazard Ratio (95% CI) ^b		0.42 (0.25, 0.68)

Page 1 of 1

Disease-free survival time is defined as the time from date of randomization until the first disease recurrence of the following events: invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence and death from any cause.

^aThe Log-rank test and Cox model are stratified by randomization stratification factors: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4) and ER/PgR status (positive or negative).

^bThe Hazard ratio is presented as neratinib vs. placebo.

Figure 3: Kaplan-Meier Plot of Disease-free Survival - FDA Censoring Rule, Centrally-confirmed ERBB2-positive Population for the aITT Population

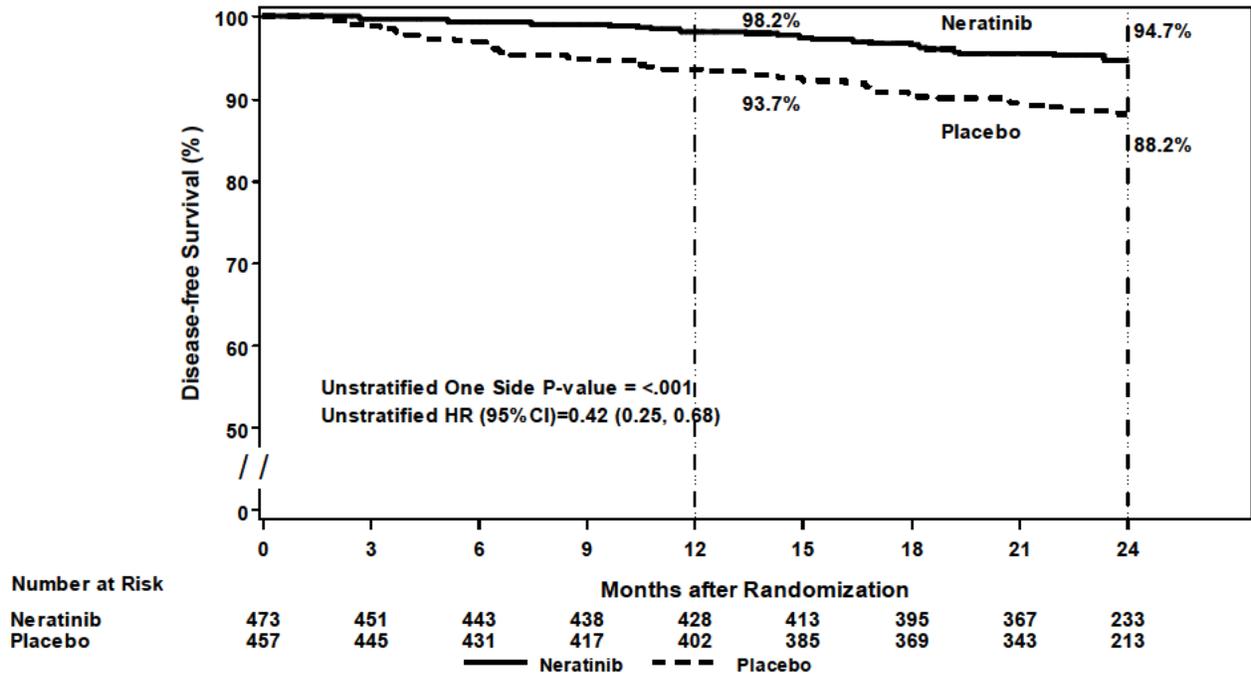


Figure 4: Forest Plot of Disease-free Survival by Subgroups - FDA Censoring Rule, aITT Population

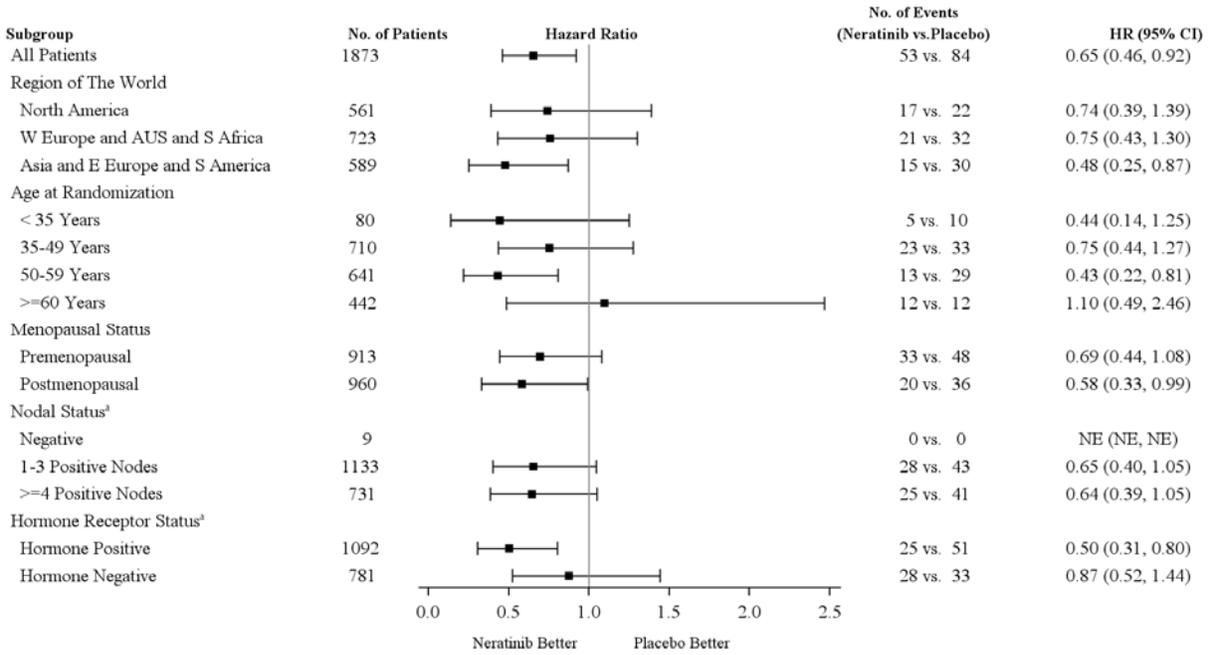
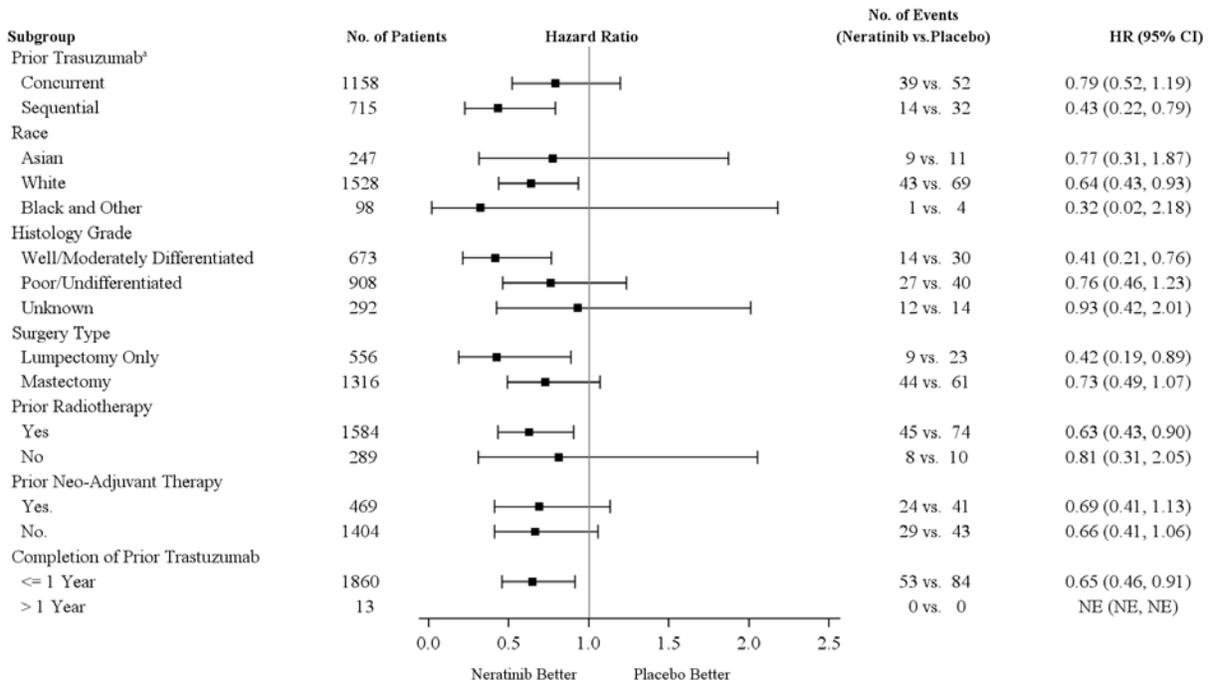


Figure 5: Forest Plot of Disease-free Survival by Subgroups - FDA Censoring Rule, aITT Population (continued)



APPENDIX 2.

Table 4: Patient Demographics, Patients with follow up >24 months vs ITT Population

	ITT			Patients with follow up >24 months		
	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)	Neratinib (N=1005)	Placebo (N=1074)	Total (N=2079)
Region ^a - n (%)						
North America	519 (36.5)	477 (33.6)	996 (35.1)	328 (32.6)	337 (31.4)	665 (32.0)
Western Europe, Australia and South Africa	487 (34.3)	532 (37.5)	1019 (35.9)	344 (34.2)	416 (38.7)	760 (36.6)
Asia Pacific, East Europe and South America	414 (29.2)	411 (28.9)	825 (29.0)	333 (33.1)	321 (29.9)	654 (31.5)
Race - n (%)						
Asian	188 (13.2)	197 (13.9)	385 (13.6)	150 (14.9)	156 (14.5)	306 (14.7)
Black or African American	27 (1.9)	47 (3.3)	74 (2.6)	13 (1.3)	27 (2.5)	40 (1.9)
White	1165 (82.0)	1135 (79.9)	2300 (81.0)	814 (81.0)	861 (80.2)	1675 (80.6)
Other	40 (2.8)	41 (2.9)	81 (2.9)	28 (2.8)	30 (2.8)	58 (2.8)
Age (year)						
n	1420	1420	2840	1005	1074	2079
Mean (SD)	52.31 (10.08)	52.27 (10.28)	52.29 (10.18)	52.22 (9.77)	52.61 (9.88)	52.42 (9.83)
Median	52.0	52.0	52.0	52.0	53.0	53.0
Q1, Q3	45.0, 59.0	45.0, 60.0	45.0, 60.0	45.0, 59.0	45.0, 60.0	45.0, 59.0
Min, Max	25, 83	23, 82	23, 83	26, 83	24, 78	24, 83
Age Group - n (%)						
< 35 yr	46 (3.2)	55 (3.9)	101 (3.6)	28 (2.8)	30 (2.8)	58 (2.8)
35 to <50 yr	523 (36.8)	515 (36.3)	1038 (36.5)	376 (37.4)	383 (35.7)	759 (36.5)
50 to <60 yr	497 (35.0)	488 (34.4)	985 (34.7)	368 (36.6)	383 (35.7)	751 (36.1)
≥ 60 yr	354 (24.9)	362 (25.5)	716 (25.2)	233 (23.2)	278 (25.9)	511 (24.6)
< 65 yr	1247 (87.8)	1245 (87.7)	2492 (87.7)	892 (88.8)	943 (87.8)	1835 (88.3)
≥ 65 yr	173 (12.2)	175 (12.3)	348 (12.3)	113 (11.2)	131 (12.2)	244 (11.7)

^a North America: CAN, US, BHS; Western Europe, Australia and South Africa: AUS, BEL, CHE, DEU, DNK, ESP, FRA, GBR, GRC, ITA, NLD, SWE, MLT, NZL; Asia Pacific, East Europe and South America: COL, MEX, PER, BGR, HUN, LTU, MKD, POL, ROM, SRB, SVK, CHN, HKG, JPN, KOR, MYS, SGP, TWN, HRV, CZE, TUR and ISR.

^b Height and weight at baseline, which are the last measurements on or before the first dose. For subjects who did not receive a dose, the baseline value is taken as the last measurement on or prior to the randomization date.

Table 5: Baseline Disease Characteristics, Patients with follow up >24 months vs ITT Population

	ITT			Patients with follow up >24 months		
	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)	Neratinib (N=1005)	Placebo (N=1074)	Total (N=2079)
ECOG Performance Status - n (%)						
0	1317 (92.7)	1303 (91.8)	2620 (92.3)	934 (92.9)	1001 (93.2)	1935 (93.1)
1	98 (6.9)	114 (8.0)	212 (7.5)	68 (6.8)	72 (6.7)	140 (6.7)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	5 (0.4)	3 (0.2)	8 (0.3)	3 (0.3)	1 (0.1)	4 (0.2)
Nodal Status ^a - n (%)						
Negative	335 (23.6)	336 (23.7)	671 (23.6)	223 (22.2)	277 (25.8)	500 (24.1)
1-3 Positive Nodes	664 (46.8)	664 (46.8)	1328 (46.8)	485 (48.3)	496 (46.2)	981 (47.2)
>= 4 Positive Nodes	421 (29.6)	420 (29.6)	841 (29.6)	297 (29.6)	301 (28.0)	598 (28.8)
Hormone Receptor Status ^a - n (%)						
Positive	816 (57.5)	815 (57.4)	1631 (57.4)	580 (57.7)	617 (57.4)	1197 (57.6)
Negative	604 (42.5)	605 (42.6)	1209 (42.6)	425 (42.3)	457 (42.6)	882 (42.4)
Prior Trastuzumab ^a - n (%)						
Concurrent	884 (62.3)	886 (62.4)	1770 (62.3)	606 (60.3)	673 (62.7)	1279 (61.5)
Sequential	536 (37.7)	534 (37.6)	1070 (37.7)	399 (39.7)	401 (37.3)	800 (38.5)
Menopausal Status at Diagnosis - n (%)						
Premenopausal	663 (46.7)	664 (46.8)	1327 (46.7)	463 (46.1)	488 (45.4)	951 (45.7)
Postmenopausal	757 (53.3)	756 (53.2)	1513 (53.3)	542 (53.9)	586 (54.6)	1128 (54.3)

^a From stratification factors.

One month is defined as 365.25/12 days.

Include patients whose DFS were > 3 months

Table 6: Prior Anti-cancer Therapy, Patients with follow up >24 months vs ITT Population

	ITT			Patients with follow up >24 months		
	Neratinib (N=1420)	Placebo (N=1420)	Total (N=2840)	Neratinib (N=1005)	Placebo (N=1074)	Total (N=2079)
Prior Radiotherapy - n (%)						
No	290 (20.4)	270 (19.0)	560 (19.7)	198 (19.7)	210 (19.6)	408 (19.6)
Yes	1130 (79.6)	1150 (81.0)	2280 (80.3)	807 (80.3)	864 (80.4)	1671 (80.4)
Prior Surgery - n (%)						
Lumpectomy only	468 (33.0)	511 (36.0)	979 (34.5)	338 (33.6)	388 (36.1)	726 (34.9)
Mastectomy	951 (67.0)	908 (63.9)	1859 (65.5)	666 (66.3)	685 (63.8)	1351 (65.0)
Prior Anti-cancer Medication - n (%)						
Yes	1420 (100)	1420 (100)	2840 (100)	1005 (100)	1074 (100)	2079 (100)
Anti-cancer Medication Type - n (%)						
Trastuzumab	1420 (100)	1420 (100)	2840 (100)	1005 (100)	1074 (100)	2079 (100)
Anthracycline only	136 (9.6)	135 (9.5)	271 (9.5)	101 (10.0)	109 (10.1)	210 (10.1)
Anthracycline + Taxane	962 (67.7)	965 (68.0)	1927 (67.9)	698 (69.5)	734 (68.3)	1432 (68.9)
Taxane only	318 (22.4)	316 (22.3)	634 (22.3)	204 (20.3)	228 (21.2)	432 (20.8)
Neither Anthracycline or Taxane	4 (0.3)	4 (0.3)	8 (0.3)	2 (0.2)	3 (0.3)	5 (0.2)
Prior Neo-adjuvant Therapy - n (%)						
No	1078 (75.9)	1041 (73.3)	2119 (74.6)	767 (76.3)	798 (74.3)	1565 (75.3)
Yes	342 (24.1)	379 (26.7)	721 (25.4)	238 (23.7)	276 (25.7)	514 (24.7)
Neo-adjuvant Therapy Type						
Trastuzumab	232 (16.3)	257 (18.1)	489 (17.2)	152 (15.1)	187 (17.4)	339 (16.3)
Anthracycline only	40 (2.8)	35 (2.5)	75 (2.6)	33 (3.3)	26 (2.4)	59 (2.8)
Anthracycline + Taxane	214 (15.1)	258 (18.2)	472 (16.6)	150 (14.9)	191 (17.8)	341 (16.4)
Taxane only	84 (5.9)	84 (5.9)	168 (5.9)	51 (5.1)	57 (5.3)	108 (5.2)
Neither Anthracycline or Taxane	4 (0.3)	2 (0.1)	6 (0.2)	4 (0.4)	2 (0.2)	6 (0.3)

^a From stratification factors.

One month is defined as 365.25/12 days, and one year is defined as 365.25 days.

Include patients whose DFS were > 3 months.

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/s/

PAMELA I BALCAZAR
03/21/2016

LALEH AMIRI KORDESTANI
03/22/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 66783

Wyeth Pharmaceuticals
Attention: Sreekumar Menon, Ph.D.
Senior Manager, Global Regulatory Affairs
87 Cambridge Park Dr.
Cambridge, MA 02140

Dear Dr. Menon:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Neratinib (HKI-272).

We also refer to the meeting between representatives of your firm and the FDA on 10 July, 2008. The purpose of the meeting was to discuss Chemistry, Manufacturing and Controls questions for EOPII.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Deborah Mesmer
Regulatory Health Project Manger for Quality
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT**

Sponsor Name:	Wyeth Pharmaceuticals
Application Number:	IND 66783
Product Name:	Neratinib (HKI-272)
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls, EOPII
Meeting Date and Time:	Thursday, 10 July, 2008 , 12:00- 13:00 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	20 June, 2008
Meeting Requestor	Jeffry Lynch, Ph.D.
Meeting Chair:	Ravi Harapanhalli, Ph.D.
Meeting Recorder	Deborah Mesmer, M.S.

FDA ATTENDEES:

CENTER FOR DRUG EVALUTATION RESEARCH

Office of New Drug Quality Assessment

Ravi Harapanhalli, Ph.D., Branch Chief
Ravindra Kasliwal, Ph.D., Review Chemist
Sarah Pope, Ph.D., Pharmaceutical Assessment Lead
Scott Goldie, Ph.D., Project Manager - Quality
Anne Marie Russell, Ph.D., Chemistry Reviewer
Arzu Selen, Ph.D., Associate Director, Biopharmaceutics
Deborah Mesmer, M.S., Project Manager – Quality

Office of Oncology Drug Products

Carl Huntley, R. Ph, M.B.A, Senior Project Manager - Clinical

EXTERNAL ATTENDEES:Wyeth Pharmaceuticals

Richat Abbas, Ph.D., Director, Early Development Clinical Pharmacology
Don Esherick, Director, Global Regulatory Affairs CMC
Arwinder Nagi, Assistant Vice President, New Products & Process Development
Kris Ghosh, Ph.D., Director, New Product Leader
Ling Zhang, Ph.D., Director, Analytical Quality Services (on teleconference)
Sherry Ku, Ph.D., Director, Pharmaceutical Development
Robert Mills, Ph.D., Senior Director, API Technology Operations
Thirunellai Venkateshwaran, Ph.D., Senior Director, Pharma New Products Quality Operations
Shreekumar Menon, Ph.D., Senior Manager, Global Regulatory Affairs CMC
Jeffry Lynch, Ph.D., Associate Director, Global Regulatory Affairs CMC

1.0 BACKGROUND

HKI-272 maleate is being developed by Wyeth for the treatment of advanced and metastatic breast cancer. The IND (66,783) for Neratinib was filed on 30 June, 2003. The early development and clinical program of HKI-272 employed capsules of HKI-272 of 10 mg, 40 mg, and 80 mg strengths. The requirement of a 240 mg strength during Phase II clinical studies (b) (4)

(b) (4) A Type B EOPII CMC meeting request was submitted and received on 07 May 2008. The meeting was granted on 14 June, 2008 for a face-to-face meeting to be held on 10 July, 2008. The meeting briefing package was received on 20 June, 2008. The preliminary responses were archived and shared with Wyeth Pharmaceuticals on 7 July, 2008, to promote an efficient discussion at the meeting scheduled for 10 July, 2008. On 10 July, 2008, Wyeth submitted a slide presentation to be used at the meeting. The minutes of the meeting discussion follow.

2.0 DISCUSSION

Question 1: Does the Agency concur with Wyeth's identification of (b) (4)

(b) (4)

FDA Response to Question 1: (b) (4)

(b) (4)

(b) (4)

(b) (4)

***Additional Comment:***

(b) (4)



Meeting Discussion: Wyeth acknowledged FDA's response. No further discussion occurred during the meeting.

Question 2: Does the Agency concur that the bridging strategy proposed to demonstrate the equivalence of the Wyeth (clinical) (b) (4) (proposed commercial) drug substance is adequate for NDA approval?

FDA Response to Question 2: The approach appears to be acceptable.

- The impurity profiles of the batches used in clinical trials should be similar or better than the batches used in animal toxicology studies, and drug substance batches that are different, qualitatively or quantitatively, in impurity profiles should be adequately qualified in animal toxicology studies prior to their use in clinical studies. Summary data for such batches and studies should be submitted to the IND file.

- In addition to the comparison

(b) (4)



Meeting Discussion: Wyeth acknowledged FDA's response and stated that they would submit the requested data. No further discussion occurred during the meeting.

Question 3: Does the Agency concur with Wyeth's proposal for assessing changes in the tablet formulation or manufacturing process made by (b) (4)?

FDA Response to Question 3: While the approach appears to be feasible, insufficient information is provided to make a definitive assessment. The following additional information is necessary to make an assessment:

- Provide the details of the single dose comparative bioavailability study performed to assess the two HKI-272 formulations, and the IVIVC study. For this study, provide information on whether or not the bioequivalence criteria were met and information regarding the power of the study. If it is submitted in a previous amendment, provide the amendment number and the date of submission.
- Provide details of the dissolution method and data to support that the dissolution method has adequate discrimination capability. Further, additional time points for dissolution data collection should be introduced between 0-30 minutes to provide a better dissolution rate profile.
- In the IVIVC study, data and analysis should be provided to support a (b) (4) correlation between in-vitro and in-vivo parameters.

Meeting Discussion: (Additional information in the form of a slide presentation was presented to address question number 3. See section 6.0 for attachments). FDA acknowledged Wyeth's efforts for exploring an IVIVC. The challenges were: (b) (4)



Question 4: Does the Agency concur with the bridging strategy proposed to demonstrate the equivalence of the Wyeth (clinical) (b) (4) (proposed commercial) drug product is adequate for NDA approval?

FDA Response to Question 4: The approach appears to be acceptable.

Meeting Discussion: Wyeth acknowledged FDA's response. No further discussion occurred during the meeting.

Question 5: Does the Agency concur that the drug product stability package and the data submission plans are adequate for NDA approval?

FDA Response to Question 5: Stability update should be accompanied by the statistical analysis of all stability indicating quality attributes as indicated in ICH Q1E. Stability updates are expected by the submission's mid cycle for a timely assessment, and they should conform to SAS transport or Excel spreadsheet format. Late submissions, if considered major, may not be reviewed or may result in extension of the clock. The expiration dating period will be evaluated as per the ICH Q1E guidance and accordingly granted. Please refer to this guidance for additional details.

Meeting Discussion: Wyeth acknowledged FDA's response. No further discussion occurred during the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION FROM PRELIMINARY RESPONSES

Additionally, we have the following comments:

- Clarify if the manufacturing process and equipment for various unit operations is similar at the Wyeth (b) (4) drug product manufacturing sites.
- What are the shapes of the commercial tablets?
- Include specifications for content uniformity in the drug product.
- Clarify the type of (b) (4) employed for drug substance (b) (4). Also, clarification and appropriate justification should be provided whether the drug substance release testing is performed prior to or subsequent (b) (4).
- Information / data concerning the (b) (4) should be provided. A three point particle size distribution specification (D₁₀, D₅₀ and D₉₀) should be included (b) (4) drug substance specifications.
- A thorough understanding of the relationships between material attributes, process parameters and CQAs should be developed and documented in the NDA. Appropriate controls at the input stage and during the process should be in place to assure that product of purported quality attributes is manufactured with a high level of confidence at the commercial scale on a routine basis.
- Include (b) (4) during drug product manufacturing.
- You are encouraged to request a CMC-specific meeting pertaining to your QbD approach in the future.

4.0 ACTION ITEMS

There were no other action items from the meeting other than those specified in the discussion section above.

5.0 CONCURRENCE:

{See appended electronic signature page}

Deborah Mesmer
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Ravi Harapanhalli, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

Attachment A: Neratinib (HKI-272)-EOPII FF meeting-11jul08.pdf

Attachment B: Neratinib (HKI-272)-EOPII-back up slides-10Jul08.pdf

Attachment A: Neratinib (HKI-272)-EOPII FF meeting-11jul08.pdf follows this page.

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

Linked Applications

Sponsor Name

Drug Name

IND 66783

WYETH
PHARMACEUTICALS
INC

HKI-272

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/s/

DEBORAH M MESMER
08/01/2008

RAVI S HARAPANHALLI
08/01/2008

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208051

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Puma Biotechnology, Inc.
Attention: Jesse Ho, PharmD, RPh
Sr. Director, Global Regulatory Lead
10880 Wilshire Blvd., Suite 2150
Los Angeles, CA 90024

Dear Dr. Ho:

Please refer to your New Drug Application (NDA) dated July 19, 2016, received July 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Nerlynx™ (neratinib maleate) Tablets, 40 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 20, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at pamela.balcazar@fda.hhs.gov, at your earliest convenience.

If you have any questions, call Pamela Balcazar, Regulatory Project Manager, at (240) 402-4203.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director (Acting)
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: June 20, 2017; 12-1PM
Meeting Location: Teleconference

Application Number: 208051
Product Name: Nerlynx (neratinib)
Indication: Early stage HER2 positive Breast Cancer
Applicant Name: Puma Biotechnology

FDA ATTENDEES (tentative)

Julia Beaver, MD, Acting Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Laleh Amiri-Kordestani, MD, Cross Discipline Team Leader, DOP1
Harpreet Singh, MD, Clinical Reviewer, DOP1
Amanda Walker, MD, Clinical Reviewer, DOP1
Joyce Cheng, PhD, Biostatistics Reviewer, DBV
Shenghui Tang, PhD, Biostatistics Team Leader, DBV
Walt Cao, PhD, Clinical Pharmacology Reviewer, OCP
Qi Liu, PhD, Clinical pharmacology Team Leader, OCP
Nan Zheng, PhD, Pharmacometrics Reviewer, OCP
Jerry Yu, PhD, Pharmacometrics Team Leader, OCP
Kimberly Ringgold, PhD, Pharmacology/Toxicology, DHOT
Todd Palmby, PhD, Pharmacology/Toxicology Team Leader, DHOT
William Pierce, PharmD, CAPT, USPHS, Associate Director Labeling, DOP1
Pamela Balcazar, MS, Regulatory Health Project Manager, DOP1

APPLICANT ATTENDEES

TBD

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in

this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues at this time.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Pamela Balcazar/Laleh Amiri Kordestani)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

You have been notified of 2 Postmarketing Requirement (1) to conduct pharmacokinetic trial to evaluate repeat doses of a moderate CYP3A4 inhibitor and (2) to conduct a carcinogenicity study in the rat. You were also notified to submit final study reports, datasets and labeling.

We have also asked that you agree to the following postmarketing commitments:

- Conduct a physiologically-based pharmacokinetic modeling/simulation study or a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.
- Conduct [REDACTED] (b) (4) a clinical pharmacokinetic trial to evaluate whether separating the dosing of H2-receptor antagonists and neratinib can minimize the drug-drug interaction potential.
- Submit the overall survival (OS) data and results from Trial 3144A2-3004-WW, ExteNET, “A Randomized, Double-Blind, Placebo-Controlled Trial of Neratinib

(HKI-272) After Trastuzumab in Women with Early-Stage HER-2/neu Overexpressed/Amplified Breast Cancer”

- Submit Final report and datasets for all PMC’s
3. Major labeling issues – 15 minutes
 4. Review Plans –5 minutes
 5. Wrap-up and Action Items – 5 minutes

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/s/

PAMELA I BALCAZAR
06/16/2017

JULIA A BEAVER
06/16/2017