

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208051Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA # NDA 208051
Product Name: Nerlynx (neratinib maleate)

PMR Description: 3223-1 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 Protocol Submission: 10/2017

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

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

Drug interaction studies of concomitant use with moderate CYP3A inhibitors have not been conducted by the applicant. Neratinib is predominantly metabolized by the CYP3A enzymes and clinical study indicated significant exposure increases when concomitant use with strong CYP3A inhibitors. Concomitant use with moderate CYP3A inhibitors may increase the neratinib exposure, which could result in safety adverse events.

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

This study will address the need for dosing modifications based on concomitant use of drugs that are moderate CYP3A inhibitors, (b) (4)

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Conduct a physiologically-based pharmacokinetic modeling/simulation or a clinical trial 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 (b) (4)

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA 208051

Product Name:

Neratinib

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*,

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

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

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

The proposed indication for neratinib is for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have completed adjuvant trastuzumab-based therapy (b) (4)

HER2-overexpressed/amplified breast cancer can be a serious and life-threatening condition as following treatment with current adjuvant therapies, 15-20% of patients recur with metastatic breast cancer (which is a serious and life-threatening condition), indicating there is an unmet need.

The carcinogenic potential of neratinib is currently unknown.

The ICH S1A guidance includes the following recommendations regarding indications and patient populations:

1. When a pharmaceutical is intended for adjuvant therapy in tumor free patients, carcinogenicity studies are usually needed.
2. For pharmaceuticals developed to treat certain serious diseases, carcinogenicity testing does not need to be conducted pre-approval, although these studies should be conducted post-approval, which speeds the availability of therapies for life-threatening or severely debilitating diseases, especially where no alternative therapy exists.

The ICH M3(R2) Guidance for Industry on *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*

[<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf>] states that for pharmaceuticals developed to treat certain serious diseases, carcinogenicity testing can be concluded postapproval.

The 2-year carcinogenicity study with neratinib in the rat was not required pre-approval to provide patients access

to this treatment sooner.

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

The patients included in the proposed indication would receive one year of extended adjuvant treatment with neratinib following (b) (4) trastuzumab-based adjuvant treatment. Carcinogenicity is a safety concern with chronic drug exposure. There is a concern the neratinib could cause additional cancers in patients. To address this concern a carcinogenicity study in the rat is being required to assess the carcinogenic potential of neratinib in rodents.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

A 2-year carcinogenicity study in the rat.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

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

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

Agreed upon:

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

- Other

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

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

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

- There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA # NDA 208051
Product Name: Neratinib

PMC Description: 3223-3
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>

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

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

The Overall Survival data not available at the time of iDFS analysis included in this application. This is important information to include in Section 14 of the package insert.

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

Not a PMR.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The data is from an existing clinical trial that does not have mature information of overall survival.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

This study will address the need for dosing modifications based on concomitant use of drugs that are moderate CYP3A inducers, (b) (4)

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Conduct a physiologically-based pharmacokinetic modeling/simulation 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. (b) (4)

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA # NDA 208051
Product Name: Neratinib

PMC Description:
3223-5 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.

PMR/PMC Schedule Milestones:

Final Report Submission: 12/2017

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

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

Drug interaction studies of concomitant use with H₂-receptor antagonists have not been conducted by the applicant. Neratinib has pH value dependent solubility and clinical study indicated significant decrease of exposure when concomitant use with proton pump inhibitor. Concomitant use with H₂-receptor antagonists may decrease the neratinib exposure, which could result in loss of neratinib activities.

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

This study will address the need for dosing modifications based on concomitant use of drugs that are H₂-receptor antagonists, (b) (4)

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

Conduct (b) (4) a clinical pharmacokinetic trial to evaluate whether separating the dosing of H ₂ -receptor antagonists and neratinib can minimize the drug-drug interaction potential. (b) (4)
--

Required

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

- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

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

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

Agreed upon:

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

Other

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

CHRISTINA D MARSHALL
07/31/2017

KATHERINE M FEDENKO
07/31/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: July 7, 2017
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 208051
Product Name and Strength: Nerlynx (neratinib) tablets, 40 mg
Submission Date: June 27, 2017
Applicant/Sponsor Name: Puma Biotechnology, Inc.
OSE RCM #: 2016-1818-2
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

Division of Oncology Products 1 (DOP1) requested that we review the revised Nerlynx container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations from Office of Pharmaceutical Quality (OPQ)^a.

2 CONCLUSION

The revised Nerlynx container label and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Puma Biotechnology. NDA #208051 Nerlynx™ (Neratinib Maleate). Amendment: Revised Carton/Container Label. Los Angeles (CA): Puma Biotechnology, Inc. 2017 June 27.

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/s/

TINGTING N GAO
07/07/2017

CHI-MING TU
07/07/2017

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

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

Memorandum

Date: June 23, 2017

To: **Pamela Balcazar, MS**
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products

From: Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NERLYNX™** (neratinib) tablets, for oral use
NDA 208051

Office of Prescription Drug Promotion comments on proposed
prescribing information (PI), container labels and carton labeling

Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI), carton labeling and container labels for NERLYNX™ (neratinib) tablets, for oral use as requested by DOP1 in the consult dated September 7, 2016.

OPDP's review of the proposed PI is based on the draft PI titled, "09Jun17_FDA_us-package-insert.docx" sent by electronic mail on June 9, 2017, to OPDP (Kevin Wright) from DOP1 (Pamela Balcazar). OPDP's comments are listed in the attached PI.

OPDP also reviewed the proposed container labels and carton labeling submitted to the electronic document on April 19, 2017. OPDP has no comments for the proposed labels and labeling.

The combined OPDP and Division of Medical Policy Programs (DMPP) review of the patient package insert (PPI) will be provided under a separate cover.

If you have any questions, please feel free to contact, Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/

KEVIN WRIGHT
06/23/2017

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

PATIENT LABELING REVIEW

Date: June 23, 2017

To: Julia Beaver, MD
Acting Director
Division of Oncology Products 1(DOP1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

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

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): NERLYNX (neratinib)

Dosage Form and Route: tablets for oral use

Application Type/Number: NDA 208051

Applicant: Puma Biotechnology, Inc.

1 INTRODUCTION

On July 19, 2016, Puma Biotechnology, Inc. submitted for the Agency's review an original New Drug Application (NDA) 208051 for NERLYNX (neratinib) tablets, proposed for use as a single agent indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on September 7, 2016 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for NERLYNX (neratinib) tablets.

2 MATERIAL REVIEWED

- Draft NERLYNX (neratinib) tablets PPI received on July 19, 2016 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 12, 2017.
- Draft NERLYNX (neratinib) tablets Prescribing Information (PI) received on July 19, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 12, 2017.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
06/23/2017

KEVIN WRIGHT
06/23/2017

BARBARA A FULLER
06/23/2017

LASHAWN M GRIFFITHS
06/23/2017

Clinical Inspection Summary

Date	March 23, 2017
From	Lauren Iacono-Connors, Reviewer Susan Thompson, M.D., Team Leader for Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation (DCCE)
To	Pamela Balcazar, Regulatory Project Manager Amanda Walker, Clinical Reviewer Harpreet Singh, Clinical Reviewer Division of Oncology Products 1
NDA #	208051
Applicant	Puma Biotechnology Inc.
Drug	Nerlynx™ (neratinib maleate)
NME	Yes
Therapeutic Classification	Standard
Proposed Indication	For extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy.
Consultation Request Date	August 12, 2016
Summary Goal Date	March 31, 2017
Action Goal Date	July 19, 2017
PDUFA Date	July 19, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study 3144A2-3004-WW were submitted to the Agency in support of NDA 208051. Four clinical sites, Dr. Beth Hellerstedt (Site 1526), Dr. Nicholas Robert (Site 1804), Dr. Arlene Chan (Site 1360), Dr. Zorica Tomasevic (Site 1191), and the study sponsor, Puma Biotechnology Inc., were selected for audit.

The primary efficacy endpoint, Invasive disease-free survival (iDFS), as determined by the clinical investigators, was verified with the source records generated at the inspected clinical sites. There were no significant inspectional findings for clinical investigators Dr. Beth Hellerstedt, Dr. Nicholas Robert, Dr. Arlene Chan, and Dr. Zorica Tomasevic, and study sponsor Puma Biotechnology, Inc.

The data from all inspected sites associated with Study 3144A2-3004-WW appear reliable.

II. BACKGROUND

Puma Biotechnology, Inc. (Puma) seeks approval of Nerlynx™ (neratinib) as a single agent for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy.

The following overview of the Study 3144A2-3004-WW is intended as background context for interpreting the inspectional findings.

Study 3144A2-3004-WW is a Phase 3, multicenter, randomized, double-blind study of neratinib versus placebo in women with early-stage ERBB2-overexpressed/amplified breast cancer after adjuvant treatment with trastuzumab. The study randomized 2840 subjects (1420 neratinib, 1420 placebo) at 476 clinical centers in 40 countries.

Study Period: Study initiation date (first subject entered): July 9, 2009

Data cut-off date for primary analysis: July 7, 2014

Primary efficacy endpoint: Invasive disease-free survival (iDFS), to include invasive local, regional, and distant recurrence, including ipsilateral or contralateral breast, and death from any cause. iDFS is a time to event outcome measure from baseline.

Objectives of Inspections:

- a. Verify iDFS as assessed by the investigator.
- b. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
- c. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Arlene Chan (Site 1360) 101 Monash Ave., Nedlands Western Australia 6009 Australia	Protocol: 3144A2-3004-WW Subjects: 46	October 31, 2016 – November 4, 2016	Preliminary Classification VAI
CI #2: Beth Hellerstedt (Site 1526) 6204 Balcones Drive Austin, TX 78731	Protocol: 3144A2-3004-WW Subjects: 17	January 9-13, 2017	Preliminary Classification NAI
CI #3: Neelima Denduluri (Formerly: Nicholas Robert) (Site 1804) 8503 Arlington Boulevard, Suite 400 Fairfax, VA 22031	Protocol: 3144A2-3004-WW Subjects: 29	December 5-6, 2016	Preliminary Classification NAI

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI #4: Zorica Tomasevic (Site 1191) Belgrade 11 000 Serbia	Protocol: 3144A2-3004-WW Subjects: 22	November 14-18, 2016	Preliminary Classification VAI
Sponsor: Puma Biotechnology Inc. 10880 West Wilshire Blvd. Suite 2150 Los Angeles, CA 90024-4800	Protocol: 3144A2-3004-WW Site Numbers: 1526, 1804, 1360, 1191, 1189 and 1860	March 15-17, 2017	Preliminary Classification NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Prof. Arlene Chan, M.D. (Site 1360)

The site screened 54 subjects and enrolled 46 subjects. At the time of this inspection 41 subjects had completed the one year treatment phase, and of those, 17 subjects had completed the extension phase (5 year follow-up). A record review was done for 23 enrolled subjects. Study subject source documents were compared to the eCRF and data listings submitted to NDA 208051. Ethics committee approvals, monitoring reports, adverse events, subject records, drug dispensing records, training, informed consents, and primary endpoints were reviewed during this inspection.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, iDFS, was verifiable with the source records generated at the site. There was no evidence of under-reporting of AEs. However, the drug dispensing records were not always an accurate accounting of drug use by study subjects. Specifically, at the Month 1 study visit, Feb 24, 2010, Subject 12831 was dispensed IP kits 506396 and 506398. The subject would run out of study drug prior to the Month 3 visit and therefore, required a resupply before the visit. Source documentation indicated that the site received a verbal manual assignment on May 4, 2010 from the IVRS (ICON) system for kit 505971 to be dispensed to the subject. An email dated May 4, 2010 shows kit 505974 was manually assigned by the IVRS system to be dispensed to the subject. The drug accountability log shows kit 505971 was dispensed to this subject on May 4, 2010. Kit 505974 was never dispensed and was logged as destroyed at the time of study closure per site guidelines on September 20, 2011.

OSI Notes: In a written response, dated November 15, 2016, to the Form FDA 483 inspectional operations, Prof. Chan acknowledged that investigational drug disposition records for Subject 12831 were not adequate. Prof. Chan explained that the IVRS system was non-functional at the time leading the study site coordinator to call the ICON IVRS Help Desk on May 4, 2010, to obtain IP for an unscheduled visit for Subject 12831. The Help Desk verbally advised allocation of kit 505971 and IP was subsequently dispensed to Subject 12831. The email confirmation from an IVRS staff member was received at approximately 8:40 PM that same date indicating that kit 505974 was to be dispensed to subject. Prof. Chan confirmed that kit 505971 was the correct IP [REDACTED] (b) (4) for Subject 12831. A corrective action plan, to include a new SOP “Management of Centrally Allocated Trial Medication”, should mitigate the inspectional finding moving forward. This inspectional observation should have no impact on study outcomes or have placed the subject at undue risk.

2. Dr. Beth Hellerstedt, M.D. (Site 1526)

The site screened 24 subjects and enrolled 17 subjects. At the time of this inspection, all subjects were off study treatment and off the study; one subject died during the course of the study. A complete record review was done for all 17 enrolled subjects. Study subject source documents were compared to the eCRF and data listings submitted to NDA 208051. Entry criteria satisfaction, safety and data monitoring, test article accountability, IRB/IEC and sponsor correspondence, ICFs, compliance with the protocol, human subject files, AERs/SAERs, and the site's adherence with the applicable regulations for the IP, Neratinib Maleate drug product, as well as the investigational plan was reviewed during this inspection.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, iDFS, was verifiable with the source records generated at the site. With a minor exception, there was no evidence of under-reporting of AEs. Briefly, on December 22, 2009, Subject 005060 reported having diarrhea, nausea, extreme fatigue, cramps, and constipation over the past week. However, AEs of ‘extreme fatigue’ and ‘constipation’ were not recorded in the eCRF or in the subject data listings submitted to the application. All other noted AEs on the study notes for the study visit were recorded in the Subject’s eCRF and datalistsings. This observation should have no impact on study outcomes or have placed Subject 005060 at undue risk.

3. Dr. Neelima Denduluri, M.D. (Site 1804)

The site screened 35 subjects and enrolled 29 subjects. At the time of this inspection, 22 subjects had completed the 12 months of study treatment. Seven subjects withdrew from study treatment due to AEs. Many subjects are continuing in an extension study to monitor survival. A complete record review was done for all 29 enrolled subjects. Study subject source documents were compared to the eCRF and data listings submitted to NDA 208051. Entry criteria satisfaction, overall protocol compliance, AEs, informed consent documentation, IRB correspondence, and test article accountability was reviewed during this inspection.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, iDFS, was verifiable with the source records generated at the site. There was no evidence of under-reporting of AEs.

4. Dr. Zorica Tomasevic, M.D. (Site 1191)

The site screened 28 subjects and enrolled 22 subjects. A record review was done for eight enrolled subjects. Study subject source documents were compared to the eCRF and data listings submitted to NDA 208051. The inspection included review of informed consent forms for all screened subjects and an audit of all enrolled study subjects' records. The audit assessed AE/SAEs, protocol deviations, entry criteria satisfaction, laboratory findings for blood samples collected during the study, radiologic imaging conducted to support the study, test article accountability, and investigator assessment of tumor response. Clinical monitoring records, delegation of authority logs, IRB approvals and correspondence, sponsor correspondence, and financial disclosure documentation were also assessed.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, iDFS, was verifiable with the source records generated at the site. With a few exceptions, there was no evidence of under-reporting of AEs. Briefly, there were three subjects who had reported AEs in their diary that were not included in the subjects' eCRFs or the datalistsings submitted to the application. For example, Subject 001496 reported palpitations on August 30, 2010, and diarrhea and chest pains on September 14-15, 2010, via their diary, that were not reported to the sponsor. Subject 001498 reported diarrhea on January 27, 2010, diarrhea on February 2, 2010, diarrhea and foot pain on 8-10 April 8-10, 2010, diarrhea on June 12-15, 2010, diarrhea and constipation on July 12, 2010, diarrhea on July 26, 2010, and diarrhea, vomiting, and headache on December 30, 2010. These adverse events, reported by the subject via their diary, were not reported to the sponsor.

Dr. Tomasevic stated in a written response to the Form FDA 483 inspectional observations, dated December 7, 2016, that at the time of the subject visits, the Principal Investigator would review all diary entries with the subject. Potential AEs were discussed and documented in the source notes according to the instructions provided in the study protocol: "*Determination of AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject*" (Protocol Amendment 3, page 87, section 27.6 – Attachment 1). The subjects were also asked about potential non-documented AEs. Dr. Tomasevic acknowledged that all AEs discussed with the subjects should have been reported to the sponsor per protocol requirements. She has since developed new processes that are being implemented that should minimize these inspectional observations moving forward. As part of the corrective action plan Dr. Tomasevic reviewed the medical charts from all subjects and confirmed that the safety of study subjects was not compromised. These inspectional observations should not importantly impact study outcomes or have placed subjects at undue risk.

Finally, the site did not maintain CT and MRI imaging used to determine [in part] disease progression. However, the reports from the ultrasounds, CT scans, and MRIs for all subjects

are included in the subject charts. Dr. Tomasevic responded in a written response to the Form FDA 483 inspectional observations, dated December 7, 2016, that the clinical investigators at this site are not certified to read medical imaging scans; therefore, the site procedure requires that a local radiologist perform the scan, read the scan, and complete and return a signed report to the clinical site. These signed radiology reports are maintained as source documentation in the subject charts and study records. As part of a corrective action, copies of all CT/MRI images performed at the Institute for Oncology and Radiology have since been retrieved and placed in the study files. Starting in December 2016, the site modified their process to obtain a copy of all medical imaging scans to include in the study file together with the radiology report. The inspectional observation should not impact study outcomes or have placed subjects at risk.

5. Sponsor: Puma Biotechnology Inc.

The inspection focused on the sponsor's control, oversight, and management of Study 3144A2-3004-WW. Records reviewed included quality assurance and clinical SOPs, monitoring plans and reports, completed financial disclosure forms, completed FDA 1572 Forms, as well as eCRF data on disease recurrence, overall survival, protocol deviations, and adverse events. Six study sites (1189, 1191, 1360, 1526, 1804, and 1860) were selected for source data review. Actions taken by the sponsor to bring non-compliant clinical sites into compliance were also assessed.

The sponsor appeared to maintain adequate oversight and control of Study 3144A2-3004-WW. Monitoring of investigator sites appeared adequate. There was no evidence of underreporting AEs. The primary efficacy endpoint data for six clinical sites were verifiable. The inspection revealed no significant deficiencies.

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Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Susan D. Thompson, M.D., Team Leader, acting for
Kassa Ayalew, M.D., M.P.H
Branch Chief
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cc:

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DOP1/Clinical Team Leader/Laleh Amiri-Kordestani
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LAUREN C IACONO-CONNORS
03/23/2017

SUSAN D THOMPSON
03/23/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 21, 2017
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 208051
Product Name and Strength: Nerlynx (neratinib) tablets, 40 mg
Submission Date: February 15, 2017
Applicant/Sponsor Name: Puma Biotechnology, Inc.
OSE RCM #: 2016-1818-1
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

Division of Oncology Products 1 (DOP1) requested that we review the revised Nerlynx container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised Nerlynx container label and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Gao T. Label and Labeling Review for Nerlynx (NDA 208051). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 31. 32 p. OSE RCM No.: 2016-1818.

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02/21/2017

CHI-MING TU
02/21/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 31, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 208051
Product Name and Strength:	Nerlynx (neratinib) tablets, 40 mg
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Puma Biotechnology, Inc.
Submission Dates:	December 22, 2016
OSE RCM #:	2016-1818
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Puma Biotechnology, Inc. submitted the container labels, carton labeling, and prescribing information (PI) for Nerlynx (neratinib) tablets for NDA 208051. This is a New Molecular Entity (NME) product with a proposed indication for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy.

The Division of Oncology Products 1 (DOP1) requested that we review the submitted Nerlynx container labels, carton labeling, and prescribing information for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed Nerlynx container labels and the carton labeling, and noted the followings:

- Puma Biotechnology, Inc. presented the product identifier twice on the principal display panel (“nerlynx neratinib tablets” (b) (4) (b) (4) We noted the Agency previously communicated to Puma to change the statement to “Nerlynx (neratinib) tablets, (b) (4)”.^a We recommend keeping only one of the product identifiers to eliminate redundancy.

^a Puma Biotechnology, Inc. NDA 208051 Nerlynx (Nertainib Maleate): Response to the FDA Information Request

- Since we are recommending the Applicant to remove (b) (4) to reduce information crowding on the principal display panel, we recommend revising the statement (b) (4) to “Each film-coated tablet contains 40 mg neratinib equivalent to 48.31 mg neratinib maleate” for clarity.
- We recommend removing the statement (b) (4) to reduce clutter on the principal display panel.
- We recommend increasing contrast between the strength statement “40 mg” in white font on (b) (4) background because white on (b) (4) provides insufficient contrast and may reduce legibility.
- The NDC number should be relocated to the top one-third of the principal display panel per 21 CFR 207.35(b)(3)(i) for the proposed Nerlynx container labels.

We noted an earlier version of proposed PI submitted November 3, 2016 did not list the 126-count bottle in Section 16 but the November 3, 2016 submission contained container label and carton labeling for a 126-count bottle. To clarify this 126-count packaging configuration, an Information Request (IR) was sent December 2, 2016.



Since both bottle of 180 tablets and bottle of 126 tablets package configurations will be stored in the specialty pharmacy, the bottle of 126 tablets should be adequately differentiated from the bottle of 180 tablets to avoid confusion. As currently presented, the net quantity statement on the bottle of 126 tablets is presented in blue font and the net quantity statement on the bottle of 180 tablets is presented in (b) (4) font, which provided adequate differentiation. We also noted the December 22, 2016 proposed PI does list the 126-count bottle in Section 16. We reviewed the December 22, 2016 proposed PI and recommend that the dose be presented as “240 mg (6 tablets)” to indicate that 6 tablets is required to construct the dose of 240 mg to

Chemistry, Manufacturing, and Controls, dated 23 November 2016. Puma Biotechnology, Inc. Los Angeles (CA): Puma Biotechnology, Inc. 2016 DEC 22.

^b Puma Biotechnology, Inc. NDA 208051 Nerlynx (Nertainib Maleate): Response to 02 December 2016 Quality Information Request. Los Angeles (CA): Puma Biotechnology, Inc. 2016 DEC 9.

minimize the risk of wrong dose errors and recommend to present prophylactic treatment with loperamide instructions in a tabular format to enhance readability and accessibility of this important information.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels, carton labeling and PI for Nerlynx may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dosage and Administration Section

- a. Revise the statement (b) (4) to “The recommended dose of NERLYNX is 240 mg (six tablets) given orally once daily” to minimize the risk of wrong dose errors.
- b. We recommend to present prophylactic treatment with loperamide instructions in a tabular format to enhance readability and accessibility of this important information.

4.2 RECOMMENDATIONS FOR PUMA BIOTECHNOLOGY, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels and Carton labeling)

1. As currently presented, the product identifier is presented twice on the principal display panel:



Present the established name under the blue “Nerlynx” in parenthesis (e.g., “(neratinib) tablets”) and remove (b) (4) to reduce information crowding on the principal display panel.

2. Remove the (b) (4) statement since it is not required per 21 CFR 201.100(b)(3) to reduce information crowding on the principal display panel.
3. Increase the prominence of the strength statement by increasing the font size of the “40 mg” statement” and ensure there is adequate contrast between the white font color and the (b) (4) background color to improve readability. With the (b) (4) statement removed, consider using the blue background for the white colored “40 mg” text for better contrast.

4. Revise the statement [REDACTED] (b) (4) to “Each film-coated tablet contains 40 mg neratinib equivalent to 48.31 mg neratinib maleate” for clarity.

B. Container labels

1. As currently presented, the NDC number is located on the side panel. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the label in accordance with 21 CFR 207.35(b)(3)(i).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nerlynx that Puma Biotechnology, Inc. submitted on December 22, 2016.

Table 2. Relevant Product Information for Nerlynx	
Initial Approval Date	N/A
Active Ingredient	neratinib
Indication	Indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer (b) (4) adjuvant trastuzumab-based therapy.
Route of Administration	Oral
Dosage Form	Tablets
Strength	40 mg
Dose and Frequency	<p>Recommended dose: 240 mg (six (b) (4) tablets) given orally once daily with food, continuously for one year at approximately the same time every day.</p> <p>Dose modification when diarrhea occurs: (b) (4) diarrhea resolves to Grade 1 or Grade 0 in longer than one week: Resume NERLYNX treatment at reduced dose (b) (4)</p>
How Supplied	Bottle of 180 tablets Bottle of 126 tablets
Storage	Store at controlled room temperature, (b) (4) excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].
Container Closure	60-cc, high density polyethylene (HDPE) white opaque, round bottle with (b) (4) and foil-lined induction seal, containing either 126 or 180 tablets. An (b) (4) desiccant (b) (4) is enclosed with the drug product in each container.

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01/31/2017

CHI-MING TU
01/31/2017

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

IND or NDA	NDA 208051
Brand Name	Nerlynx
Generic Name	Neratinib maleate
Sponsor	Puma Biotechnology
Indication	Nerlynx as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy
Dosage Form	Tablets
Drug Class	Tyrosine Kinase Inhibitor
Therapeutic Dosing Regimen	240 mg once daily with food
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Neratinib 240 mg [REDACTED] (b) (4)
Submission Number and Date	001 and 7/19/2016
Review Division	DOP1

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of neratinib 240 mg and neratinib 240 mg with ketoconazole was detected in this TQT study. However in this study, neratinib 240 mg in combination with ketoconazole was studied under fasted conditions. This leads to attainment of lower exposures (by 25%) relative to the highest clinical exposure scenario of neratinib 240 mg administered in fed state in combination with ketoconazole. Based on the exposure-QTc relationship observed from the QTc study, QTc prolongation with the once daily oral dosing regimen of neratinib 240 mg is not expected.

The study was conducted in 2 parts. Part A administered a single dose of neratinib 240 mg, placebo, or moxifloxacin 400 mg in a fed state. Part B administered neratinib 240 mg with ketoconazole 400 mg or placebo with ketoconazole 400 mg in a fasting state. The largest upper bounds of the 2-sided 90% CI for the mean differences i) between neratinib 240 mg

and placebo and ii) between neratinib 240 mg with ketoconazole 400 mg and placebo with ketoconazole 400 mg, are below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for $\Delta\Delta\text{QTcN}$ moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 7 and Figure 8, indicating that assay sensitivity was established.

In this randomized, placebo- and open-label moxifloxacin-controlled, crossover study (3144A1-105-US), 52 healthy subjects received neratinib 240 mg, placebo, moxifloxacin 400 mg, neratinib 240 mg with ketoconazole 400 mg and placebo with ketoconazole 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Nerlynx 240 mg (part A) and Nerlynx 240 mg + Ketoconazole 400 mg (Part B) and the Largest Lower Bound for Moxifloxacin (Part A) (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcN}$ (ms)	90% CI (ms)
Nerlynx 240 mg	4	1.0	(-1.2, 3.3)
Moxifloxacin 400 mg	4	8.7	(6.5, 10.9)*
Nerlynx 240 mg + Ketoconazole 400 mg	8	1.4	(-1.0, 3.7)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 5.6 ms (see Table 10).

The supratherapeutic exposures of neratinib were attained in the study by coadministration of ketoconazole 400 mg with 240 mg neratinib in fasted state. This produced mean C_{max} values 2.4-fold of the mean C_{max} for the proposed therapeutic dose (240 mg neratinib with food). No higher doses have been evaluated. High fat meals increase C_{max} and AUC exposure for neratinib to 2-fold values. Ketoconazole increases C_{max} and AUC for neratinib up to 3.2- and 4.8-fold respectively. However in this study the neratinib 240 mg alone data was collected under fed conditions whereas the neratinib in combination with ketoconazole data was collected under fasted conditions. The later leads to attainment of lower exposures relative to the highest clinical exposure scenario (240 mg neratinib in combination with ketoconazole with a high fat meal). The exposure of therapeutic dose of neratinib administered in fasted state with multiple doses of ketoconazole is expected to be lower than that in fed state by 25%. Within the studied exposure range (2.4-fold of normal therapeutic exposure), no exposure-response relationship was seen between neratinib or its metabolites and ΔQTcF .

2 PROPOSED LABEL

The label proposed by the sponsor is as follows:



The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of NERLYNX on the QTc interval was evaluated in a (b) (4) randomized, placebo (b) (4) controlled, double-blind (b) (4) single-dose, crossover study in 60 healthy subjects. At 2.4-fold the therapeutic (b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Neratinib (HKI-272) is an irreversible pan-erythroblastic leukemia viral oncogene homolog tyrosine kinase inhibitor (TKI) that blocks signal transduction through 3 epidermal growth factor receptors (erbB), erbB1, erbB2, and erbB4. Neratinib is being developed for the treatment of patients with erbB2-positive breast cancer.

3.2 MARKET APPROVAL STATUS

Neratinib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

The potential for QT prolongation and hemodynamic effects of neratinib were assessed in *in vitro* assays and/or *in vivo* cardiovascular dog studies. In the hERG assay, the IC₅₀ of the rapidly-activating, delayed-rectifier cardiac potassium channel current for neratinib was 1.9 mM (1058 ng/mL). No toxicologically significant effects were observed on the cardiovascular system of dogs following neratinib oral dosages of 5, 10, or 20 mg/kg; the C_{max} exposure in dogs at 20 mg/kg was estimated to be 1 to 2 times the exposure in humans at the clinical dose of 240 mg. In repeat-dose toxicity studies in mice, rats, and dogs, neratinib did not produce any changes in heart weight, and no macroscopic or microscopic findings were observed in the heart. No ECG changes were observed in the 1-month and 9-month repeat-dose

toxicity studies in dogs (max dose = 6 mg/kg), with associated C_{max} for male and female dogs of 77.3 and 68.9 ng/mL respectively in the 9 month study. This is similar to the C_{max} in humans for the 240 mg QD clinical dose (73.5 ng/mL). The plasma binding for neratinib in both human and dog is approximately 99%. No QTc effects are anticipated at plasma concentrations >100 fold those associated with unbound C_{max} at the human clinical dose of 240 mg QD.

3.4 PREVIOUS CLINICAL EXPERIENCE

The safety of neratinib was evaluated in 3252 patients and healthy volunteers in 31 studies. This included 157 subjects exposed to doses from 40 to 200 mg/day, 2969 patients/healthy volunteers exposed to 240 mg/day neratinib, and 126 exposed to doses of neratinib from 320 to 800 mg/day. Overall, patients were exposed to doses ranging from 40 mg to 400 mg per day and healthy volunteers were exposed to single doses up to 800 mg per day.

The incidence of AEs of cardiac safety were lower in the neratinib arm versus placebo arm in the pivotal controlled trial (Study 3144A2-3004-WW): cardiac arrhythmia 3.8% vs. 4.1%, cardiac failure 6.7% vs. 8.5%, ischemic heart disorders 0.6% vs. 1.0%, and electrocardiogram QT prolonged 3.5% vs. 6.6% (neratinib vs. placebo, respectively). In addition, data from studies of neratinib monotherapy for the treatment of breast cancer, including Study PUMA-NER-6201, 3144A2-3003-WW, and 3144A1-201-WW, were reviewed for cardiac safety events and were supportive of the findings from the pivotal study.

There were no adverse events of torsades de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, or seizure.

In Study 3144A2-3004-WW, the incidence of Grade 3 syncope was higher in the neratinib (0.7%) versus placebo (0.3%) arm; all events of Grade 3 syncope in the neratinib arm occurred in the setting of other adverse events, including diarrhea, nausea, vomiting, dizziness, and dehydration.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of neratinib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under NDA 208051. The sponsor submitted the study report 3144A1-105-US for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Single Dose, Crossover, Placebo-and Moxifloxacin-Controlled Study of the Effects of Neratinib (HKI-272) on Cardiac Repolarization in Healthy Adult Subjects

4.2.2 Protocol Number

3144A1-105-US

4.2.3 Study Dates

May 2008 to August 2008

4.2.4 Objectives

The primary objective of the study was to assess the effect on the corrected QT (QTc) after the administration of a single oral dose of neratinib 240 mg. The secondary objectives of this study were to characterize the pharmacokinetic (PK)/pharmacodynamic (PD) relationships, and provide additional safety information.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, single-dose, double-blind (with respect to neratinib), crossover, placebo- and open-label moxifloxacin-controlled study in healthy subjects, conducted at a single investigational site. The study was conducted in 2 parts with treatments in each part randomly assigned utilizing a crossover design. Part A consisted of 3 periods in which subjects were administered a single dose of test article (neratinib 240 mg, placebo, or moxifloxacin 400 mg) in a fed state. Part B consisted of 2 periods in which subjects were administered a single dose of test article (neratinib 240 mg or placebo) concomitantly with ketoconazole 400 mg in a fasting state. Subjects were randomly assigned to 1 of 12 dosage administration sequences, which consisted of a combination of each of the 5 treatment arms: neratinib, placebo, moxifloxacin, neratinib co-administered with ketoconazole, and placebo co-administered with ketoconazole. Each neratinib dose was separated by a minimum 14-day washout period.

Table 2: Randomization Sequence, Study 3144A1-105-US

Sequence	Part A			Part B	
	Period 1	Period 2	Period 3	Period 4	Period 5
1	A	C	B	D	E
2	A	C	B	E	D
3	A	B	C	D	E
4	A	B	C	E	D
5	C	A	B	D	E
6	C	A	B	E	D
7	C	B	A	D	E
8	C	B	A	E	D
9	B	A	C	D	E
10	B	A	C	E	D
11	B	C	A	D	E
12	B	C	A	E	D

Treatment groups: A=Placebo; B=Moxifloxacin 400-mg tablets; C=neratinib (240-mg tablets); D=Placebo coadministered with ketoconazole (400-mg tablets); E=neratinib (240-mg tablets) coadministered with ketoconazole 400-mg tablets.

Subjects were randomly assigned to 1 of the 12 dosage administration sequences on study day -1 of part A, which consisted of 3 periods as shown in Table 2. Each subject participated in the study for approximately 9 weeks, inclusive of a screening evaluation within 21 days before test article administration, admission to the unit on study day-1, and a subsequent 14-day (13-night) inpatient stay for each part. Each period was separated by a 5-day washout. After an outpatient washout of at least 9 days, the subjects participated in part B of the study, which consisted of 2 periods. Subjects returned for admission to part B

of the study on day -1, and participated in two 4-day (3-night) inpatient stays separated by a 5-day outpatient washout period for part B. This crossover design facilitated a within-subject comparison of QTc between active treatment and placebo, and allowed the application of individualized corrections for QTc.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Moxifloxacin was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The study had 2 parts. Subjects were randomly assigned to 1 of 12 dosage administration sequences, which consisted of each of the following treatment arms:

A=Placebo

B=Moxifloxacin 400-mg tablets

C=Neratinib 240-mg tablets

D=Placebo co-administered with ketoconazole 400-mg tablets

E=Neratinib 240-mg tablets co-administered with ketoconazole 400-mg tablets

4.2.6.2 Sponsor's Justification for Doses

In phase 2 studies, neratinib is being administered at doses of 240 mg with food. Single 240-mg oral doses of neratinib administered with food are well tolerated in healthy subjects and can serve as a “therapeutic” regimen in a QT study. However, the “supratherapeutic” concentrations of neratinib necessary to account for the potential variability in the target patient population cannot be achieved by administration of high doses of neratinib alone. After administration of single doses of neratinib greater than 400 mg, C_{max}, and AUC do not increase in a dose dependent manner, and tolerability is diminished. Nevertheless, supratherapeutic concentrations can be attained without diminished tolerability by coadministration of neratinib with ketoconazole. Single 240-mg oral doses of neratinib administered with multiple doses of ketoconazole (as in study 3144A1-106) will be evaluated in the supratherapeutic period of the QT study. The C_{max} achieved by coadministration of ketoconazole (201 ng/mL) is 2.7-fold greater than the C_{max} observed in patients with cancer (75.3 ng/mL) or healthy subjects (74.4 ng/mL) administered 240 mg of neratinib with food. In summary, we propose to evaluate the effect of therapeutic and supratherapeutic concentrations of neratinib on cardiac repolarization.

Reviewer's Comment: The rationale for increasing exposure with concomitant ketoconazole is reasonable as 240 mg is the established MTD and the PK above 240 mg are less than dose-proportional. However the use of fasted state for the concomitant medication may not be appropriate over the fed state for boosting neratinib concentrations, since highest clinically relevant exposures would be achieved with dosing in fed state.

4.2.6.3 Instructions with Regard to Meals

In Part A (240 mg neratinib alone) neratinib was administered with food, as is intended for clinical administration. In Part B of the study (240 mg neratinib plus multiple oral doses of ketoconazole 400 mg) neratinib was administered in the fasted state after an overnight fast.

Reviewer's Comment: The applicant indicated in their highlights of clinical pharmacology table that coadministration with a high fat meal can increase the C_{max} and AUC of neratinib by as much as 100%. While the use of administration in the fed state for Part A is useful for the therapeutic setting, not administering with food for the supratherapeutic part of the study limits the range of exposures evaluated to less than what would have been possible in patients receiving ketoconazole with a high fat meal.

4.2.6.4 ECG and PK Assessments

Triplicate electrocardiogram (ECG) recordings were obtained on day 1 at -1, -0.5, and 0 hour (immediately before dose administration), and at 1.5, 3, 4, 5, 6, 8, 12, 24 and 48 hours after test article administration in all periods.

Blood samples were collected to measure concentrations of neratinib and metabolites (all periods), moxifloxacin (period in which moxifloxacin is administered during part A), or ketoconazole (both periods of part B) on study day 1 within 2 hours before test article administration (hour -2) and at 1.5, 3, 4, 5, 6, 8, 12, 24, and 48 hours after test article administration.

Reviewer's Comment: The sponsor's timing of the ECGs and PK collection is acceptable, since it captures the effects near T_{max} (6 hours for neratinib and 4 and 6 hours for various metabolites) and any possible delayed effects over 24 hours.

4.2.6.5 Baseline

Sponsor used the average QTc on day 1 at -1, -0.5 hour, and 0 hour as baselines.

4.2.7 ECG Collection

Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 60 subjects enrolled and 52 subjects (86.7%) completed the study. Eight (8) subjects (13.3%) prematurely discontinued participation in the study. Fifty-six (56) subjects received neratinib 240 mg, 53 subjects received neratinib 240 mg co-administered with ketoconazole 400 mg or placebo co-administered with ketoconazole, and 59 subjects received moxifloxacin 400 mg in this study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was baseline-adjusted means differences in population-specific correction (QTcN) between neratinib 240 mg versus placebo and neratinib 240 mg with ketoconazole 400 mg versus placebo with ketoconazole 400 mg. The sponsor used a mixed

model and the results were presented in Table 3 and Table 4. The model included treatment, sequence, period, time, and treatment by time interaction term as fixed effect, baseline as a covariate, and subject as a random effect. The sponsor concluded neratinib 240 mg with or without ketoconazole have no QTcN prolongation effect, as the upper bounds of the 2-sided 95% CI for the mean differences between neratinib 240 mg therapeutic and suprathapeutic doses and placebo with or without ketoconazole were below 10 ms.

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Table 3: Sponsor's $\Delta\Delta$ QTcN Analyses for Neratinib 240 mg

Time (Hours)	LSM	90% CI
1.5	0.1452	(-2.04, 2.33)
3	-1.437	(-3.62, 0.75)
4	1.1133	(-1.07, 3.30)
5	-1.4828	(-3.67, 0.70)
6	-0.9811	(-3.17, 1.20)
8	-0.7891	(-2.98, 1.40)
12	0.8197	(-1.37, 3.01)
24	-1.4612	(-3.65, 0.72)
48	-0.9237	(-3.11, 1.26)

Abbreviations: CI=confidence interval; LSM=least squares mean; QTcN=corrected QT based on a population-specific correction formula.

Source: 3144A1-105-US Study Report, Table 9-4, page 59/420

Table 4: Sponsor's $\Delta\Delta$ QTcN Analyses for Neratinib 240 mg with Ketoconazole 400 mg

Time (Hours)	LSM	90% CI
1.5	-1.9094	(-4.29, 0.47)
3	-4.9378	(-7.31,-2.56)
4	-2.9459	(-5.32,-0.57)
5	-0.6031	(-2.98, 1.77)
6	0.2536	(-2.12, 2.63)
8	1.3272	(-1.05, 3.70)
12	-2.9177	(-5.29,-0.54)
24	-3.235	(-5.61,-0.86)
48	-0.895	(-3.28, 1.49)

Abbreviations: CI=confidence interval; LSM=least squares mean; QTcN=corrected QT based on a population-specific correction formula.

Source: 3144A1-105-US Study Report, Table 9-5, page 61/420

Reviewer's Comments: We provided our independent analysis results in Section 5.2. Our results of QTcN and QTcF are similar to the sponsor's results of QTcN.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the $\Delta\Delta$ QTcN effect for moxifloxacin. The results are presented in Table 5. The lower bounds of the 2-sided 90% CI for the mean differences between moxifloxacin and placebo were greater than or equal to 5 ms at 4 of the 8 time points, therefore establishing assay sensitivity.

Table 5: Sponsor's Δ QTcN Analyses for Moxifloxacin 400 mg

Time (Hours)	LSM	p-Value	90% CI
1.5	3.631	0.0058	(1.47, 5.80)
3	6.4897	<0.0001	(4.33, 8.65)
4	8.5914	<0.0001	(6.43, 10.75)
5	6.5374	<0.0001	(4.38, 8.69)
6	6.7735	<0.0001	(4.62, 8.93)
8	7.954	<0.0001	(5.80, 10.11)
12	6.7777	<0.0001	(4.62, 8.93)
24	3.9073	0.003	(1.74, 6.07)
48	-0.298	0.8209	(-2.46, 1.87)

Abbreviations: CI=confidence interval; LSM=least squares mean; QTcN=corrected QT based on a population-specific correction formula

Source: 3144A1-105-US Study Report, Table 9-3, page 58/420

Reviewer's Comments: We provided our independent analysis results in Section 5.2. Our results of QTcN and QTcF are similar to the sponsor's results of QTcN.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject's absolute QTc $>$ 480 ms and Δ QTc $>$ 60 ms.

4.2.8.3 Safety Analysis

No serious adverse events (SAEs) or deaths were reported during this study. Neratinib 240 mg was well tolerated when given to healthy subjects as a single oral dose alone, or in combination with ketoconazole 400 mg. Forty-two (42) subjects (70.0%) had at least 1 treatment-emergent adverse event (TEAE). Gastrointestinal disorders (GI) and nervous system disorders accounted for the most commonly reported TEAEs. The most commonly reported TEAEs, regardless of severity were diarrhea (25 subjects, 41.7%), headache (19 subjects, 31.7%), nausea (17 subjects, 28.3%), dizziness (9 subjects, 15.0%), vomiting (8 subjects, 13.3%), and abdominal pain (7 subjects, 11.7%). All the TEAEs reported for this study were considered to be mild by the principal investigator, except for ventricular extrasystoles, which was reported after administration of moxifloxacin, and was considered to be moderate. In part A, the therapeutic dose comparison period of the study, the frequency of TEAEs was higher in the subjects receiving neratinib 240 mg (23 subjects, 41.1%), than in the subjects receiving placebo (12 subjects, 20.7%). In part B, the suprathreshold dose comparison period of the study, the frequency of TEAEs was higher in the subjects receiving neratinib 240 mg coadministered with ketoconazole 400 mg (31 subjects, 57.4%), than the subjects receiving placebo and ketoconazole 400 mg (9 subjects, 17.0%). No subjects had TEAEs during the poststudy period. All TEAEs were resolved by the final study

evaluation with the exception of a mild headache and contact dermatitis reported for 1 subject while the subject was receiving placebo coadministered with ketoconazole 400 mg. No SAEs or deaths were reported during this study.

The treatment-related TEAEs reported for $\geq 5\%$ of subjects who received neratinib 240 mg were diarrhea, abdominal pain, headache, and nausea. The treatment-related TEAEs reported for $\geq 5\%$ of subjects receiving a single dose of neratinib 240 mg with multiple doses of ketoconazole 400 mg were diarrhea, nausea, headache, vomiting, and dizziness. No trends of clinical importance were noted in clinical laboratory results, ECG results, or vital signs measurements.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 6 (neratinib) and Table 7 (neratinib + ketoconazole). C_{max} and AUC values in the thorough QT study were 2.4- and 3.1-fold higher, respectively, following administration of 240 mg neratinib in combination with ketoconazole compared with 240 mg neratinib alone, the intended clinical dose.

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Table 6: Summary of Mean Pharmacokinetic Parameters of Neratinib, M3 and M7 Following Single Oral Dose of Neratinib 240 mg in Healthy Subjects Under Fed Conditions, Study 3144A1-105-US.

Dosing Regimen	Analyte		C _{max} (ng/mL)	T _{max} (hr)	t _{1/2} (hr)	AUC _T (ng ² hr/mL)	AUC (ng ² hr/mL)	Vz/F (L)	CL/F (L/hr)
Neratinib 240 mg	Neratinib	N	55	55	53	55	53	53	53
		Mean	68.01	6.50	12.15	1100	1236	3935	227
		SD	27.04	3.38	1.98	456	480	1651	94
		SE	3.65	0.46	0.27	61	66	227	13
		Min	25.80	1.50	8.30	382	502	1776	91
		Median	65.90	5.00	12.28	1066	1179	3398	204
		Max	120.00	24.00	16.73	2400	2640	7714	478
		CV%	40	52	16	41	39	42	42
		Geo. Mean	62.67	5.94	11.99	1004	1145	3626	210
Neratinib 240 mg	WYE12 1529 (M3)	N	55	55	43	55	43	NA	NA
		Mean	11.86	5.50	6.36	73	123	NA	NA
		SD	5.53	3.13	3.18	60	76	NA	NA
		SE	0.75	0.42	0.48	8	12	NA	NA
		Min	3.77	1.50	1.96	2	40	NA	NA
		Median	10.70	5.00	5.82	56	99	NA	NA
		Max	29.60	24.00	16.95	323	416	NA	NA
		CV%	47	57	50	82	62	NA	NA
		Geo. Mean	10.63	5.03	5.64	54	106	NA	NA
Neratinib 240 mg	% of Parent WYE12 1592 (M7)	N	55	55	49	55	49	NA	NA
		Mean	11.17	5.76	9.03	96	151	NA	NA
		SD	5.52	3.39	3.78	82	93	NA	NA
		SE	0.74	0.46	0.54	11	13	NA	NA
		Min	4.69	1.50	2.12	18	29	NA	NA
		Median	9.96	5.00	8.97	59	134	NA	NA
		Max	32.40	24.00	24.04	437	509	NA	NA
		CV%	49	59	42	86	62	NA	NA
		Geo. Mean	10.15	5.16	8.25	72	129	NA	NA
Neratinib 240 mg	% of Parent	(%)	17.4	NA	NA	6.6	NA	NA	NA
		(%)	16.4	NA	NA	8.7	NA	NA	NA

(Source: Sponsor's Clinical Study Report, Table 8-1)

Table 7: Summary of Mean Pharmacokinetic Parameters of Neratinib, M3 and M7 Following Single Oral Dose of Neratinib 240 mg in combination with Multiple Oral Doses of Ketoconazole 400 mg in Healthy Subjects Under Fasting Conditions, Study 3144A1-105-US.

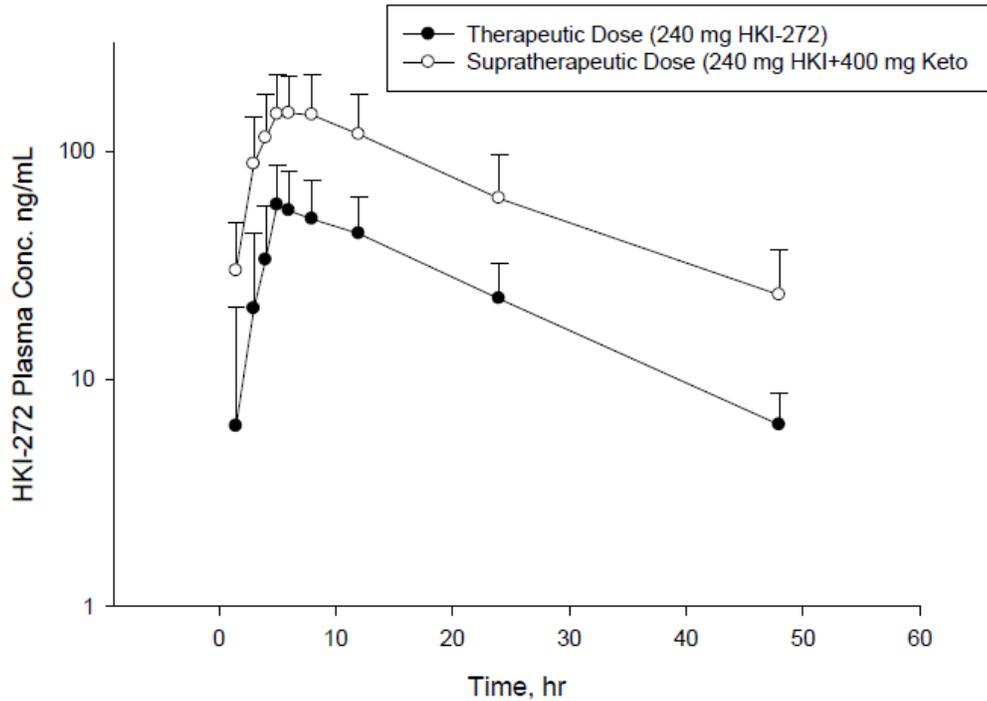
Dosing Regimen	Analyte	N	C _{max} (ng/mL)	T _{max} (hr)	t _{1/2} (hr)	AUC _T (ng*hr/mL)	AUC (ng*hr/mL)	V _Z /F (L)	CL/F (L/hr)
Neratinib240 mg +Keto	Neratinib	N	55	55	53	54	53	53	53
		Mean	162.57	6.75	14.96	3268	3801	1917	96
		SD	74.95	3.01	3.60	1548	1846	1554	97
		SE	10.11	0.41	0.49	211	254	213	13
		Min	22.10	4.00	7.43	302	401	689	28
		Median	153.00	6.00	14.54	3501	4020	1293	60
		Max	327.00	24.00	26.87	7178	8475	9022	599
		CV%	46	45	24	47	49	81	101
		Geo. Mean	142.35	6.35	14.55	2797	3239	1555	74
		Neratinib240 mg +Keto	WYE121529 (M3)	N	6	6	1	6	1
Mean	3.93			14.17	11.48	24	64	NA	NA
SD	0.41			8.06	NA	19	NA	NA	NA
SE	0.17			3.29	NA	8	NA	NA	NA
Min	3.44			5.00	11.48	3	64	NA	NA
Median	3.88			12.00	11.48	22	64	NA	NA
Max	4.44			24.00	11.48	59	64	NA	NA
CV%	10			57	NA	81	NA	NA	NA
Geo. Mean	3.91			12.21	11.48	17	64	NA	NA
% of Parent (%)	2.4			NA	NA	0.7	NA	NA	NA
Neratinib240 mg +Keto	WYE121592 (M7)	N	55	55	54	54	54	NA	NA
		Mean	41.62	4.35	7.73	419	487	NA	NA
		SD	26.18	0.98	3.08	331	341	NA	NA
		SE	3.53	0.13	0.42	45	46	NA	NA
		Min	7.01	1.50	2.69	28	61	NA	NA
		Median	37.30	4.00	7.37	368	438	NA	NA
		Max	123.00	6.00	15.53	1741	1797	NA	NA
		CV%	63	23	40	79	70	NA	NA
		Geo. Mean	33.96	4.21	7.12	303	375	NA	NA
		% of Parent (%)	25.6	NA	NA	12.8	NA	NA	NA

Abbreviations: AUC=area under curve; AUC_T=area under the concentration-time curve in 1 dosage interval; F=bioavailability; C_{max}=maximum observed concentration; CL/F=apparent clearance; CV=coefficient of variance; Geo=geometrical; M3=neratinib pyridine N-oxide; M7=neratinib dimethylamine N-oxide; Max=maximum; Min=minimum; SD=standard deviation; SE=standard error; NA: Not Applicable; T_{max}=time of maximum observed concentration; t_{1/2}=terminal elimination half-life; WYE=Wyeth; V_Z/F=apparent volume of distribution during the terminal.

(Source: Sponsor's Clinical Study Report, Table 8-2)

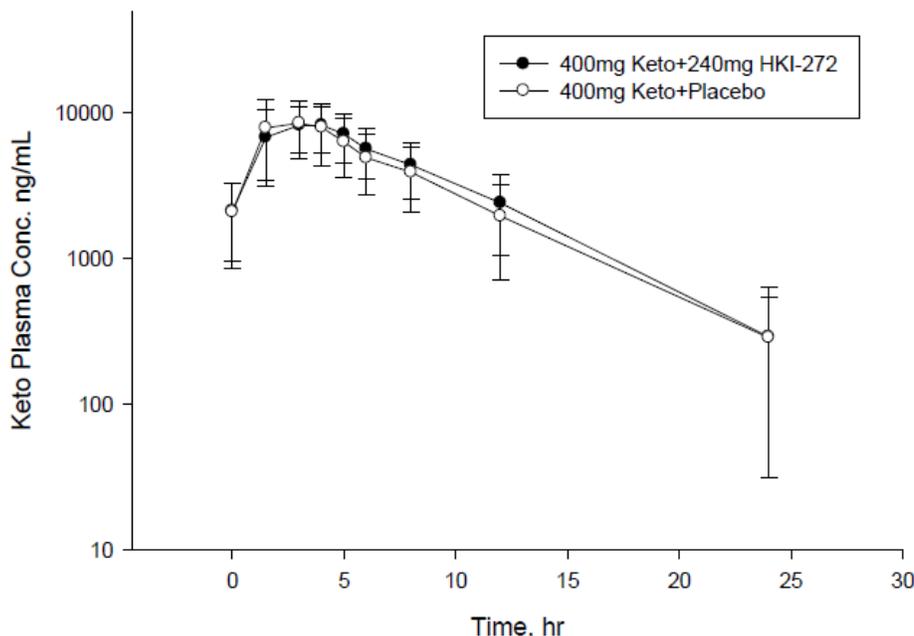
The time course of neratinib and ketoconazole plasma concentrations after the therapeutic and suprathematic doses are shown in Figure 1 and Figure 2.

Figure 1: Neratinib Plasma Concentration vs. Time Profiles (Mean \pm Standard Deviation) Following Single Oral Dose of Neratinib 240 mg (Therapeutic Dose) and Neratinib 240 mg in Combination with Multiple Oral Doses of Ketoconazole 400 mg (Suprathematic Dose) in Healthy Subjects in Study 3144A1-105-US.



(Source: Sponsor's Clinical Study Report, Figure 8-1)

Figure 2: Ketoconazole Plasma Concentration vs. Time Profiles (Mean \pm Standard Deviation) Following Multiple Oral Doses of Ketoconazole in Combination with Neratinib 240 mg or Placebo in Healthy Subjects Under Fasting Conditions, 3144A1-105-US.



(Source: Sponsor's Clinical Study Report, Figure 8-2)

4.2.8.4.2 Exposure-Response Analysis

The PK/PD relationship between QTcN versus neratinib, ketoconazole and moxifloxacin were examined graphically and statistically. Linear regression models on change from baseline QTcN versus log-transformed concentrations were fit with postdose data for all subjects included in the statistical analysis for each analyte separately. Table 8 presents the results of the linear regression models for each analyte.

Table 8: Estimated Coefficients From Regression of Change in QTcN on Log-Transformed Neratinib, Ketoconazole and Moxifloxacin Concentrations, in Study 3144A1-105-US.

Analyte	Label	Estimate	P-value	95% CI
Neratinib	Intercept	-5.41	<0.0001	(-7.8097, -3.0158)
	Log neratinib Conc	-0.48	0.0978	(-1.0412, 0.08782)
Ketoconazole	Intercept	-20.01	<0.0001	(-22.6339, -17.3831)
	Log Keto Conc	1.80	<0.0001	(1.4884, 2.1143)
Moxifloxacin	Intercept	-8.99	0.0001	(-13.5669, -4.4313)
	Log Moxi Conc	1.04	0.0016	(0.3942, 1.6804)

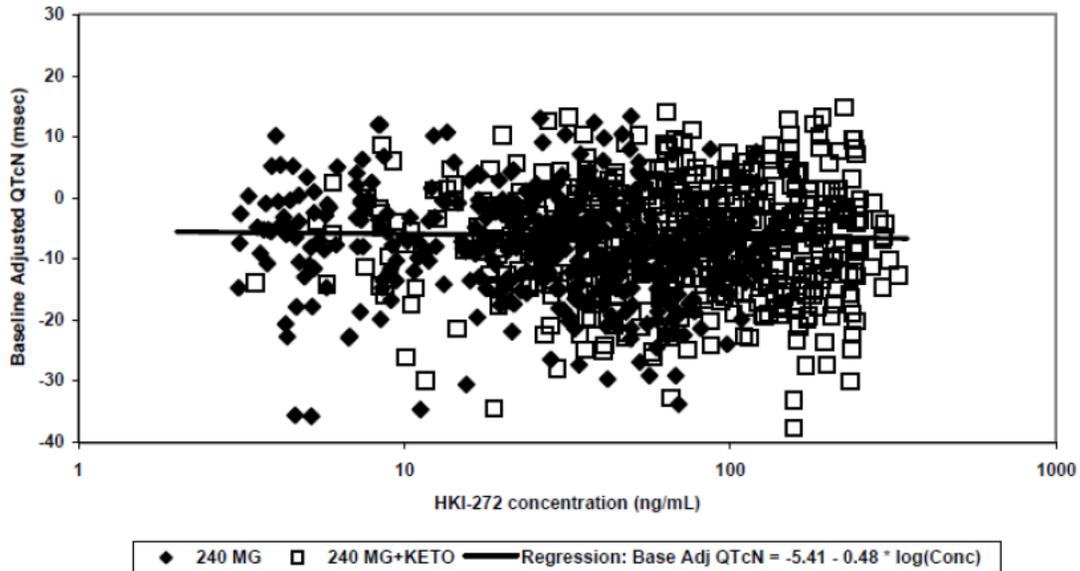
Abbreviations: CI=confidence interval; Conc=concentration, Keto=ketoconazole; Moxi=moxifloxacin; QTcN=corrected QT based on a population-specific correction formula.

(Source: Sponsor's Clinical Study Report, Table 9-6)

Figure 3 presents the individual QTcN change from baseline values compared with neratinib plasma concentrations after administration of neratinib 240 mg, and neratinib 240

mg coadministered with ketoconazole. The slope coefficient on log-transformed neratinib concentrations of -0.48 was not significantly different from 0 ($p=0.0978$) and the 95% CI contained 0.

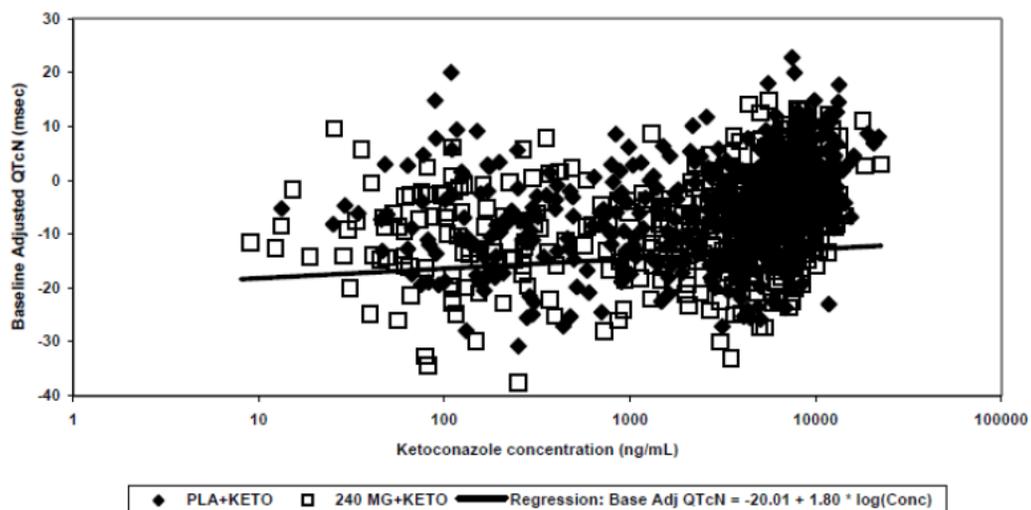
Figure 3: Scatter Plots of Individual Change from Baseline QTcN Versus Neratinib Concentrations (All Postdose Time Point Included), Study 3144A1-105-US.



(Source: Sponsor's Clinical Study Report, Figure 9-6)

Figure 4 presents the individual QTcN change from baseline values compared with ketoconazole plasma concentrations after administration of placebo with ketoconazole, and neratinib 240 mg with ketoconazole. The slope coefficient on log-transformed ketoconazole concentrations of 1.80 was significantly different from 0 ($p<0.0001$), and the lower bound of the 95% CI was greater than 0.

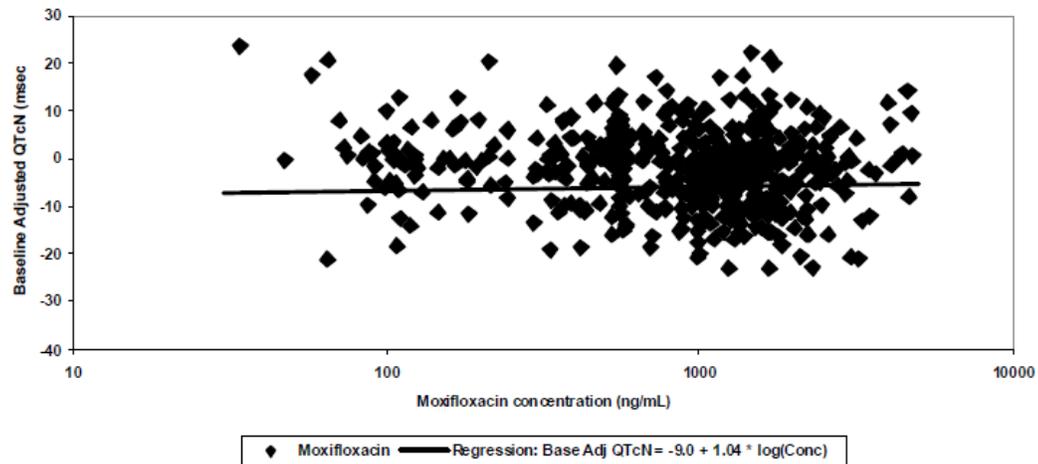
Figure 4: Scatter Plots of Individual Change from Baseline QTcN Versus Ketoconazole Concentrations (All Postdose Time Point Included), Study 3144A1-105-US.



(Source: Sponsor's Clinical Study Report, Figure 9-7)

Figure 5 presents the individual QTcN values and change from baseline values compared with moxifloxacin plasma concentrations, after administration of moxifloxacin 400 mg. The slope coefficient on log-transformed moxifloxacin concentrations of 1.04 was significantly different from 0 ($p=0.0016$), and the lower bound of the 95% CI was greater than 0.

Figure 5: Scatter Plots of Individual Change from Baseline QTcN Versus Moxifloxacin Concentrations (All Postdose Time Point Included), Study 3144A1-105-US.



(Source: Sponsor's Clinical Study Report, Figure 9-8)

Reviewer's Analysis: The reviewer's analysis was performed utilizing the $\Delta\Delta QTcF$ data rather than the Applicant's $\Delta\Delta QTcN$ data and is presented in Section 5.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

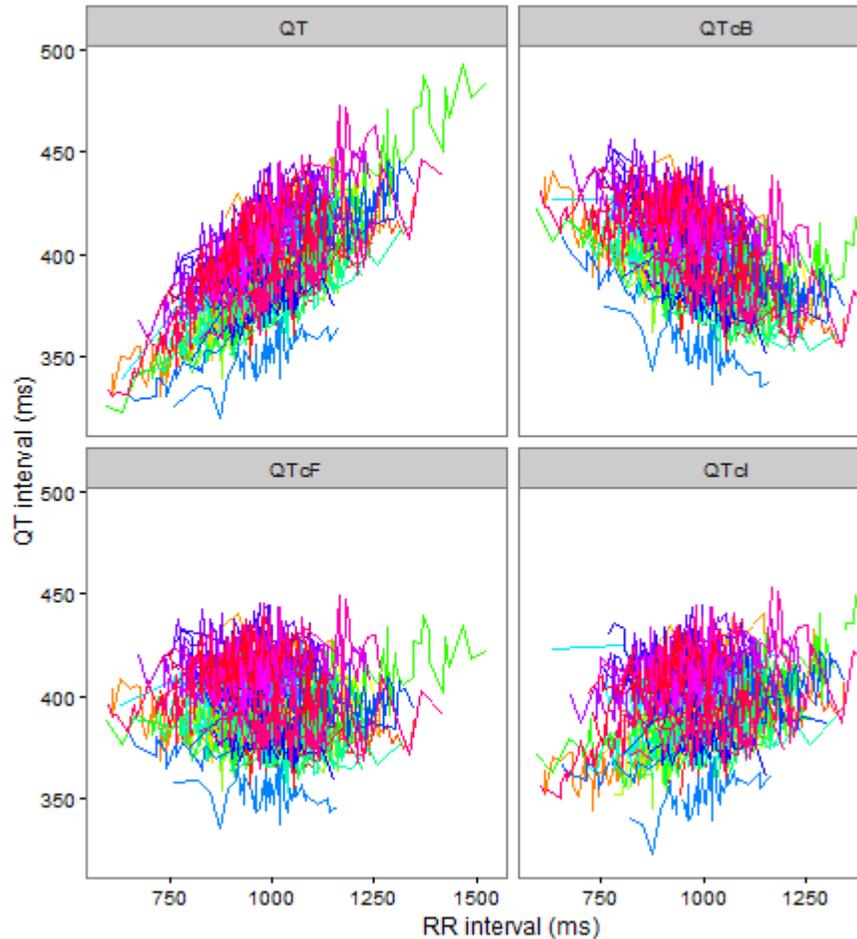
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 3, it appears that QTcF is better than QTcN and QTcI. To be consistent with the sponsor's analyses, this reviewer used QTcN in the primary statistical analysis. We performed a secondary analysis using QTcF and obtained similar results.

Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcF		QTcI		QTcN	
	N	MSSS	N	MSSS	N	MSSS
Placebo	58	0.00203	57	0.00439	57	0.00330
Moxifloxacin 400 mg	59	0.00284	58	0.00488	58	0.00403
Neratinib 240 mg	56	0.00191	55	0.00229	55	0.00204
Neratinib 240 mg + ketoconazole	54	0.00354	53	0.00594	53	0.00583
Placebo + ketoconazole	53	0.00276	52	0.00540	52	0.00534
All	60	0.00145	59	0.00454	59	0.00332

The relationship between different correction methods and RR is presented in Figure 6.

Figure 6: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Nerlynx

The statistical reviewer used mixed model to analyze the Δ QTcN and Δ QTcF effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in **Table 10**, **Table 11**, **Table 12** and **Table 13**. The largest upper bounds of the 2-sided 90% CI for the mean differences between neratinib and placebo, and between neratinib with ketoconazole and placebo with ketoconazole are lower than 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

Table 10: Analysis Results of Δ QTcN and $\Delta\Delta$ QTcN for Nerlynx 240 mg and Moxifloxacin 400 mg

		Treatment Group								
		Nerlynx 240 mg				Moxifloxacin 400 mg				
		Δ QTcN		$\Delta\Delta$ QTcN		Δ QTcN		$\Delta\Delta$ QTcN		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
1.5	-10.6	56	-10.4	0.2	(-2.0, 2.4)	58	-7.1	3.5	(1.3, 5.7)	(0.5, 6.5)
3	-7.9	56	-9.0	-1.1	(-3.3, 1.1)	59	-1.4	6.5	(4.3, 8.7)	(3.5, 9.5)
4	-7.4	56	-6.3	1.0	(-1.2, 3.3)	59	1.3	8.7	(6.5, 10.9)	(5.6, 11.7)
5	-6.7	56	-8.2	-1.5	(-3.8, 0.8)	59	-0.2	6.6	(4.3, 8.8)	(3.5, 9.7)
6	-8.9	56	-9.9	-1.0	(-3.4, 1.5)	59	-1.8	7.1	(4.7, 9.5)	(3.8, 10.3)
8	-8.4	55	-9.3	-0.9	(-3.2, 1.4)	59	-0.3	8.1	(5.8, 10.4)	(5.0, 11.2)
12	-10.7	56	-9.7	1.0	(-1.2, 3.3)	59	-3.6	7.1	(4.9, 9.4)	(4.1, 10.2)
24	-4.0	56	-5.5	-1.5	(-3.7, 0.8)	58	0.0	4.1	(1.8, 6.3)	(1.0, 7.1)
48	-3.6	56	-4.4	-0.8	(-3.5, 1.9)	59	-4.2	-0.6	(-3.3, 2.1)	(-4.2, 3.1)

* Bonferroni method was applied for multiple endpoint adjustment of 4 time points (significant at the 0.025 level).

Table 11: Analysis Results of Δ QTcN and $\Delta\Delta$ QTcN for Nerlynx 240 mg and Ketoconazole 400 mg

		Treatment Group			
		Nerlynx 240 MG + Ketoconazole 400 mg			
		Δ QTcN		$\Delta\Delta$ QTcN	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
1.5	0.8	54	-1.1	-1.9	(-4.0, 0.3)
3	3.1	54	-1.9	-4.9	(-7.2, -2.7)
4	1.8	54	-1.3	-3.1	(-5.3, -1.0)
5	-4.6	54	-5.3	-0.7	(-2.8, 1.4)
6	-8.9	54	-8.6	0.3	(-2.1, 2.6)
8	-10.8	54	-9.4	1.4	(-1.0, 3.7)
12	-10.4	54	-13.0	-2.5	(-4.8, -0.3)
24	-5.9	54	-8.9	-2.9	(-5.5, -0.3)
48	-11.1	53	-12.0	-0.8	(-3.6, 2.0)

Table 12: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Nerlynx 240 mg and Moxifloxacin 400 mg

Time (h)	Treatment Group									
	Placebo	Nerlynx 240 mg				Moxifloxacin 400 mg				
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		
LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI	
1.5	-6.4	56	-5.7	0.7	(-1.4, 2.9)	58	-2.1	4.3	(2.2, 6.4)	(1.4, 7.2)
3	-5.8	56	-7.2	-1.3	(-3.5, 0.8)	59	1.5	7.3	(5.1, 9.4)	(4.4, 10.2)
4	-6.1	56	-4.5	1.6	(-0.5, 3.8)	59	3.2	9.3	(7.2, 11.5)	(6.4, 12.3)
5	-2.9	56	-4.5	-1.6	(-3.8, 0.7)	59	4.0	6.9	(4.7, 9.2)	(3.8, 10.0)
6	-3.3	56	-4.9	-1.7	(-4.0, 0.7)	59	4.0	7.3	(4.9, 9.6)	(4.1, 10.5)
8	-5.6	55	-6.6	-1.1	(-3.3, 1.1)	59	2.9	8.4	(6.3, 10.6)	(5.5, 11.4)
12	-6.5	56	-6.5	-0.0	(-2.2, 2.2)	59	0.6	7.0	(4.9, 9.2)	(4.1, 10.0)
24	-5.1	56	-6.8	-1.7	(-3.8, 0.4)	58	-1.1	4.0	(1.9, 6.0)	(1.2, 6.8)
48	-3.0	56	-3.0	-0.0	(-2.5, 2.5)	59	-3.2	-0.2	(-2.6, 2.3)	(-3.5, 3.2)

* Bonferroni method was applied for multiple endpoint adjustment of 4 time points (significant at the 0.025 level).

Table 13: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Nerlynx 240 mg + Ketoconazole

Time (h)	Treatment Group				
	Placebo	Nerlynx 240 mg + Ketoconazole 400 mg			
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF	
LS Mean	N	LS Mean	LS Mean	90% CI	
1.5	2.3	54	-0.0	-2.3	(-4.5, -0.1)
3	3.6	54	0.6	-3.0	(-5.2, -0.8)
4	2.9	54	0.9	-2.0	(-4.2, 0.2)
5	3.1	54	0.7	-2.5	(-4.6, -0.3)
6	-1.4	54	-2.2	-0.7	(-3.2, 1.8)
8	-7.0	54	-4.7	2.3	(-0.2, 4.7)
12	-4.3	54	-6.9	-2.6	(-4.7, -0.4)
24	-5.4	54	-7.3	-1.9	(-4.5, 0.7)
48	-8.4	53	-9.7	-1.2	(-3.9, 1.5)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 10 and Table 12. The largest unadjusted 90% lower

confidence interval is 6.5 ms (QTcN) and 7.2 ms (QTcF). By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 5.6 ms (QTcN) and 6.4 ms (QTcF), which indicates that an at least 5 ms QTcN and QTcF effects due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of $\Delta\Delta\text{QTcN}$ and $\Delta\Delta\text{QTcF}$ Over Time

The following figure displays the time profile of $\Delta\Delta\text{QTcN}$ and $\Delta\Delta\text{QTcF}$ for different treatment groups.

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Figure 7: Mean and 90% CI $\Delta\Delta$ QTcN Time Course

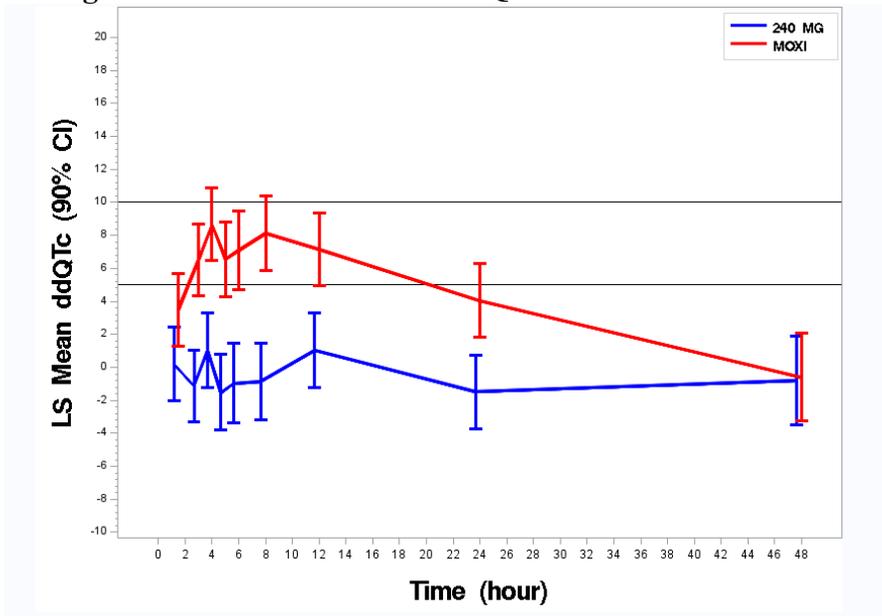
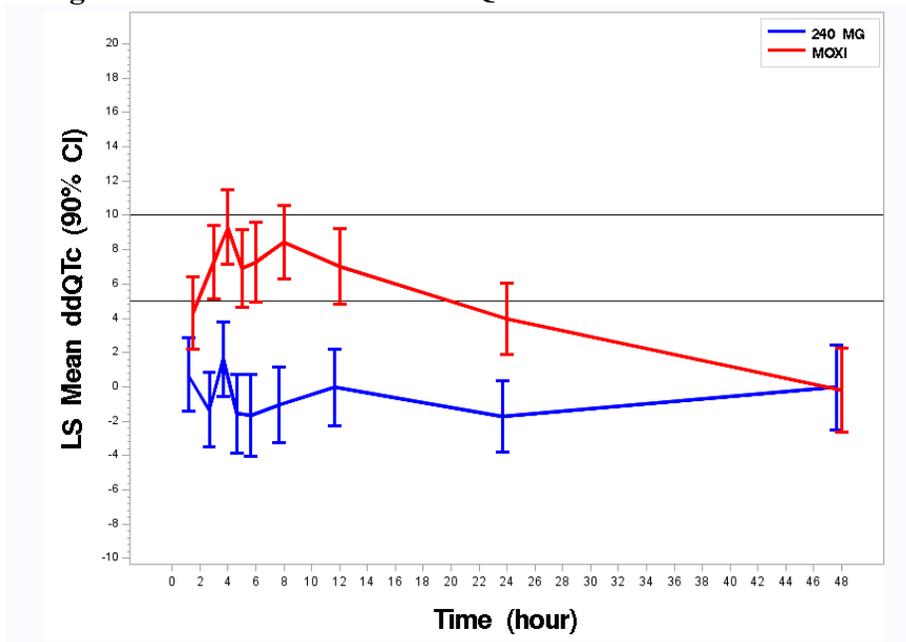


Figure 8: Mean and 90% CI $\Delta\Delta$ QTcF Time Course



5.2.1.4 Categorical Analysis

Table 14 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and > 500 ms. No subject's QTcN is above 480 ms.

Table 14: Categorical Analysis for QTcN

Treatment Group	Total N	Value <=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500 ms
Nerlynx 240 mg	56	56 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nerlynx 240 mg + Ketoconazole 400 mg	54	54 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	59	59 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	58	58 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo + Ketoconazole 400 mg	53	53 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 15 lists the number of subjects with changes from baseline QTc ≤ 30 ms, between 30 and 60 ms, between 60 ms and 90, and >90 ms. No subject's change from baseline is above 60 ms.

Table 15: Categorical Analysis of Δ QTcN

Treatment Group	Total N	Value <=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
Nerlynx 240 mg	56	56 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nerlynx 240 mg + Ketoconazole 400 mg	54	54 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	59	59 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	58	58 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo + Ketoconazole 400	53	53 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 16 and Table 17. The largest upper bounds of the 2-sided 90% CI for the mean differences between neratinib and placebo (in part A), and between neratinib with

ketoconazole and placebo with ketoconazole (in part B) are lower than 2.0 bpm and 3.3 bpm,

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respectively. The categorical analysis of HR is given in

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Table 18. No subject who experienced HR interval greater than 100 bpm is in Nerlynx 240 mg.

Table 16: Analysis Results of Δ HR and $\Delta\Delta$ HR for Nerlynx 240 mg and Moxifloxacin 400 mg

		Treatment Group									
		Placebo		Nerlynx 240 mg				Moxifloxacin 400 mg			
		Δ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI		
1.5	5.1	56	5.7	0.6	(-0.8, 2.0)	58	6.2	1.1	(-0.3, 2.5)		
3	2.4	56	2.2	-0.2	(-1.4, 1.0)	59	3.3	0.8	(-0.4, 2.0)		
4	1.5	56	2.3	0.8	(-0.5, 2.0)	59	2.3	0.9	(-0.4, 2.1)		
5	4.7	56	4.7	0.0	(-1.4, 1.4)	59	5.0	0.3	(-1.1, 1.7)		
6	7.2	56	6.3	-0.9	(-2.5, 0.7)	59	7.2	-0.1	(-1.7, 1.5)		
8	3.6	55	3.5	-0.1	(-1.8, 1.6)	59	3.8	0.2	(-1.5, 1.9)		
12	5.4	56	4.1	-1.3	(-3.1, 0.4)	59	5.0	-0.4	(-2.1, 1.3)		
24	-1.3	56	-1.5	-0.2	(-1.4, 0.9)	58	-1.4	-0.1	(-1.3, 1.1)		
48	0.7	56	1.9	1.3	(-0.5, 3.0)	59	1.1	0.4	(-1.3, 2.1)		

Table 17: Analysis Results of Δ HR and $\Delta\Delta$ HR for Nerlynx 240 mg + Ketoconazole

		Treatment Group				
		Placebo	Nerlynx 240 mg + Ketoconazole 400 mg			
		Δ HR	Δ HR		$\Delta\Delta$ HR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	
1.5	1.8	54	1.2	-0.5	(-1.6, 0.6)	
3	0.7	54	2.7	2.0	(0.8, 3.2)	
4	1.3	54	2.7	1.3	(0.1, 2.6)	
5	9.1	54	7.1	-2.0	(-3.8, -0.3)	
6	8.9	54	7.7	-1.2	(-2.8, 0.4)	
8	4.3	54	5.5	1.2	(-0.4, 2.8)	
12	7.2	54	7.3	0.1	(-1.6, 1.7)	
24	0.6	54	2.1	1.5	(-0.3, 3.3)	
48	3.1	53	2.8	-0.3	(-1.9, 1.2)	

Table 18: Categorical Analysis for HR

Treatment Group	Total N	HR≤100 bpm	HR>100 bpm
Nerlynx 240 mg	56	56 (100%)	0 (0.0%)
Nerlynx 240 mg + Ketoconazole 400 mg	54	54 (100%)	0 (0.0%)
Moxifloxacin 400 mg	59	59 (100%)	0 (0.0%)
Placebo	58	57 (98.3%)	1 (1.7%)
Placebo + Ketoconazole 400 mg	53	53 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 19 and Table 20. The largest upper bounds of the 2-sided 90% CI for the mean differences between neratinib and placebo (in part A), and between neratinib with ketoconazole and placebo with ketoconazole (in part B) are lower than 6.2 ms and 5.4 ms, respectively. The categorical analysis of PR is given in Table 21. Fourteen subject who experienced PR interval greater than 200 ms are in neratinib 240 mg and neratinib with ketoconazole groups (the same number as subjects with placebo and placebo with ketoconazole groups).

Table 19: Analysis Results of Δ PR and $\Delta\Delta$ PR for Nerlynx 240 mg and Moxifloxacin 400 mg

	Treatment Group								
	Placebo	Nerlynx 240 mg				Moxifloxacin 400 mg			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1.5	-4.7	56	-4.2	0.5	(-1.5, 2.5)	58	-4.8	-0.1	(-2.0, 1.9)
3	-5.6	56	-5.4	0.2	(-1.6, 2.1)	59	-5.0	0.7	(-1.2, 2.5)
4	-5.6	56	-5.5	0.1	(-1.7, 1.8)	59	-5.0	0.6	(-1.1, 2.3)
5	-5.6	56	-6.1	-0.5	(-2.6, 1.7)	59	-5.9	-0.3	(-2.4, 1.8)
6	-5.5	56	-6.8	-1.4	(-3.6, 0.9)	59	-6.9	-1.4	(-3.7, 0.8)
8	-6.6	55	-6.0	0.6	(-1.6, 2.8)	59	-6.4	0.2	(-2.0, 2.4)
12	-6.1	56	-2.5	3.6	(1.1, 6.2)	59	-5.1	1.0	(-1.5, 3.5)
24	-1.6	56	1.2	2.8	(0.9, 4.6)	58	0.5	2.0	(0.2, 3.9)
48	-0.8	56	0.4	1.2	(-1.1, 3.5)	59	0.5	1.3	(-1.0, 3.6)

Table 20: Analysis Results of Δ PR and $\Delta\Delta$ PR for Nerlynx 240 mg + Ketoconazole

		Treatment Group			
		Nerlynx 240 mg + Ketoconazole 400 mg			
		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
1.5	-1.0	54	-2.1	-1.1	(-2.7, 0.5)
3	-2.7	54	-4.2	-1.5	(-3.0, -0.1)
4	-3.6	54	-3.1	0.5	(-1.0, 2.0)
5	-6.8	54	-5.7	1.0	(-1.3, 3.3)
6	-8.5	54	-6.8	1.7	(-0.3, 3.8)
8	-8.5	54	-8.5	-0.0	(-2.2, 2.2)
12	-8.5	54	-6.6	2.0	(-0.5, 4.5)
24	-2.9	54	-1.8	1.1	(-1.3, 3.5)
48	-3.3	53	-0.1	3.2	(1.0, 5.4)

Table 21: Categorical Analysis for PR

Treatment Group	Total N	PR \leq 200 ms	PR $>$ 200 ms
Nerlynx 240 mg	56	48 (85.7%)	8 (14.3%)
Nerlynx 240 mg + Ketoconazole 400 mg	54	48 (88.9%)	6 (11.1%)
Moxifloxacin 400 mg	59	56 (94.9%)	3 (5.1%)
Placebo	58	51 (87.9%)	7 (12.1%)
Placebo + Ketoconazole 400 mg	53	46 (86.8%)	7 (13.2%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as a fixed effect and baseline value as a covariate. The analysis results are listed in Table 22 and Table 23. The largest upper bounds of the 2-sided 90% CI for the mean differences between neratinib and placebo (in part A), and between neratinib with ketoconazole and placebo with ketoconazole (in part B) are lower than 1.1 ms and 1.9 ms, respectively. The categorical analysis of QRS is given in Table 24. No subject who experienced QRS interval greater than 110 ms are in neratinib 240 mg and neratinib with ketoconazole groups.

Table 22: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Nerlynx 240 mg and Moxifloxacin 400 mg

		Treatment Group								
		Placebo	Nerlynx 240 mg				Moxifloxacin 400 mg			
		Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	
1.5	-0.3	56	-0.9	-0.6	(-1.4, 0.3)	58	-0.6	-0.3	(-1.2, 0.6)	
3	-0.0	56	-1.0	-1.0	(-1.7, -0.2)	59	-0.9	-0.9	(-1.7, -0.1)	
4	-0.9	56	-0.6	0.3	(-0.5, 1.1)	59	-0.9	0.0	(-0.8, 0.8)	
5	0.5	56	-0.3	-0.8	(-1.8, 0.1)	59	-0.2	-0.8	(-1.7, 0.2)	
6	-0.1	56	-0.3	-0.2	(-1.1, 0.7)	59	-1.0	-0.9	(-1.8, -0.0)	
8	-0.5	55	-0.9	-0.4	(-1.3, 0.5)	59	-0.8	-0.3	(-1.2, 0.6)	
12	-0.6	56	-0.4	0.2	(-0.8, 1.1)	59	-0.9	-0.3	(-1.3, 0.7)	
24	0.2	56	-0.5	-0.7	(-1.6, 0.1)	58	-0.5	-0.7	(-1.5, 0.2)	
48	0.4	56	-1.0	-1.4	(-2.3, -0.4)	59	0.0	-0.4	(-1.3, 0.5)	

Table 23: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Nerlynx 240 mg + Ketoconazole

		Treatment Group			
		Placebo	Nerlynx 240 mg + Ketoconazole 400 mg		
		Δ QRS	Δ QRS		$\Delta\Delta$ QRS
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
1.5	-1.0	54	-0.7	0.3	(-0.7, 1.3)
3	-0.3	54	-1.1	-0.9	(-1.8, 0.1)
4	-0.7	54	-1.1	-0.4	(-1.4, 0.6)
5	0.7	54	-0.0	-0.7	(-1.7, 0.2)
6	-0.1	54	-1.0	-0.8	(-1.8, 0.1)
8	-0.6	54	-1.7	-1.0	(-1.9, -0.2)
12	-0.6	54	-0.9	-0.3	(-1.3, 0.6)
24	-1.2	54	-1.2	-0.0	(-1.1, 1.1)
48	-1.4	53	-0.7	0.6	(-0.6, 1.9)

Table 24: Categorical Analysis for QRS

Treatment Group	Total N	QRS≤110 ms	QRS>110 ms
Nerlynx 240 mg	56	56 (100%)	0 (0.0%)
Nerlynx 240 mg + Ketoconazole 400 mg	54	54 (100%)	0 (0.0%)
Moxifloxacin 400 mg	59	59 (100%)	0 (0.0%)
Placebo	58	58 (100%)	0 (0.0%)
Placebo + Ketoconazole 400 mg	53	53 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔQTc and neratinib and between ΔQTc and ketoconazole were investigated by linear mixed-effects modeling. The model used $QTcF$ change from baseline ($\Delta QTcF$) as the dependent variable and observed drug concentrations as the continuous variable (0 for the placebo treatment), treatment (active (IND=1) or placebo (IND=0)), day and nominal time postdose as categorical factors, and random effect on intercept. The general model formula is shown below.

$$\Delta QTc_{ijk} = (\mu + TRT_j + t_k + \eta_{\mu,i}) + \theta_1 C_{ijk} + \theta_2 Keto_{ijk} + \varepsilon_{ijk}$$

Where i is the i^{th} subject, j is the j^{th} treatment, k is the k^{th} time point relative to dosing, μ is the intercept, TRT_j is the j^{th} treatment effect (active/placebo), t_k is the k^{th} time effect, C_{ijk} is the neratinib (or metabolite) concentration at the k^{th} time point for Treatment j for Subject i . $Keto_{ijk}$ is the ketoconazole concentration at the k^{th} time point for Treatment j for Subject i . $\eta_{\mu,i}$ is the subject-specific random effect for the intercept, having mean [0,0]. ε are independent residuals having mean zero and variance σ^2 . θ_1 and θ_2 are fixed effect slope parameters for neratinib and ketoconazole concentrations, respectively.

The relationships between Δ QTcF and neratinib concentrations and ketoconazole concentrations are visualized in Figure 9. There was a statistically significant exposure-response relationship for ketoconazole (slope [95% CI] = 0.434 [0.0492, 0.82] ms per μ g/mL of ketoconazole; p-value=0.029). No significant exposure-response relationship was established for neratinib plasma concentration (slope [95% CI] = 0.00773 [-0.00958, 0.02504] ms per ng/mL of neratinib; p-value=0.385).

Figure 9. Δ QTcF vs. Neratinib Plasma Concentrations (left panel) and Δ QTcF vs. Ketoconazole Plasma Concentrations (right panel). In the left panel, red symbols indicate data from the 240 mg neratinib alone administration and the green symbols indicate data from neratinib 240 mg dosing in combination with ketoconazole. In the right panel, red symbols are from neratinib 240 mg dosing in combination with ketoconazole.

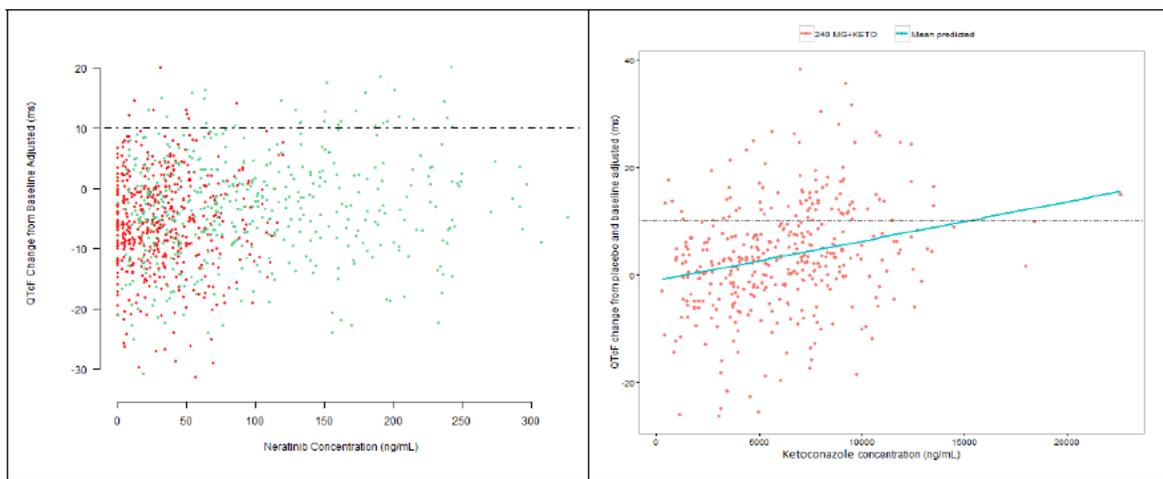
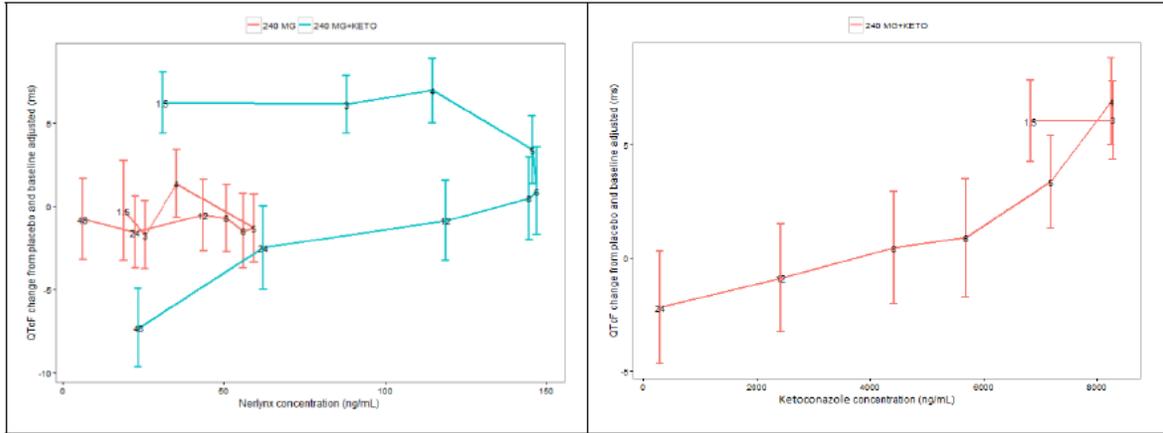


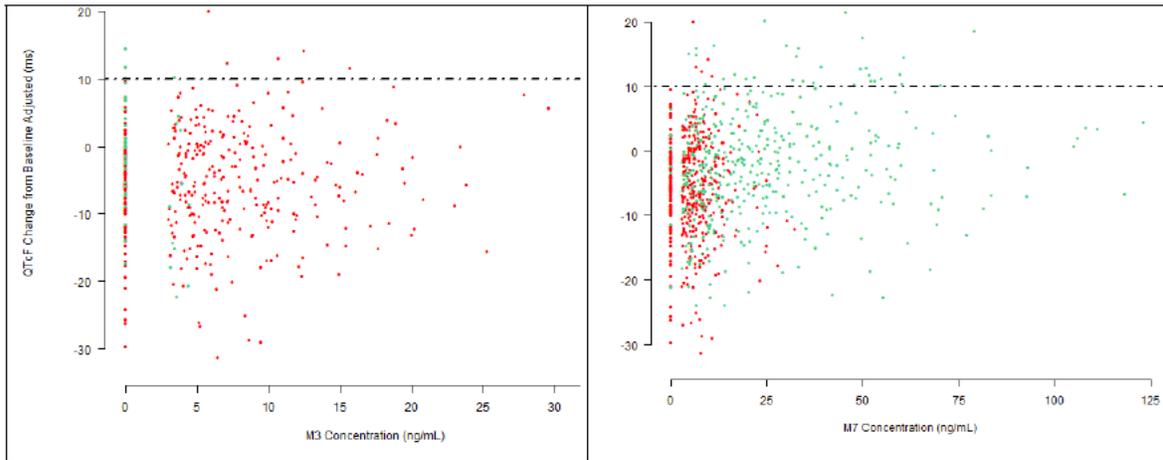
Figure 10 indicates a disconnect between neratinib exposures and Δ QTcF when given in combination with ketoconazole. In the left panel (neratinib plasma concentrations), there appears to be no slope for the 240 mg neratinib alone group (red line and points) indicating that neratinib does not influence the Δ QTcF at these concentrations. However, we see change in the Δ QTcF for the data for 240 mg neratinib in combination with 400 mg ketoconazole (left panel, blue line and points). The timecourse of effect is discordant with neratinib concentrations (left panel, blue line and points), while the effect shows concordance with ketoconazole concentrations (right panel). These plots suggest that the observed effect on Δ QTcF for the combination treatment (neratinib with ketoconazole) correlates with ketoconazole concentrations. This correlation with ketoconazole is also supported by literature data (H Zhu, et al. *J. Clin Pharmacol* **2010**;50:1106-1111) that suggest that ketoconazole may prolong the QTc interval.

Figure 10. $\Delta\Delta\text{QTcF}$ vs. Neratinib Plasma Concentrations (left panel) Connected Sequentially by Time and $\Delta\Delta\text{QTcF}$ vs. Ketoconazole Concentrations (right panel) Connected Sequentially by Time. Numbers on Top of the Data Point Indicate the Time of the Observations.



The same analysis was repeated for the metabolites M3 and M7 in combination with ketoconazole instead of neratinib. Each analysis indicated no significant slope for each of the two neratinib metabolites and a significant slope for ketoconazole, after adjusting for the effect of ketoconazole. Figure 11 depicts the ΔQTcF vs M3 or M7 concentrations and the lack of exposure-response relationship for these two metabolites when neratinib is administered alone, or after adjusting for the effect of ketoconazole when neratinib is administered with ketoconazole.

Figure 11. ΔQTcF vs. M3 Plasma Concentrations (left panel) and ΔQTcF vs. M7 Concentrations (right panel). Red symbols indicate data from the 240 mg neratinib alone administration and the green symbols indicate data from neratinib 240 mg dosing in combination with ketoconazole.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effects on PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	240 mg PO QD <u>Single Ascending and Multiple Dose in Cancer Patients (A1-102)</u> <ul style="list-style-type: none">After a single 240 mg neratinib dose, the C_{max} was 75.9 ng/mL (CV = 17%) and mean AUC was 1217 ng•hr/mL (CV = 39%)After multiple doses of neratinib 240 mg PO on Day 21, C_{max} was 73.5 ng/mL (CV = 37%) and mean AUC_{ss} was 939 ng•hr/mL (CV = 34%) <u>Single Ascending Dose in Healthy Subjects (A1-107)</u> <ul style="list-style-type: none">After a single 240 mg neratinib dose, C_{max} was 74.4 ng/mL (CV = 28%) and the mean AUC was 1357 ng•hr/mL (CV=28%)	
Maximum tolerated dose	240 mg PO QD	
Principal adverse events	The most common adverse drug reactions of any grade reported in patients in the neratinib arm in the pivotal study were diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, decreased appetite, muscle spasms, abdominal pain upper, stomatitis, dry skin, dyspepsia, alanine and aspartate aminotransferase increased, nail disorder, epistaxis and urinary tract infection. The most common dose limiting adverse event was diarrhea.	
Maximum dose tested	Single Dose	400 mg PO (Study A1-102) 640 mg PO with high fat meal (Study A1-107) 800 mg PO fasted (Study A1-107)
	Multiple Dose	400 mg PO QD

Exposures Achieved at Maximum Tested Dose	Single Dose	<p><u>Study (A1-102) in Cancer Patients</u></p> <ul style="list-style-type: none"> After a single 400 mg neratinib dose, the C_{max} was 76.5 ng/mL (CV = 52%) and mean AUC was 1833 ng•hr/mL (CV = 42%) <p><u>Single Ascending Dose in Healthy Subjects (A1-107)</u></p> <ul style="list-style-type: none"> After a single 800 mg neratinib dose under fasted conditions, the C_{max} was 121 ng/mL (CV = 39%) and mean AUC was 2624 ng•hr/mL (CV = 51%) After a single 640 mg neratinib dose under fed conditions, the C_{max} was 161 ng/mL (CV = 20%) and mean AUC was 3866 ng•hr/mL (CV = 35%)
	Multiple Dose	<p><u>Study (A1-102) in Cancer Patients (A1-102)</u></p> <ul style="list-style-type: none"> After multiple doses of neratinib 400 mg PO on Day 21, C_{max} was 105 ng/mL (CV = 43%) and mean AUC_{ss} was 1704 ng•hr/mL (CV = 20%)
Range of linear PK	<ul style="list-style-type: none"> Following single and multiple doses of 240 mg QD PO of neratinib in cancer patients, exposure increased with increasing dose but was not dose linear; the dose ranges evaluated 40 mg and 400 mg (Study A1-102). 	
Accumulation at steady state	Mean (%CV): 1.18(36) 240 mg QD, Day 21:Day 1	
Metabolites	<p>There are 4 major human metabolites. Pyridine N-oxide (M3), N-Desmethyl (M6), Dimethylamine N-oxide (M7), and Bis-N-oxide (M11)</p> <p>M6, M3, M7 and M11 are EGFR, HER2 and HER4 kinase inhibitors. The inhibitory activity of M6, M3, M7 and M11 are similar to that of neratinib for EGFR; M3, M7 and M11 similar IC₅₀ with HER4. M3 and neratinib have similar IC₅₀ values for HER2, but M7 and M11 have IC₅₀ values ~20 fold higher</p> <p>Fraction of each metabolite have not been characterized.</p>	

Absorption	Absolute/Relative Bioavailability	<ul style="list-style-type: none"> Absolute bioavailability of neratinib has not been assessed as there is no clinical IV formulation.
	T _{max}	<p>Median (range): <u>Study A1-1116 in healthy subjects</u></p> <ul style="list-style-type: none"> neratinib: T_{max} 6 hours (4-8 hours) M3: T_{max} 4 hours (2-6 hours) M6: T_{max} 6 hours (4-8 hours) M7: T_{max} 4 hours (2-8 hours)
Distribution	Vd/F or Vd	<p><u>Study A1-107 in healthy subjects</u></p> <ul style="list-style-type: none"> Following a single dose of 240 mg neratinib, the Vd/F was 2921 L (CV = 20%) <p><u>Single Ascending and Multiple Dose in Cancer Patients (A1-102)</u></p> <ul style="list-style-type: none"> Following a single dose of 240 mg neratinib, the Vd/F was 4258 L (CV = 27%) Following multiple doses of neratinib once daily 240 mg, on Day 21 the Vd/F was 6433 L (CV = 19%)
	% bound	<ul style="list-style-type: none"> In vitro protein binding of neratinib in human plasma was greater than 99% and independent of concentration.
Elimination	Route	<ul style="list-style-type: none"> Following a single oral administration of 200 mg [¹⁴C] neratinib to healthy subjects (study 3144A1-1108-US), a mean (SD) of 97.1% (8.5%) and 1.13% (0.26%) of the total dose was recovered in the feces and urine, respectively.
	Terminal t _{1/2}	<p><u>Study A1-1116 in healthy subjects</u></p> <ul style="list-style-type: none"> Following 7 days of once-daily 240 mg oral doses of neratinib, the mean (CV%) plasma half-life of neratinib, M3, M6, and M7 was 14.6 (38%), 21.6 (177%), 13.8 (50%) and 10.4 (33%) hours, respectively.
	CL/F or CL	<p><u>Study A1-107 in healthy subjects</u></p> <ul style="list-style-type: none"> Following a single dose of 240 mg neratinib, the mean (%CV) CL/F was 189 L/hour (28%) <p><u>Single Ascending and Multiple Dose in Cancer Patients (A1-102)</u></p> <ul style="list-style-type: none"> Following a single dose of 240 mg neratinib, the mean (%CV) CL/F was 216 L/hour (34%) Following multiple doses of neratinib once daily 240 mg, on Day 21 the mean (%CV) CLs/F was 281 L/hour (40%)

Intrinsic Factors	Age	Population PK analysis suggests that age has no clinically important effect on the exposure of neratinib.
	Sex	Population PK analysis suggests that sex has no clinically important effect on the exposure of neratinib.
	Race	Population PK analysis suggests that race has no clinically important effect on the exposure of neratinib.
	Hepatic & Renal Impairment	<ul style="list-style-type: none"> • Following a single oral dose of neratinib 120 mg with food, neratinib mean C_{max} and AUC values were 18.5 ng/mL and 296 ng•h/mL in healthy subjects, 31.2 ng/mL and 394 ng•h/mL in Child-Pugh class A subjects, 17.1 ng/mL and 286 ng•h/mL in Child-Pugh class B subjects, and 47.0 ng/mL and 767 ng•h/mL in Child-Pugh class C subjects, respectively. In non-oncology patients with severe pre-existing hepatic impairment (Child Pugh Class C), the clearance of neratinib was decreased and exposure to neratinib was increased by about 3-fold as compared to healthy volunteers. • Dedicated pharmacokinetic studies in patients with renal impairment or undergoing hemodialysis have not been carried out.

Extrinsic Factors	Drug interactions	<p><u>Ketoconazole (Strong CYP3A4 Inhibitor)</u></p> <ul style="list-style-type: none"> • Coadministration of neratinib with ketoconazole increased neratinib C_{max} and AUC_{inf} by 3.2-fold and 4.8-fold, respectively, relative to neratinib administered alone. • The least squares geometric mean (LSGM) ratios (and 90% CIs) for C_{max} and AUC_{inf} of neratinib were 321% (241- 428%), and 481% (359-645%), respectively, following coadministration of neratinib with multiple doses of ketoconazole, relative to neratinib administered alone. <p><u>Rifampin (Strong CYP3A4 Inducer)</u></p> <ul style="list-style-type: none"> • Coadministration of neratinib with rifampin decreased neratinib mean C_{max} and AUC by 76% and 87%, respectively, relative to neratinib administered alone. • The least squares geometric mean (LSGM) ratios (and 90% CIs) for C_{max} and AUC of neratinib were 24.1% (19.5- 29.7%), and 12.7% (10.3-15.6%), respectively, following coadministration of neratinib with multiple doses of rifampin, relative to neratinib administered alone. <p><u>Lansoprazole (Proton-pump Inhibitor)</u></p> <ul style="list-style-type: none"> • Coadministration of neratinib with lansoprazole decreased neratinib C_{max} and AUC_{inf} by 70% and 65%, respectively, relative to neratinib administered alone. • The ratios (90% CIs) of the geometric least square means of neratinib C_{max} and AUC_{inf} were 29% (22.2%-37.9%) and 34.8% (28.7%-42.2%) respectively, following administration of neratinib with multiple doses of lansoprazole, relative to neratinib administered alone. <p><u>Digoxin (Sensitive P-g-P Substrate)</u></p> <ul style="list-style-type: none"> • Exposure to digoxin increased when coadministered with multiple oral doses of neratinib 240 mg with increases of 54% and 32% for C_{max} and AUC, respectively, compared with exposures associated with digoxin administration alone.
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	Food Effects	<ul style="list-style-type: none"> • The ratios (90% CIs) of the adjusted geometric means for AUC_{inf} of neratinib 240 mg after a standard meal relative to neratinib administration after an overnight fast was 113% (103%-124%). The corresponding ratios (90% CIs) of the adjusted geometric means for C_{max} of neratinib 240 mg after a standard meal relative to neratinib administration after an overnight fast was 117% (97.0%-142%). • Administration of 240 mg neratinib with a standard meal resulted in geometric mean C_{max} and AUC_{inf} values of 45.6 ng/mL (CV = 52%) and 868 ng•hour/mL (CV = 34%), compared with 39.0 ng/mL (CV = 50%) and 771 ng•hour/mL (CV = 41%), under fasted conditions. • Administration of neratinib 240 mg under fasting conditions and with a high fat meal resulted in mean C_{max} values of 44.6 ng/mL (CV = 34%) and 74.4 ng/mL (CV = 28%), respectively, and mean values of AUC were 667 ng•hour/mL (CV = 40%) and 1357 ng•hour/mL (CV = 28%), respectively. The median t_{max} was 4 hours under fasting conditions, and 6 hours when given with food. Statistical comparison indicated a high fat meal increased the C_{max} and AUC by approximately 100% when compared with the exposure under fasting conditions. • Based on these studies neratinib should be administered with food.
Expected High Clinical Exposure Scenario		<ul style="list-style-type: none"> • In case of overdose with neratinib there is no known antidote. The treatment of overdose of neratinib should consist of general supportive measures.

<p>Preclinical Cardiac Safety</p>	<p>The potential for QT prolongation and hemodynamic effects of neratinib were assessed in in vitro assays and/or in vivo cardiovascular dog studies. In the hERG assay, the IC₅₀ of the rapidly-activating, delayed-rectifier cardiac potassium channel current for neratinib was 1.9 μM (1058 ng/mL). No toxicologically significant effects were observed on the cardiovascular system of dogs following neratinib oral dosages of 5, 10, or 20 mg/kg; the C_{max} exposure in dogs at 20 mg/kg was estimated to be 1 to 2 times the exposure in humans at the clinical dose of 240 mg. In repeat-dose toxicity studies in mice, rats, and dogs, neratinib did not produce any changes in heart weight, and no macroscopic or microscopic findings were observed in the heart. No ECG changes were observed in the 1-month and 9-month repeat-dose toxicity studies in dogs (max dose = 6mg/kg), with associated C_{max} for male and female dogs of 77.3 and 68.9 ng/mL respectively in the 9 month study. This is similar to the C_{max} in humans for the 240 mg QD clinical dose (73.5 ng/mL). The plasma binding for neratinib in both human and dog is approximately 99%. No QTc effects are anticipated at plasma concentrations >100 fold those associated with unbound C_{max} at the human clinical dose of 240 mg QD.</p>
<p>Clinical Cardiac Safety</p>	<p>The safety of neratinib was evaluated in 3252 patients and healthy volunteers in 31 studies. This included 157 subjects exposed to doses from 40 to 200 mg/day, 2969 patients/healthy volunteers exposed to 240 mg/day neratinib, and 126 exposed to doses of neratinib from 320 to 800 mg/day. Overall, patients were exposed to doses ranging from 40 mg to 400 mg per day and healthy volunteers were exposed to single doses up to 800 mg per day.</p> <p>The incidence of AEs of cardiac safety were lower in the neratinib arm versus placebo arm in the pivotal controlled trial (Study 3144A2-3004-WW): cardiac arrhythmia 3.8% vs. 4.1%, cardiac failure 6.7% vs. 8.5%, ischemic heart disorders 0.6% vs. 1.0%, and electrocardiogram QT prolonged 3.5% vs. 6.6% (neratinib vs. placebo, respectively). In addition, data from studies of neratinib monotherapy for the treatment of breast cancer, including Study PUMA-NER-6201, 3144A2-3003-WW, and 3144A1-201-WW, were reviewed for cardiac safety events and were supportive of the findings from the pivotal study.</p> <p>There were no adverse events of torsades de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, or seizure.</p> <p>In Study 3144A2-3004-WW, the incidence of Grade 3 syncope was higher in the neratinib (0.7%) versus placebo (0.3%) arm; all events of Grade 3 syncope in the neratinib arm occurred in the setting of other adverse events, including diarrhea, nausea, vomiting, dizziness, and dehydration.</p>

6.2 SCHEDULE OF ASSESSMENTS

PART A: Periods 1 Through 3, Days -1 Through 5

Study Day	-1 ^a	1											2	3	4 to 5 ^b
Study Hour	-2	-1	-0.5	0	1.5	3	4	5	6	8	12	24	48		
Inpatient admission	X														
Washout														X	
Brief physical assessment	X														
Pregnancy test (women only)	X														
Urine drug screen	X														
Laboratory evaluation ^c	X	X										X	X		
Vital signs ^d	X	X ^e			X ^f		X ^f								
12-Lead ECG (single)	X														
12-Lead ECG (triplicate)		X	X	X ^g	X	X	X	X	X	X	X	X	X	X	
Randomization ^h		X													
Test article administration				X											
PGx blood sample collection ⁱ	X														
PK blood sample collection for HKI-272	X				X	X	X	X	X	X	X	X	X	X	
PK blood sample collection for moxifloxacin ⁱ	X				X	X	X	X	X	X	X	X	X	X	
Adverse event recording	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Nonstudy medication monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→	

Abbreviations: ECG = electrocardiogram; PGx = pharmacogenomic; PK = pharmacokinetic.

- Period 1 only.
- Periods 1 and 2 only. Subjects will leave the site after Day 3 procedures for period 3.
- Hematology, blood chemistry, coagulation, and urinalysis. All laboratory evaluations will be fasting.
- Supine blood pressure, pulse rate, and respiratory rate after at least 5 minutes of rest, and oral temperature.
- Three (3) measurements of supine blood pressure and pulse rate after at least 5 minutes of rest.
- Supine blood pressure and pulse rate after at least 5 minutes of rest.
- Immediately before test article administration.
- Subjects will be randomly assigned after the completion of admission procedures and the evaluation of the hour -2 QTc interval has been completed.
- PK blood sample collection for moxifloxacin should only occur during the period in which the open-label moxifloxacin is administered.

PART B: Periods 4 and 5, Days -1 Through 8

Study Day	-1	1											2	3	4 to 8 ^a	FSE ^b
Study Hour	-2	-1	-0.5	0	1.5	3	4	5	6	8	12	24	48			
Inpatient admission	X															
Outpatient														X		
Brief physical assessment	X															
Physical examination															X	
Pregnancy test (women only)	X															
Urine drug screen	X															
Laboratory evaluation ^c	X	X										X	X		X	
Vital signs ^d	X	X ^e			X ^f		X ^f									
12-Lead ECG (single)	X															
12-Lead ECG (triplicate)		X	X	X ^g	X	X	X	X	X	X	X	X	X	X		
Ketoconazole administration	X ^h			X								X	X			
Test article administration				X												
PK blood sample collection for HKI-272	X				X	X	X	X	X	X	X	X	X	X	X ⁱ	
PK blood sample collection for ketoconazole	X				X	X	X	X	X	X	X	X	X	X	X ⁱ	
Adverse event recording	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	
Nonstudy medication monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	

Abbreviations: ECG = electrocardiogram; FSE = final study evaluation; PK = pharmacokinetic

- Period 4 only.
- Period 5 only, or early termination.
- Hematology, blood chemistry, coagulation, and urinalysis. All laboratory evaluations will be fasting.
- Supine blood pressure, pulse rate, and respiratory rate after at least 5 minutes of rest, and oral temperature.
- Three (3) measurements of supine blood pressure and pulse rate after at least 5 minutes of rest.
- Supine blood pressure and pulse rate after at least 5 minutes of rest.
- Immediately before test article administration.
- Ketoconazole administration in the evening of day -1, approximately 12 hours before test article administration on day 1.
- Early termination only.

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

/s/

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12/21/2016

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

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208051

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Nerlynx™ (neratinib) tablets

Applicant: Puma Biotechnology

Receipt Date: July 19, 2016

Goal Date: July 19, 2017

1. Regulatory History and Applicant's Main Proposals

This application was submitted as an NME 505(b)(1) NDA application on July 19, 2016. The applicant is seeking approval for extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 13, 2016. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

Selected Requirements of Prescribing Information

HIGHLIGHTS GENERAL FORMAT

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

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- NO** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment: *Horizontal line doesn't extend on the left side the column*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

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

Selected Requirements of Prescribing Information

• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A

Selected Requirements of Prescribing Information

15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

YES

Selected Requirements of Prescribing Information

22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

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

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

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

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

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

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

PAMELA I BALCAZAR
09/16/2016

ALICE KACUBA
09/16/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 208051 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Nerlynx Established/Proper Name: neratinib maleate Dosage Form: tablet Strengths: 40 mg		
Applicant: Puma Biotechnology Inc. Agent for Applicant (if applicable):		
Date of Application: 7/18/2016 Date of Receipt: 7/19/2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: 7/19/2017		Action Goal Date (if different):
Filing Date: 9/19/2016		Date of Filing Meeting: 9/1/2016
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): HER-2 positive breast cancer		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 066783

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>				

<i>to the supporting IND(s) if not already entered into electronic archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	standard
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm If yes, explain in comment column.	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes , # years requested: (b) (4)					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

<input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

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

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

2

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

3

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

	<input type="checkbox"/> Instructions for Use (IFU)			
	<input type="checkbox"/> Medication Guide (MedGuide)			
	<input checked="" type="checkbox"/> Carton labeling			
	<input checked="" type="checkbox"/> Immediate container labels			
	<input type="checkbox"/> Diluent labeling			
	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Only animal data
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Consult will be sent after filing meeting
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Consult will be sent after filing meeting
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Consult will be sent after filing meeting

4

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

OTC Labeling				
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults				
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT interdisciplinary review team. Consult will be sent after filing meeting
Meeting Minutes/SPAs				
End-of Phase 2 meeting(s)? Date(s): 7/10/2008-CMC	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/21/2016	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): 3/10/2015 –carc 6/9/2015 carc	<input checked="" type="checkbox"/>			

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 1, 2016

BACKGROUND: Puma Biotechnology is submitted an NME 505(b)(1) NDA for neratinib maleate tablets (Nerlynx). It is proposed to be used as a single agent indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pamela Balcazar	N
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Laleh Amiri-Kordestani		Y
Division Director/Deputy	Geoffrey Kim		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Amanda Walker (safety) Harpreet Singh (efficacy)	Y
			Y
	TL:	Laleh Amiri-Kordestani	Y
Clinical Pharmacology	Reviewer:	Walt (Xianhua) Cao	Y
	TL:	Qi Liu	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Jerry Yu	Y
	TL	Nam Atiqur (TL)	Y
Biostatistics	Reviewer:	Joyce Chen	N
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kimberly Ringgold	Y
	TL:	Todd Palmby	Y

Product Quality (CMC) Review Team:	ATL:	Xiao Chen	Y
	RBPM:	Kristine Leahy	Y
• Drug Substance	1° Reviewer:	Gaetan Ladouceur	Y
	2° Reviewer	Kasturi Srinivasachar	N
• Drug Product	1° Reviewer:	Amit Mitra	Y
	2° Reviewer	Anamitro Banerjee	N
• Process and Microbiology	1° Reviewer:	Huiquan Wu	Y
	2° Reviewer	Rakhi Shah	Y
• Facility	1° Reviewer:	Ephrem Hunde	Y
	2° Reviewer	Ruth Moore	N
• Biopharmaceutics	Reviewer:	Zhuojun (Joan) Zhao	Y
	TL:	Okpo Eradiri	N
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Till Olickal	Y
	TL:	Naomi Redd	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:		
Other reviewers/disciplines			
Other attendees	Elleni Alebachew, RPM		Y
	Amarilys Vega		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none">• 505 b)(2) filing issues:<ul style="list-style-type: none">○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none">• Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none">• Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> No comments</p>

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

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 12/13/2016

21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Sharepoint site has the planner.

Deliverable	Date
NDA Received	7/19/2016
AOM/Dataset orientation	8/29/2016
Filing Meeting (by Day 45)	9/1/2016
Filing determination (by Day 60)	By 9/17/2016
Mid-cycle Meeting	12/13/2016
Secondary Reviews	03/26/2017
Primary Reviews	03/29/2017
CDTL Review	06/07/2017
ODAC	April 2017
PDUFA Goal Date	7/19/2017

Labeling meetings will be scheduled after filing meeting

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

PAMELA I BALCAZAR
09/06/2016

ALICE KACUBA
09/07/2016