

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125409Orig1s0051

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

1.3.3 Debarment Certification

Genentech, Inc. 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 for the investigation of product, Perjeta[®] (pertuzumab), in connection with this Supplemental Biologic License Application.

Signed by: Michelle H. Rohrer
Michelle H. Rohrer, Ph.D.
Vice President, U.S. Regulatory Affairs

4/30/2013
Date

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125409 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DOP1 PDUFA Goal Date: 6-8-12 Stamp Date: 12-8-11

Proprietary Name: (b) (4)

Established/Generic Name: pertuzumab

Dosage Form: Liquid single use vial

Applicant/Sponsor: Genentech, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For the treatment of patients with 1st Line HER2-positive metastatic breast cancer

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdcrpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

Amy Tilley
Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

AMY R TILLEY
02/24/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA #	NDA Supplement # BLA Supplement # 125409/051	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: Perjeta Established/Proper Name: pertuzumab Dosage Form: Injection		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Amy Tilley		Division: DOP1
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action = Accelerated Approval • User Fee Goal Date is <u>10-31-13</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

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

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input checked="" type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLAs: Subpart E <input checked="" type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates N/A</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Burst & IA</p>

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Accelerated Approval Letter 9-30-13
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	9-27-13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	4-30-13
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	N/A
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 7-2-13 <input type="checkbox"/> DMEPA <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 9-25-13 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	7-12-13
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>7-10-13</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	8-6-13
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg N/A
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	N/A
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	9-12-13
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	Draft Minutes Included
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9-30-13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9-27-13
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None PMR=2 PMC=2
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	9-25-13
• Clinical review(s) (<i>indicate date for each review</i>)	9-25-13
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 6-6-13; 8-27-13

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None 9-9-13
Statistical Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None 5-31-13; 9-9-13
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None 5-31-13; 9-9-13
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None 9-9-13
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None 9-9-13; Pharmacometrics 9-9-13
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		<input checked="" type="checkbox"/> None
Nonclinical		<input checked="" type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)		<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)		<input type="checkbox"/> None requested
Product Quality		<input checked="" type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		<input type="checkbox"/> None
❖ Microbiology Reviews		<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		<input type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

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/s/

AMY R TILLEY
09/30/2013

ALICE KACUBA
09/30/2013

From: Tilley, Amy
Sent: Friday, September 27, 2013 9:38 AM
To: 'Josephine Ing'
Subject: *URGENT* sBLA 125409 51 - Perjeta - FDA Label Revisions 9-27-13

Importance: High

Follow Up Flag: Follow up
Due By: Friday, September 27, 2013 2:00 PM
Flag Status: Red

Attachments: Perjeta FDA rev label 9-26-13 RJ edits.doc
Josephine,

Below is the revised label for Perjeta. Please respond as soon as possible.



Perjeta FDA
label 9-26-13

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/27/2013

From: Josephine Ing [ing.josephine@gene.com]
Sent: Thursday, September 26, 2013 1:43 PM
To: Tilley, Amy
Subject: Re: Minor edits to label in Highlights re sBLA 125409 51 Perjeta
Hi Amy,

Yes, we agree the revisions.

Thanks
Josephine

On Thu, Sep 26, 2013 at 10:33 AM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:
[Josephine](#),

We made the following minor revisions to the label in Highlights. Please confirm via email that Genentech accepts the following minor revisions to the Perjeta label.

----- **RECENT MAJOR CHANGES** -----

Indications and Usage (1.2)	09/2013
Dosage and Administration (2.1)	04/2013
Dosage and Administration (2.1, 2.2)	09/2013
Contraindications (4)	09/2013
Warnings and Precautions (5.2, 5.3, 5.4, 5.5)	09/2013

See 17 for **PATIENT COUNSELING INFORMATION**.

Revised: 09/2013

Thank you.

Amy

From: Josephine Ing [mailto:ing.josephine@gene.com]
Sent: Wednesday, September 25, 2013 10:09 PM
To: Tilley, Amy
Subject: Re: Addtl rev Format Highlights and TOC re sBLA 125409 51 Perjeta - FDA Revised label 9-25-13

Amy,

Attached is a clean label. It has been officially submitted to the BLA as Sequence 0183.

Thanks
Josephine

On Wed, Sep 25, 2013 at 1:17 PM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:
[Josephine](#),

Per our telephone conversation, below is how the Highlights and TOC should appear in the label.

Please include this formatting in your revised label prior to submitting to us.

Thank you.

Amy

From: Tilley, Amy
Sent: Wednesday, September 25, 2013 1:53 PM
To: 'Josephine Ing'
Subject: sBLA 125409 51 Perjeta - FDA Revised label 9-25-13
Importance: High

[Josephine](#),

As per discussed earlier today, below is the FDA revised Perjeta label.

We respectfully request your response as soon as possible both via email and as an official submission to the sBLA.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
[☎ 301.796.3994](tel:301.796.3994) (phone) • [301.796.9845](tel:301.796.9845) (fax) | [✉ amy.tilley@fda.hhs.gov](mailto:amy.tilley@fda.hhs.gov)

--

Josephine Ing | Product Development Regulatory | Genentech, Inc. | 📞p:(650) 225-2330 |
📧m: (b) (6)

--

Josephine Ing | Product Development Regulatory | Genentech, Inc. | 📞p:(65

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/s/

AMY R TILLEY
09/26/2013

From: Tilley, Amy
Sent: Wednesday, September 25, 2013 4:18 PM
To: 'Josephine Ing'
Subject: Addtl rev Format Highlights and TOC re sBLA 125409 51 Perjeta - FDA Revised label 9-25-13

Importance: High

Attachments: Revised formatting for highlights and toc.doc; FDA rev label 9-25-13.doc
Josephine,

Per our telephone conversation, below is how the Highlights and TOC should appear in the label.

Please include this formatting in your revised label prior to submitting to us.



Revised
formatting for high

Thank you.

Amy

From: Tilley, Amy
Sent: Wednesday, September 25, 2013 1:53 PM
To: 'Josephine Ing'
Subject: sBLA 125409 51 Perjeta - FDA Revised label 9-25-13
Importance: High

Josephine,

As per discussed earlier today, below is the FDA revised Perjeta label.



FDA rev label
9-25-13.doc (2 M

We respectfully request your response as soon as possible both via email and as an official submission to the sBLA.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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immediately following this page

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/s/

AMY R TILLEY
09/25/2013

From: Tilley, Amy
Sent: Wednesday, September 25, 2013 1:53 PM
To: 'Josephine Ing'
Subject: sBLA 125409 51 Perjeta - FDA Revised label 9-25-13

Importance: High

Follow Up Flag: Follow up
Due By: Thursday, September 26, 2013 10:00 AM
Flag Status: Red

Attachments: FDA rev label 9-25-13.doc
[Josephine,](#)

As per discussed earlier today, below is the FDA revised Perjeta label.



FDA rev label
9-25-13.doc (2 MB)

We respectfully request your response as soon as possible both via email and as an official submission to the sBLA.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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immediately following this page

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/s/

AMY R TILLEY
09/25/2013

From: Tilley, Amy
Sent: Tuesday, September 24, 2013 2:01 PM
To: 'Josephine Ing'
Subject: sBLA 125409 51 Perjeta - FDA revised label 9-24-13

Follow Up Flag: Follow up
Due By: Wednesday, September 25, 2013 12:00 AM
Flag Status: Red

Attachments: FDA rev label 9-24-13.doc
[Josephine,](#)

[Below is the FDA revised label for sBLA 125409 51 Perjeta.](#)



FDA rev label
9-24-13.doc (2 MB)

[We respectfully request your response by COB today your time.](#)

[Please confirm receipt of this email.](#)

[Thank you.](#)

[*Amy Tilley*](#)

[Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
301.796.3994 \(phone\) • 301.796.9845 \(fax\) | \[✉ amy.tilley@fda.hhs.gov\]\(mailto:amy.tilley@fda.hhs.gov\)](#)

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/s/

AMY R TILLEY
09/24/2013

From: Tilley, Amy
Sent: Wednesday, September 18, 2013 6:28 PM
To: 'Josephine Ing'
Subject: Time Sensitive sBLA 125409 51 - Clinical Safety IR

Follow Up Flag: Follow up
Due By: Friday, September 20, 2013 3:00 PM
Flag Status: Red
Josephine,

Please table similar to the following with information from the three regimens in TRYPHAENA:

NEOSPHERE (WO20697): Completion of Treatment (Reviewer Table)

	H+T N=107	P+H+T N=107
Neoadjuvant Period	N=107	N=107
Pertuzumab	--	95%
Trastuzumab	98%	94%
Docetaxel	99%	95%
Adjuvant Period	N=103	N=102
FEC	100%	94%
Trastuzumab	96%	89%
1 yr of trastuzumab therapy*	92%	83%

We respectfully request your response to the above **no later than 3 pm Friday, September 20, 2013.**

Please confirm receipt of this email.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/18/2013

From: Tilley, Amy
Sent: Wednesday, September 18, 2013 10:34 AM
To: 'Josephine Ing'
Subject: Time Sensitive - sBLA 125409 51 Perjeta - PMR-PMC Timelines needed

Importance: High

Follow Up Flag: Follow up
Due By: Friday, September 20, 2013 12:00 PM
Flag Status: Red

Josephine,

Below are the revised PMRs and PMCs for the Perjeta Efficacy Supplement for which we are requesting your proposed timetable of the Milestones.

We respectfully request your response **no later than 12 noon on Friday, September 20, 2013.**

PMRs:

- 1) Submit the final disease-free survival (DFS) analysis of trial BO25126 (APHINITY) as defined in your protocol and Statistical Analysis Plan (SAP).

Submit a timetable for:

Final Protocol Submission:
Trial Completion:
Final Report Submission:

- 2) Conduct a clinical trial to further assess the cardiac safety of neoadjuvant anthracycline/taxane-based chemotherapy regimens when administered in combination with neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early stage HER2-positive breast cancer.

Submit a timetable for:

Final Protocol Submission:
Trial Completion:
Final Report Submission:

PMCs:

- 1) Submit the final event-free survival (EFS) analysis of trial WO20697 (NEOSPHERE).

Submit a timetable:

Final Protocol Submission:

Trial Completion:
Final Report Submission:

- 2) Conduct a study of pretreatment molecular subtyping of tumors from patients treated in the postmarketing cardiac safety trial (PMR#2) and submit an exploratory analysis of the relationship of pathological complete response with the different tumor subtypes.

Submit a timetable:

Final Protocol Submission:
Study Completion:
Final Report Submission:

Kindly confirm receipt of this email.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/18/2013

From: Tilley, Amy
Sent: Tuesday, September 17, 2013 10:48 AM
To: 'Josephine Ing'
Subject: *Urgent Time Sensitive* sBLA 125409/51 - Clinical Information Request

Josephine,

Please submit all the available meeting minutes and/or summary documents from the APHINITY DSMB Periodic Reviews.

We respectfully request your response to this IR both via email and as an official submission **no later than 3 pm on September 18, 2013.**

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/18/2013

From: Tilley, Amy
Sent: Tuesday, September 17, 2013 12:28 PM
To: 'Josephine Ing'
Subject: sBLA 125409/51 Perjeta - FDA Revised Label

Follow Up Flag: Follow up
Due By: Thursday, September 19, 2013 10:00 AM
Flag Status: Red

Attachments: FDA Revised Label 9-17-13.doc
[Josephine,](#)

[Below is the FDA Revised Label for Perjeta.](#)



FDA Revised
el 9-17-13.do

We respectfully request your response **no later than 10 am on Thursday, September 19, 2013.**

Please confirm receipt of this email.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/18/2013

From: Tilley, Amy
Sent: Monday, September 09, 2013 5:25 PM
To: 'Josephine Ing'
Subject: RE: sBLA 125409 51 Perjeta – Revise updated PMR Milestones
[Josephine,](#)

The Agency thinks your proposed updated milestones are too long.

Please justify the deadlines.

Send the revised updated milestone information via email only until we reach agreement on the milestones.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

From: Josephine Ing [<mailto:ing.josephine@gene.com>]
Sent: Friday, September 06, 2013 8:26 PM
To: Tilley, Amy
Subject: Re: sBLA 125409 51 Perjeta - Clinical Requests Updated PMR Milestones

Dear Amy,

We propose the following revised milestones:

Draft Protocol Submission: 11/2013

Final Protocol Submission: 01/2014

Primary Study Report Submission (neoadjuvant): 06/2017

Update Study Report Submission (adjuvant): 06/2018

Trial Completion: 06/2021

Final Study Report Submission: 12/2021

The formal submission is planned for Monday and will be Sequence 0175.

Thanks

Josephine

On Fri, Sep 6, 2013 at 6:44 AM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:
Josephine,

Please submit updated Milestones regarding the PMR discussed during the TCON. The draft Milestones are below.

Draft Milestones to be updated:

Draft Protocol Submission: 02/2014

Final Protocol Submission: 04/2014

Primary Study Report Submission (neoadjuvant): 09/2017

Update Study Report Submission (adjuvant): 09/2018

Trial Completion: 08/2021

Final Study Report Submission: 03/2022

Please send the updated Milestone information both via email and as a an official submission as soon as possible.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

📞 [301.796.3994](tel:301.796.3994) (phone) • [301.796.9845](tel:301.796.9845) (fax) | ✉ amy.tilley@fda.hhs.gov

Josephine Ing | Product Development Regulatory | Genentech, Inc. | 📞: (650) 225-2330 |
📧: (b) (6)

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/s/

AMY R TILLEY
09/10/2013

From: Tilley, Amy
Sent: Friday, September 06, 2013 9:44 AM
To: 'Josephine Ing'
Subject: sBLA 125409 51 Perjeta - Clinical Requests Updated PMR Milestones

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, September 11, 2013 12:00 PM
Flag Status: Red
[Josephine,](#)

Please submit updated Milestones regarding the PMR discussed during the TCON. The draft Milestones are below.

Draft Milestones to be updated:

Draft Protocol Submission: 02/2014
Final Protocol Submission: 04/2014
Primary Study Report Submission (neoadjuvant): 09/2017
Update Study Report Submission (adjuvant): 09/2018
Trial Completion: 08/2021
Final Study Report Submission: 03/2022

Please send the updated Milestone information both via email and as an official submission as soon as possible.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
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☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/06/2013

From: Tilley, Amy
Sent: Wednesday, September 04, 2013 1:34 PM
To: Josephine Ing Josephine.ing@gene.com
Subject: sBLA 125409 Perjeta - FDA Revised Label

Importance: High

Follow Up Flag: Follow up
Due By: Friday, September 06, 2013 3:00 PM
Flag Status: Flagged

Attachments: FDA rev label 9-3-13.doc
[Josephine,](#)

Below is the revised FDA Perjeta Label for Genentech's review.



FDA rev label
i-13.doc (2 Mi)

We respectfully request your response to this email **no later than 3 pm on Friday, September 6, 2013.**

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/04/2013

From: Tilley, Amy
Sent: Tuesday, August 27, 2013 4:39 PM
To: 'Josephine Ing'
Subject: *Time Sensitive* sBLA 125409/51 Perjeta - FDA Revised Label

Attachments: FDA Revised label 8-27-13_Latest Document.doc
Josephine,

Below is a copy of the FDA Revised Label regarding sBLA 125409/51 Perjeta.

We request your response both via email and as an official submission to this application **no later than 3 pm on August 29, 2013.**



FDA Revised
l 8-27-13_Lat

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

Never doubt that a small group of thoughtful, committed people can change the world; indeed, it's the only thing that ever has.

--Margaret Mead, The Wagon and the Star

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immediately following this page

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/s/

AMY R TILLEY
08/27/2013

From: Tilley, Amy
Sent: Monday, August 26, 2013 4:54 PM
To: 'Josephine Ing'
Subject: 2nd Urgent Time Sensitive sBLA 125409/51 - Clinical Safety IR

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, August 27, 2013 3:00 PM
Flag Status: Red
Josephine,

Below is the second Clinical Safety Information Request below for which we request your response by **no later than 3 pm August 27, 2013.**

- 1) In Table 3 of the response to the Clinical IR sent on 8-8-13 for the cardiac toxicity in the TRYPHAENA study it is listed that 4 additional patients (3901, 3902, 3699 and 3076) experience central declines but no local decline. However, in the Safety Update Report dated July 30, 2013 in Table 15 only 3 patients are listed as having a central reading decline only (Pts 3901, 3902 and 3699). Please verify which one is correct?
- 2) Please verify the number of patients that withdrew from treatment in the neoadjuvant phase of NEOSPHERE due to safety reasons.

Arm A: none

Arm B: Pt 2380 stopped docetaxel therapy due to hypersensitivity but continue pertuzumab+trastuzumab; Pt 1747 died after receiving all 4 cycles of neoadjuvant therapy

Arm C: Pt 1760 stopped all therapy due to symptomatic CHF and Pt 2141 stopped all therapy due to drug hypersensitivity

Arm D: Pt 3843 withdrew from treatment due to neutropenia and Pt 2022 due to ulcerative colitis

In addition, the Safety Update Report on Table 4 lists three patients as withdrawing from the neoadjuvant treatment phase in the Ptz+D arm due to safety reasons (including one death). Please give patient number for the death. Also, when did the patient withdraw and when did the patient die?

Kindly confirm receipt of this email.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products

1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
08/26/2013

From: Tilley, Amy
Sent: Monday, August 26, 2013 3:43 PM
To: 'Josephine Ing'
Subject: *Urgent Time Sensitive* sBLA 125409/51 - Clinical Safety IR

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, August 27, 2013 3:00 PM
Flag Status: Red
Josephine,

We request your response to the Clinical Safety Information Request below **no later than 3 pm August 27, 2013.**

As outlined in 3.5.1.2 in the primary CSR for BO22280, patients were allowed to have additional chemotherapy after surgery if considered necessary. Please provide the number of patients and in each treatment arm that received additional chemotherapy during adjuvant trastuzumab treatment. Please also include the chemotherapy regimen administered.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
08/26/2013

From: Cortazar, Patricia
Sent: Tuesday, August 13, 2013 3:23 PM
To: Josephine Ing (ing.josephine@gene.com)
Cc: Tilley, Amy
Subject: IR Need urgent response Perjeta sBLA 125409/51 sent 8-13-13

Importance: High

Body System/Adverse Reactions	Trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab n=108 Frequency rate %		PERJETA + docetaxel n=94 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions								
Fatigue	27.1	0.0	26.2	0.9	12.0	0.0	25.5	1.1
Asthenia	17.8	0.0	20.6	1.9	2.8	0.0	16.0	2.1
Edema peripheral	10.3	0.0	2.8	0.0	0.9	0.0	5.3	0.0
Mucosal inflammation	21.5	0.0	26.2	1.9	2.8	0.0	25.5	0.0
Pyrexia	10.3	0.0	16.8	0.0	8.3	0.0	8.5	0.0
Skin and subcutaneous tissue disorders								
Alopecia	66.4	0.0	65.4	0.0	2.8	0.0	67.0	0.0
Rash	21.5	1.9	26.2	1.9	11.1	0.0	28.7	1.1
Gastrointestinal disorders								
Diarrhea	33.6	3.7	45.8	5.6	27.8	0.0	54.3	4.3
Nausea	36.4	0.0	39.3	0.0	13.9	0.0	36.2	1.1
Vomiting	12.1	0.0	13.1	0.0	4.6	0.0	16.0	2.1
Stomatitis	7.5	0.0	17.8	0.0	4.6	0.0	9.6	0.0
Blood and lymphatic system disorders								
Neutropenia	63.6	58.9	50.5	44.9	0.9	0.9	64.9	57.4
Leukopenia	21.5	11.2	9.3	4.7	0.0	0.0	13.8	8.5
Nervous system disorders								
Headache	11.2	0.0	11.2	0.0	13.9	0.0	12.8	0.0
Dysgeusia	10.3	0.0	15.0	0.0	4.6	0.0	7.4	0.0
Peripheral Sensory Neuropathy	12.1	0.9	8.4	0.9	1.9	0.0	10.6	0.0
Musculoskeletal and connective tissue disorders								
Bone Pain	10.3	0.0	9.3	0.9	0.0	0.0	4.3	0.0
Myalgia	22.4	0.0	22.4	0.0	9.3	0.0	21.3	0.0
Arthralgia	8.4	0.0	10.3	0.0	4.6	0.0	9.6	0.0
Metabolism and nutrition disorders								
Decreased appetite	6.5	0.0	14.0	0.0	1.9	0.0	14.9	0.0
Psychiatric disorders								

Insomnia	11.2	0.0	8.4	0.0	3.7	0.0	8.5	0.0
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Dear Josephine,

Attached is the safety table from the NEOSPHERE study that you submitted per our request. We added two rows: one for peripheral neuropathy and another for bone pain. The numbers in red reflect some minor discrepancies with the numbers Genentech provided. Please ask your team to recheck the numbers. Please submit the table in a word document, once the definite percentages are incorporated. It would be ideal to have a response back tomorrow morning in time for our labeling meeting.

Thank you,

Patricia Cortazar, M.D.
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products (OHOP)
Division of Oncology Products 1 (DOP1)
Clinical Team Leader
Breast Oncology Group

10903 New Hampshire Avenue
WO 22 Room 2333
Silver Spring, MD 20993
301-796-1346

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/s/

AMY R TILLEY
08/16/2013

From: Cortazar, Patricia
Sent: Sunday, August 11, 2013 12:41 PM
To: Josephine Ing ing.josephine@gene.com
Cc: Tilley, Amy
Subject: Clin Resp re Spon Resp to sBLA 125409 Perjeta - Clinical IR sent 8-8-13

Importance: High

Josephine,
Thank you for the response. Could you please ask your team to let us know if patients: 3126, 3858, 3721, 3981, 3987, 2093, 3153, 3571, 3722, 3783 and 3842 recovered from the LVEF drop? Particularly important is the information on recovery of symptomatic LV dysfunction of patients 3288, 3723, 3580 and 3136.
I will appreciate if you can send us this information tomorrow before COB.

Thank you

Patricia Cortazar, M.D.
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products (OHOP)
Division of Oncology Products 1 (DOP1)
Clinical Team Leader
Breast Oncology Group

10903 New Hampshire Avenue
WO 22 Room 2333
Silver Spring, MD 20993
301-796-1346

From: Tilley, Amy
Sent: Friday, August 09, 2013 3:30 PM
To: Cortazar, Patricia
Subject: Spon Resp re ****URGENT**** sBLA 125409 Perjeta - Clinical IR sent 8-8-13

From: Josephine Ing [<mailto:ing.josephine@gene.com>]
Sent: Friday, August 09, 2013 3:12 PM
To: Tilley, Amy
Subject: Re: ****URGENT**** sBLA 125409 Perjeta - Clinical IR sent 8-8-13

Dear Amy,

Pls see below for the response. The formal submission will follow to the BLA on Monday.

Company Response

The Sponsor's interpretation of the table includes AE LVD or CHF reporting as well as LVEF declines $\geq 10\%$ and drop to less than 50% for all patients in the specified study period (neoadjuvant, adjuvant, and follow-up).

We have provided Table 1 in the same format as previously provided for NEOSPHERE. For consistency, it includes AE LVD or CHF reporting as well as LVEF declines $\geq 10\%$ and drop to less than 50% based on local readings for each of the study periods in which the onset was reported. If a patient experienced two separate events (with recovery) in two separate periods, the event would be counted once in each period.

As TRYPHAENA included both local and central LVEF readings, AE LVD is based on local readings. Additional central readings that meet the criteria of LVEF declines $\geq 10\%$ and drop to less than 50% but do not have a corresponding local decline are provided in Table 3 and are not reported as AE LVD. Symptomatic LV Dysfunction (CHF) is reported as event regardless of LVEF measurements.

For clarity and completeness, the Sponsor has added an additional row to Table 1 titled "TOTAL" so the interpretation of cardiac events is more accurate. For instance, if you add up the events in FEC+P+H/P+H+D, there are a total of 8 events experienced across 5 patients.

If the patient had an AE LVD or CHF across three periods, the event is counted once per period. For example, Patient 3287 experienced an event in all 3 periods. In the Table 2 below, this event is counted once in the neoadjuvant period, once in the adjuvant period, and once in the follow-up period. In the TOTAL row, this patient is only counted once.

Patients entering the adjuvant period are reported in Figure 2 of the TRYPHAENA CSR update and Table 4 of the Safety Update report.

Table 1 Cardiac Toxicity in TRYPHAENA (neoadjuvant, adjuvant and follow up periods)

	FEC+P+H/ P+H+D N=72	FEC/ P+H+D N=75	TCH+P N=76
NEOADJUVANT PERIOD	72	75	76
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%)	4 (5.6%)	1 (1.3%)	2 (2.6%)
asymptomatic			
Symptomatic LV Dysfunction (CHF)	0	2 ^a (2.7%)	0
ADJUVANT PERIOD	68	65	67
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%)	3 (4.4%)	5 (7.7%)	2 (3.0%)
asymptomatic			
Symptomatic LV Dysfunction (CHF)	-		1 (1.5%)
FOLLOW-UP PERIOD	70	75	74
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%)	1 (1.4%)	2 (2.7%)	2 (2.7%)
asymptomatic			
Symptomatic LV Dysfunction (CHF)	-	1 (1.3%)	
TOTAL (patient may have experienced an event in more than one period)	72	75	76
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%)	5 (6.9%)	6 (8%)	6 (7.9%)
asymptomatic			
Symptomatic LV Dysfunction (CHF)		3 ^a (4%)	1 (1.3%)

Additional Notes:

Events are counted in the treatment period in which the onset was reported

^a Patient 3288 experienced symptomatic LVD during FEC treatment, prior to Perjeta, Herceptin and Docetaxel. The patient receive discontinued FEC and continued on study to receive Perjeta, Herceptin and Docetaxel. Additionally, the patient did not meet criteria (LVEF Decline $\geq 10\%$ and drop to less than 50%), but is included in the table as the patient reported symptomatic LVD (baseline 54%, local LVEF at symptomatic LVD onset was 48%).

Table 2 Patient with Cardiac Toxicity in TRYPHAENA (neoadjuvant, adjuvant and follow up periods)

LVEF declines are based on local readings only

	FEC+P+H/ P+H+D N=72	FEC/ P+H+D N=75	TCH+P N=76
NEOADJUVANT PERIOD	72	75	76
	3287		
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%)	3332		3093
asymptomatic	3858	3985	3153
	3887		
Symptomatic LV Dysfunction (CHF)	-	3723	-
		3288^a	
ADJUVANT PERIOD	68	65	67
		3377	
	3126	3422	
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%)	3287	3981	3722
asymptomatic	3332	3985	3842
		3987	
Symptomatic LV Dysfunction (CHF)	-	-	3136
FOLLOW-UP PERIOD	70	75	74
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%)		3288	3571
asymptomatic	3287	3721	3783

Symptomatic LV Dysfunction (CHF)	-	3580	-
TOTAL (patient may have experienced an event in more than one period)	72	75	76
		3377	3093
	3126	3422	3153
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%)	3287	3721	3571
	3332	3981	3722
asymptomatic	3858	3985	3783
	3887	3987	3842
		3288^a	
Symptomatic LV Dysfunction (CHF)	-	3723	3136
		3580	

Additional notes:

^aPatient 3288 did not meet criteria (LVEF Decline \geq 10% and drop to less than 50%), but is included in the table as the patient reported symptomatic LVD (baseline 54%, local LVEF at symptomatic LVD onset was 48%). Event occurred prior to Perjeta, Herceptin and docetaxel administration.

Patient 3287 experienced separate events in each of the three study periods all of which recovered/resolved with no sequelae.

Patients 3985 and 3332 experienced separate events in two separate study periods all of which recovered (2 patients with 5 events)

Patient 3377, and 3422 experienced a LVEF decline which spanned two study periods and is correctly reported as one event and resolved with no sequelae. Patient 3887 experienced a LVEF decline which spanned two study periods and is correctly reported as one event, the LVEF has recovered to 50% but the AE event remains asymptomatic and ongoing (Grade 1 asymptomatic).

Patient 3648 reports AE LVD (Grade 1) but did not meet criteria (LVEF Decline \geq 10% and drop to less than 50%), LVEF of 55% at AE onset date and, therefore, is not included in the Table 1 and Table 2.

LVEF declines based on central LVEF readings but do not report AE LVD, consistent with protocol reporting requirements are detailed in Table 3.

Table 3 Patients with LVEF declines based on central LVEF assessments in TRYPHAENA (neoadjuvant, adjuvant and follow up periods)

	FEC+P+H/ P+H+D N=72	FEC/ P+H+D N=75	TCH+P N=76
NEOADJUVANT PERIOD	72	75	76
CENTRAL LVEF Decline $\geq 10\%$ and drop to less than 50% asymptomatic	-	3901 3422	3076
ADJUVANT PERIOD	68	65	67
CENTRAL LVEF Decline $\geq 10\%$ and drop to less than 50%, asymptomatic	-	3901 3902	-
FOLLOW-UP PERIOD	70	75	74
CENTRAL LVEF Decline $\geq 10\%$ and drop to less than 50% asymptomatic	-	-	-

Additional notes:

Patients 3901, 3902, 3699 and 3076 experienced central declines but no local decline. Therefore, an AE LVD was not reported.

Let me know if you have any questions.

Thanks

Josephine

On Thu, Aug 8, 2013 at 11:52 AM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:

Josephine,

Please tell your team that we liked very much the way they submitted the cardiac safety information. Can you send us a similar table for the TRYPHAENA study? We would need a response by COB tomorrow, Washington, DC time.

As always, submit your response both via email and as an official response to the BLA.

Cardiac Toxicity in TRYPHAENA (neoadjuvant, adjuvant and follow up periods)

	FEC x 3→D x 3 Per + Tras x 6	FEC x 3→D x 3 + Per+Tras x 3	TCH x 6 + Per x 6
NEOADJUVANT PERIOD	N= 72	N= 75	N= 76
LVEF Decline $\geq 10\%$ and drop to less than 50%	4 (5.6%)	4 (5.3%)	3 (3.9%)
Symptomatic LV Dysfunction (CHF)	1 (1.4%)	2 (2.7%)	
ADJUVANT PERIOD	N= 66	N= 64	N= 63
LVEF Decline $\geq 10\%$ and drop to less than 50%	3 (4.5%)	2 (3.1%)	2 (3.2%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (1.6%)
FOLLOW-UP PERIOD	N= 21	N= 18	N= 23
LVEF Decline $\geq 10\%$ and drop to less than 50%	1 (4.8%)	3 (16.7%)	1 (4.3%)
Symptomatic LV Dysfunction (CHF)	0	1 (5.6%)	0

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology
Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ [301.796.3994](tel:301.796.3994) (phone) ● [301.796.9845](tel:301.796.9845) (fax) | ✉ amy.tilley@fda.hhs.gov

Never doubt that a small group of thoughtful, committed people can change the world; indeed, it's the only thing that ever has.

--Margaret Mead, The Wagon and the Star

From: Josephine Ing [mailto:ing.josephine@gene.com]
Sent: Tuesday, August 06, 2013 3:41 PM
To: Cortazar, Patricia
Cc: Josephine Ing (ing.josephine@gene.com); Tilley, Amy
Subject: Re: Urgent IR

Dear Dr. Cortazar,

Pls see below. The official submission to the BLA will follow tomorrow.

The Sponsor's interpretation of Table 3 includes AE LVD or CHF reporting as well as LVEF declines $\geq 10\%$ and drop to less than 50% for all patients in the specified study period (neoadjuvant, adjuvant, and follow-up).

The table has been updated with AE LVD or CHF reporting as well as LVEF declines $\geq 10\%$ and drop to less than 50% for each of the study periods in which the onset was reported. If a patient experienced two separate

events (with recovery) in two separate periods, the event would be counted once in each period.

For clarity and completeness, the Sponsor has added an additional row to Table 3 titled “TOTAL” so the interpretation of cardiac events is more accurate. For instance, if you add up the events in Arm B, there are a total of 12 events experienced across 9 patients.

If the patient had an AE LVD or CHF across two periods, the event is counted once per period. For example, Patient 2027 experienced an event in both the neoadjuvant and follow-up period. In the table below, this event is counted once in the neoadjuvant period and once in the follow-up period. In the TOTAL row, this patient is only counted once.

The text written in red represents changes made and the green text is additional data provided by the Sponsor. Patients entering the adjuvant period are reported in Table 3 of the CSR update and Table 4 of the Safety Update report.

Table 3 Cardiac Toxicity in NEOSPHERE (neoadjuvant, adjuvant and follow up periods)

	T+D N=107	T+P+D N=107	T+P N=108	P+D N=94
NEOADJUVANT PERIOD	107	107	108	94
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%) asymptomatic	1 (0.9%)	3 (2.8%)	0	1 (1.1%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0
ADJUVANT PERIOD	103	102	94	88
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%) asymptomatic	1 (1.0%)	6 (6.1%)	0	5 (5.3%)
Symptomatic LV Dysfunction (CHF)	0	0	0	0
FOLLOW-UP PERIOD	97	99	96	86
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%) asymptomatic	0	3 (3.0%)	1 (1.0%)	2 (2.3%)
Symptomatic LV Dysfunction (CHF)	0	0	0	0
TOTAL	107	107	108	94
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%) asymptomatic	2 (1.9%)	9 (8.4%)	1 (0.9%)	7 (7.4%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0

The data provided in Table A provides patient identification to support the numbers presented in Table 3. These patient identifications are based on AE LVD or CHF as well as LVEF declines $\geq 10\%$ and a drop to less than 50% in the study period in which the AE began. Further details are captured in the patient narratives.

Table A Patients with Cardiac Toxicity in NEOSPHERE (neoadjuvant, adjuvant and follow up periods)

	T+D N=107	T+P+D N=107	T+P N=108	P+D N=94
NEOADJUVANT PERIOD				
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%) asymptomatic	4000	2027 3851 4401	-	1960
Symptomatic LV Dysfunction (CHF)	-	-	1760	-
ADJUVANT PERIOD				
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%) asymptomatic	3821	2043 2362 3823 3845 3851 4005	-	1960 2287 2743 3811 4016
Symptomatic LV Dysfunction (CHF)	-	-	-	-
FOLLOW-UP PERIOD				
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%) asymptomatic	-	2027 3853 4401	3049	2022 4006
Symptomatic LV Dysfunction (CHF)	-	-	-	-
TOTAL (patient may have experienced an event in more than one period)				

		2027		1960
		2043		2022
		2362		2287
		3823		2743
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%) asymptomatic	3821	3845	3049	3811
	4000	3851		4006
		3853		4016
		4005		
		4401		
Symptomatic LV Dysfunction (CHF)	-	-	1760	-

Additional information

- Patients 2027, 3851, 1960 and 4401 experienced two separate events in separate study periods all of which recovered (4 patients with 8 events).
- Patient 2362 experienced a LVEF decline which spanned two study periods and is correctly reported as one event.
- Patient 1760 (coronary artery stent present as baseline) experienced an on-going LVD throughout the neoadjuvant and follow-up treatment periods.

Regards

Josephine

On Mon, Aug 5, 2013 at 2:54 PM, Cortazar, Patricia
 <Patricia.Cortazar@fda.hhs.gov> wrote:

Dear Josephine,

Could you please ask your team to provide the information missing in the table below? Basically, we need to know how many patients entered the follow-up period and the number of patients who had cardiac events as described in the table. Also, please let us know if you disagree with the numbers already in the table. I will appreciate if you can respond by tomorrow.

Thank you,

Patricia Cortazar

Table 3 Cardiac Toxicity in NEOSPHERE (neoadjuvant, adjuvant and follow up periods)

	T+D N=107	T+P+D N=107	T+P N=108	P+D N=94
NEOADJUVANT PERIOD	107	107	108	94
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%)	1 (0.9%)	3 (2.8%)	0	1 (1.1%)
asymptomatic				
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0
ADJUVANT PERIOD	99	98	92	84
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%)	1 (1.0%)	6 (6.1%)	0	1 (1.2%)
asymptomatic				
Symptomatic LV Dysfunction (CHF)	0	0	0	0
FOLLOW-UP PERIOD				
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%)		2		

asymptomatic
Symptomatic LV Dysfunction (CHF)

0	0

0

Patricia Cortazar, M.D.

U.S. Food and Drug Administration

Center for Drug Evaluation and Research

Office of Hematology Oncology Products (OHOP)

Division of Oncology Products 1 (DOP1)

Clinical Team Leader

Breast Oncology Group

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--

Josephine Ing | Product Development Regulatory | Genentech, Inc. | 📞: [\(650\) 225-2330](tel:(650)225-2330) |

📧: (b) (6)

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Josephine Ing | Product Development Regulatory | Genentech, Inc. | 📞: (650) 225-2330 |

📧: (b) (6)

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/s/

AMY R TILLEY
08/12/2013

From: Tilley, Amy
 Sent: Thursday, August 08, 2013 2:52 PM
 To: 'Josephine Ing' ing.josephine@gene.com
 Subject: ****URGENT**** sBLA 125409 Perjeta - Clinical IR sent 8-8-13

Importance: High

Follow Up Flag: Follow up
 Due By: Friday, August 09, 2013 4:00 PM
 Flag Status: Flagged
 Josephine,

Please tell your team that we liked very much the way they submitted the cardiac safety information. Can you send us a similar table for the TRYPHAENA study?

We would need a response by COB tomorrow, Washington, DC time.

As always, submit your response both via email and as an official response to the BLA.

Cardiac Toxicity in TRYPHAENA (neoadjuvant, adjuvant and follow up periods)

	FEC x 3→D x 3 Per + Tras x 6	FEC x 3→D x 3 + Per+Tras x 3	TCH x 6 + Per x 6
NEOADJUVANT PERIOD	N= 72	N= 75	N= 76
LVEF Decline $\geq 10\%$ and drop to less than 50%	4 (5.6%)	4 (5.3%)	3 (3.9%)
Symptomatic LV Dysfunction (CHF)	1 (1.4%)	2 (2.7%)	
ADJUVANT PERIOD	N= 66	N= 64	N= 63
LVEF Decline $\geq 10\%$ and drop to less than 50%	3 (4.5%)	2 (3.1%)	2 (3.2%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (1.6%)
FOLLOW-UP PERIOD	N= 21	N= 18	N= 23
LVEF Decline $\geq 10\%$ and drop to less than 50%	1 (4.8%)	3 (16.7%)	1 (4.3%)
Symptomatic LV Dysfunction (CHF)	0	1 (5.6%)	0

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

*Never doubt that a small group of thoughtful, committed people can
change the world; indeed, it's the only thing that ever has.*

--Margaret Mead, The Wagon and the Star

From: Josephine Ing [mailto:ing.josephine@gene.com]
Sent: Tuesday, August 06, 2013 3:41 PM
To: Cortazar, Patricia
Cc: Josephine Ing (ing.josephine@gene.com); Tilley, Amy
Subject: Re: Urgent IR

Dear Dr. Cortazar,

Pls see below. The official submission to the BLA will follow tomorrow.

The Sponsor's interpretation of Table 3 includes AE LVD or CHF reporting as well as LVEF declines $\geq 10\%$ and drop to less than 50% for all patients in the specified study period (neoadjuvant, adjuvant, and follow-up).

The table has been updated with AE LVD or CHF reporting as well as LVEF declines $\geq 10\%$ and drop to less than 50% for each of the study periods in which the onset was reported. If a patient experienced two separate events (with recovery) in two separate periods, the event would be counted once in each period.

For clarity and completeness, the Sponsor has added an additional row to Table 3 titled "TOTAL" so the interpretation of cardiac events is more accurate. For instance, if you add up the events in Arm B, there are a total of 12 events experienced across 9 patients.

If the patient had an AE LVD or CHF across two periods, the event is counted once per period. For example, Patient 2027 experienced an event in both the neoadjuvant and follow-up period. In the table below, this event is counted once in the neoadjuvant period and once in the follow-up period. In the TOTAL row, this patient is only counted once.

The text written in red represents changes made and the green text is additional data provided by the Sponsor. Patients entering the adjuvant period are reported in Table 3 of the CSR update and Table 4 of the Safety Update report.

Table 3 Cardiac Toxicity in NEOSPHERE (neoadjuvant, adjuvant and follow up periods)

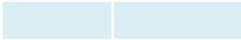
	T+D N=107	T+P+D N=107	T+P N=108	P+D N=94
NEOADJUVANT PERIOD	107	107	108	94
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%) asymptomatic	1 (0.9%)	3 (2.8%)	0	1 (1.1%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0
ADJUVANT PERIOD	103	102	94	88
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%) asymptomatic	1 (1.0%)	6 (6.1%)	0	5 (5.3%)
Symptomatic LV Dysfunction (CHF)	0	0	0	0
FOLLOW-UP PERIOD	97	99	96	86
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%) asymptomatic	0	3 (3.0%)	1 (1.0%)	2 (2.3%)
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TOTAL	107	107	108	94
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%) asymptomatic	2 (1.9%)	9 (8.4%)	1 (0.9%)	7 (7.4%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0

The data provided in Table A provides patient identification to support the numbers presented in Table 3. These patient identifications are based on AE LVD or CHF as well as LVEF declines $\geq 10\%$ and a drop to less than 50% in the study period in which the AE began. Further details are captured in the patient narratives.

Table A Patients with Cardiac Toxicity in NEOSPHERE (neoadjuvant, adjuvant and follow up periods)

	T+D N=107	T+P+D N=107	T+P N=108	P+D N=94
NEOADJUVANT PERIOD				
LV Dysfunction (LVEF Decline $\geq 10\%$ and drop to less than 50%) asymptomatic	4000	2027 3851	-	1960

		4401		
Symptomatic LV Dysfunction (CHF)	-	-	1760	-
ADJUVANT PERIOD				
		2043		1960
		2362		2287
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%) asymptomatic	3821	3823	-	2743
		3845		3811
		3851		4016
		4005		
Symptomatic LV Dysfunction (CHF)	-	-	-	-
FOLLOW-UP PERIOD				
		2027		2022
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%) asymptomatic	-	3853	3049	4006
		4401		
Symptomatic LV Dysfunction (CHF)	-	-	-	-
TOTAL (patient may have experienced an event in more than one period)				
		2027		1960
		2043		2022
		2362		2287
		3823		2743
LV Dysfunction (LVEF Decline \geq10% and drop to less than 50%) asymptomatic	3821	3845	3049	3811
	4000	3851		4006
		3853		4016
		4005		
		4401		
Symptomatic LV Dysfunction (CHF)	-	-	1760	-



Additional information

- Patients 2027, 3851, 1960 and 4401 experienced two separate events in separate study periods all of which recovered (4 patients with 8 events).
- Patient 2362 experienced a LVEF decline which spanned two study periods and is correctly reported as one event.
- Patient 1760 (coronary artery stent present as baseline) experienced an on-going LVD throughout the neoadjuvant and follow-up treatment periods.

Regards
Josephine

On Mon, Aug 5, 2013 at 2:54 PM, Cortazar, Patricia <Patricia.Cortazar@fda.hhs.gov> wrote:

Dear Josephine,

Could you please ask your team to provide the information missing in the table below? Basically, we need to know how many patients entered the follow-up period and the number of patients who had cardiac events as described in the table. Also, please let us know if you disagree with the numbers already in the table. I will appreciate if you can respond by tomorrow.

Thank you,
Patricia Cortazar

Table 3 Cardiac Toxicity in NEOSPHERE (neoadjuvant, adjuvant and follow up periods)

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ADJUVANT PERIOD	99	98	92	84
LV Dysfunction (LVEF Decline \geq 10% and drop to less than 50%) asymptomatic	1 (1.0%)	6 (6.1%)	0	1 (1.2%)
Symptomatic LV Dysfunction (CHF)	0	0	0	0
FOLLOW-UP PERIOD				
LV Dysfunction (LVEF Decline \geq 10% and drop to less than 50%)		2		

asymptomatic

Symptomatic LV Dysfunction (CHF)

0	0

0

Patricia Cortazar, M.D.
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products (OHOP)
Division of Oncology Products 1 (DOP1)
Clinical Team Leader
Breast Oncology Group

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Silver Spring, MD 20993
[301-796-1346](tel:301-796-1346)

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Josephine Ing | Product Development Regulatory | Genentech, Inc. | [p:\(650\) 225-2330](tel:(650)225-2330) |
m: (b) (6)

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/s/

AMY R TILLEY
08/08/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 26, 2013
Application Number: sBLA 125409/51
Product Name: Perjeta
Sponsor/Applicant Name: Genentech, Inc.

Subject: Request for Informal Teleconference to discuss the upcoming ODAC in September to review the sBLA for Perjeta for the neoadjuvant treatment of breast cancer

FDA Participants :

Robert Justice, M.D., Director, DOP1
Amna Ibrahim, M.D., Deputy Director, DOP1
Patricia Cortazar, M.D., Clinical Team Leader
Laleh Amiri-Kordestani, M.D., Clinical Reviewer
Shenghui Tang, Ph.D., Biostatistics Team Leader
Lijun Zhang, Ph.D., Biostatistics Reviewer
Amy Tilley, Regulatory Project Manager

Genentech Participants :

Mark (Kip) Benyunes, M.D., Senior Group Medical Director, Clinical Science
Dietmar Berger, M.D., Vice President, Oncology HER Franchise Development
Sandra Horning, M.D., Senior Vice President, Oncology
Josephine Ing, Associate Group Director, Product Development Regulatory
Karen Jones, Vice President, Product Development Regulatory
Colin Neate, M.Sc., Senior Statistical Scientist, Biostatistics
Teresa Perney, Ph.D., Director Product Development Regulatory
Graham Ross, M.D., Global Clinical Science Leader, Clinical Science

1.0 BACKGROUND:

As the approval pathway in the neoadjuvant treatment of breast cancer is new, Genentech appreciates the guidance provided thus far regarding potential review issues but also acknowledges the complexity and breadth of topics that may be discussed at the advisory committee to be held September 12, 2013. In order to prepare for a more effective meeting, Genentech would like to coordinate with the Agency to ensure that both parties meet their objectives to facilitate a productive discussion and to achieve an agreeable outcome.

2.0 DISCUSSION:

1. What are the topics that you plan to discuss?

FDA Response/Mtg Discussion:

During the September 2013 ODAC, the Agency will be discussing the introduction, background, and neoadjuvant trials of pCR as the Endpoint to support Accelerated Approval.

Also being discussed will be the Draft Guidance, how this application differs from the Draft Guidance, and what will be needed for an NME.

2. Will you have external experts presenting?

FDA Response/Mtg Discussion:

No

3. How does FDA intend to structure the agenda for the ODAC?

FDA Response/Mtg Discussion:

a. How much time will be allocated for the Sponsor presentation?

FDA Response/Mtg Discussion:

Sponsors are generally allotted 45 mins for their ODAC presentations.

b. Who will be presenting for FDA?

FDA Response/Mtg Discussion:

**Patricia Cortazar, M.D., Clinical Team Leader
Laleh Amiri-Kordestani, M.D., Clinical Reviewer (Efficacy)
Suparna Wedam, M.D., Clinical Reviewer (Safety)**

4. On which specific safety issues does FDA intend to focus?

FDA Response/Mtg Discussion:

The safety issue the Agency will be focusing on is Cardio toxicity.

Do you anticipate focusing primarily on the neoadjuvant period or do you plan to include a discussion of the adjuvant and post-treatment follow-up periods during which pertuzumab is not given?

FDA Response/Mtg Discussion:

The Agency will focus on both the neoadjuvant and adjuvant/post-treatment follow-up periods.

5. What approach will FDA use to present efficacy?

FDA Response/Mtg Discussion:

The approach the Agency will use to present efficacy will be the discussion of the following topics:

- **Agency preferred endpoints**
- **Support of the protocols defined endpoint**
- **Subgroup analyses of HR +**
- **Supportive trials**
- **Neoadjuvant trial in the context of other trials**
- **Confirmatory trial design**

3.0 ACTION ITEMS:

None

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/s/

AMY R TILLEY
08/06/2013

From: Cortazar, Patricia
Sent: Monday, August 05, 2013 5:54 PM
To: Josephine Ing (ing.josephine@gene.com)
Cc: Tilley, Amy
Subject: Urgent IR Perjeta sBLA 125409/51 sent 8-5-13

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, August 06, 2013 3:00 PM
Flag Status: Red

Dear Josephine,

Could you please ask your team to provide the information missing in the table below? Basically, we need to know how many patients entered the follow-up period and the number of patients who had cardiac events as described in the table. Also, please let us know if you disagree with the numbers already in the table. I will appreciate if you can respond by tomorrow.

Thank you,
 Patricia Cortazar

Table 3 Cardiac Toxicity in NEOSPHERE (neoadjuvant, adjuvant and follow up periods)

	T+D N=107	T+P+D N=107	T+P N=108	P+D N=94
NEOADJUVANT PERIOD	107	107	108	94
LV Dysfunction (LVEF Decline \geq 10% and drop to less than 50%) asymptomatic	1 (0.9%)	3 (2.8%)	0	1 (1.1%)
Symptomatic LV Dysfunction (CHF)	0	0	1 (0.9%)	0
ADJUVANT PERIOD	99	98	92	84
LV Dysfunction (LVEF Decline \geq 10% and drop to less than 50%) asymptomatic	1 (1.0%)	6 (6.1%)	0	1 (1.2%)
Symptomatic LV Dysfunction (CHF)	0	0	0	0
FOLLOW-UP PERIOD				
LV Dysfunction (LVEF Decline \geq 10% and drop to less than 50%) asymptomatic		2		
Symptomatic LV Dysfunction (CHF)	0	0		0

Patricia Cortazar, M.D.
 U.S. Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Hematology Oncology Products (OHOP)
 Division of Oncology Products 1 (DOP1)

Clinical Team Leader
Breast Oncology Group

10903 New Hampshire Avenue
WO 22 Room 2333
Silver Spring, MD 20993
301-796-1346

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/s/

AMY R TILLEY
08/06/2013

From: Tilley, Amy
Sent: Wednesday, July 31, 2013 3:14 PM
To: 'Josephine Ing'
Subject: *TIME SENSITIVE* sBLA 125409 51 Perjeta - Clinical Safety IR

Follow Up Flag: Follow up
Due By: Friday, August 02, 2013 3:30 PM
Flag Status: Red
Josephine,

Below is a Clinical Safety Information Request for sBLA 125409 51 Perjeta.

We respectfully request your response **no later than 3 pm on Friday, August 9th or sooner (preferably by August 2nd).**

Please clarify the number of patients in NEOSPHERE that completed adjuvant therapy in each treatment arm. As per the updated CSR (cutoff date March 9, 2012) it appears that 98 patients in Arm A, 90 patients in Arm B, 88 patients in Arm C and 73 patients in Arm D completed adjuvant trastuzumab therapy (Table 13 in Section 5.2.1). The most recent safety update with a cutoff date of February 28, 2013 lists that 98 patients in Arm A, 94 patients in Arm B, 90 patients in Arm C and 74 patients in Arm D as completing adjuvant therapy (Table 4 in Section 2.2.1).

In addition, please clarify the number of patients that entered the adjuvant treatment phase in each treatment arm and the number of patients that completed adjuvant FEC therapy.

Your prompt response is greatly appreciated.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

Never doubt that a small group of thoughtful, committed people can change the world; indeed, it's the only thing that ever has.

--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
07/31/2013

From: Cortazar, Patricia
Sent: Wednesday, July 24, 2013 4:39 PM
To: Josephine Ing (ing.josephine@gene.com)
Cc: Tilley, Amy
Subject: Put in DARRTs & Print for AP Urgent IR

Follow Up Flag: Follow up
Due By: Thursday, July 25, 2013 12:00 PM
Flag Status: Red

Dear Josephine,

We have an urgent request. Please submit the following pathology reports (English version) from the TRYPHAENA study. We need a response hopefully by Friday.

Patient	Site#
3127	158960
3131	158960
3133	158960
3700	158979
3856	166612
3859	166612
3863	166612
3889	167638
3896	167638
3993	158960

Thank you,

Patricia Cortazar, M.D.
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology Oncology Products (OHOP)
Division of Oncology Products 1 (DOP1)
Clinical Team Leader
Breast Oncology Group

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Silver Spring, MD 20993
301-796-1346

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/s/

AMY R TILLEY
07/29/2013

From: Josephine Ing ing.josephine@gene.co

Sent: Tuesday, July 23, 2013 3:27 PM

To: Tilley, Amy

Subject: Re: Question re the APHINITY Trial - Perjeta sBLA 125409/51
Amy,

As of today, July 23, 2013, 4793/4800 patients are enrolled in APHINITY. Nineteen patients are currently in screening. The last patient entered screening on July 19, 2013.

The latest surgery date among the 19 patients in screening is July 18, 2013. Considering the allowed 8-week screening period per protocol, we expect the last patient to be enrolled by September 12, 2013 based on the latest surgery date.

Thanks

Josephine

On Tue, Jul 23, 2013 at 9:05 AM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:
Josephine,

Can you provide us with the status of the APHINITY trial in terms of accrual? Are you still accruing patients or is the trial fully accrued?

If you are still accruing, when do you think the trial will be fully accrued?

Thanks.

Amy

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/s/

AMY R TILLEY
07/23/2013

From: Tilley, Amy
Sent: Wednesday, July 17, 2013 10:13 AM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: RE: Perjeta sBLA 125409/51 - Request for Informal TCON Scheduled

Importance: High
Josephine,

Per our telephone conversation yesterday and your emailed request below, we have scheduled an informal TCON with Genentech on July 26, 2013 from 3 - 4 pm. Please note that there may be a brief delay in our calling in to the TCON as we generally have a 10 - 15 min internal discussion prior to calling a sponsor.

Our tentative attendees are as follows:

Richard Pazdur, MD, Office Director, OHOP
Robert Justice, MD, Division Director, DOP1
Amna Ibrahim, MD, Deputy Division Director, DOP1
Patricia Cortazar, MD, Clinical Team Leader
Laleh Amiri Kordestani, MD, Clinical Reviewer
Suparna Wedam, MD, Clinical Reviewer
Shenghui Tang, PhD, Biostatistics Team Leader
Lijun Zhang, PhD, Biostatistics Reviewer
Amy Tilley, Regulatory Project Manager

Kindly reply to this email with Genentech's attendees and the call in information.

Thank you.

Amy

From: Josephine Ing [<mailto:ing.josephine@gene.com>]
Sent: Tuesday, July 16, 2013 2:05 AM
To: Cortazar, Patricia
Cc: Tilley, Amy
Subject: Perjeta sBLA 125409/51 - Request for Informal Teleconference

Dear Dr. Cortazar,

We are looking forward to a robust clinical and scientific discussion at the upcoming ODAC in September to review the sBLA for Perjeta for the neoadjuvant treatment of breast cancer.

As the approval pathway in this setting is new, we appreciate the guidance provided thus far regarding potential review issues but also acknowledge the complexity and breadth of topics that may be discussed at the advisory committee. In order to prepare for a more effective meeting, we would like to coordinate with you to ensure that we both meet our objectives to facilitate a productive discussion and to achieve an agreeable outcome.

We would like to request an informal 1-hour teleconference with relevant members of the FDA review team on July 30th, July 31st, or August 1st between 9:00AM – 2:00PM EDT to better understand and gain alignment where possible on the key issues that will be put forward.

We would like the Agency's input on the following questions:

1. What are the topics that you plan to discuss?
2. Will you have external experts presenting?
3. How does FDA intend to structure the agenda for the ODAC?
 - a. How much time will be allocated for the Sponsor presentation?
 - b. Who will be presenting for FDA?
4. On which specific safety issues does FDA intend to focus? Do you anticipate focusing primarily on the neoadjuvant period or do you plan to include a discussion of the adjuvant and post-treatment follow-up periods during which pertuzumab is not given?
5. What approach will FDA use to present efficacy?

I look forward to your response.

Kind Regards,

Josephine

--

Josephine Ing | Product Development Regulatory | Genentech, Inc. | 📞: (650) 225-2330 |

📧: (b) (6)

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/s/

AMY R TILLEY
07/17/2013

From: Tilley, Amy
Sent: Tuesday, July 16, 2013 2:28 PM
To: 'Josephine Ing' ing.josephine@gene.com
Cc: Cortazar, Patricia
Subject: *TIME SENSITIVE - NEED TODAY* sBLA 125409/51 Perjeta - Clinical IR

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, July 16, 2013 5:00 PM
Flag Status: Flagged

Josephine,

Please email to Dr. Cortazar the last version of the APHINITY trial including the statistical analysis plan.

We request this information be emailed today if possible.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

*Never doubt that a small group of thoughtful, committed people can change the world;
indeed, it's the only thing that ever has.*

--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
07/16/2013

From: Tilley, Amy
Sent: Wednesday, July 03, 2013 4:08 PM
To: 'Josephine Ing'
Subject: *Time Sensitive* sBLA 125409 51 - Clinical IR sent 7-3-13

Importance: High
Josephine,

Please provide information on the number of patients who had the following features in all treatment arms:

- 1) axillary node fine needle aspiration at baseline,
- 2) sentinel lymph node biopsy before neoadjuvant therapy
- 3) sentinel lymph node biopsy after neoadjuvant therapy
- 4) post neoadjuvant sentinel lymph node biopsy followed by axillary surgical dissection

We respectfully request your response **no later than 3 pm on July 10, 2013.**

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
07/03/2013

From: Tilley, Amy
Sent: Tuesday, July 02, 2013 2:21 PM
To: 'Josephine Ing'
Subject: sBLA 125409 51 Perjeta - Safety IR sent 7-2-13

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, July 10, 2013 3:00 PM
Flag Status: Flagged
Josephine,

Below is the Safety Information Request for sBLA 125409/51 Perjeta.

Please provide dose intensity for docetaxel received by patients in WO20697. This information was provided for patients on Arm C (T+P) in the updated CSR (Table 19) but was not provided for patients on Arms A, B and D in the primary or updated CSR.

We respectfully request your response **by 3 pm on July 10, 2013.**

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
07/02/2013

From: Tilley, Amy
Sent: Friday, June 28, 2013 2:14 PM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: sBLA 125409 51 Perjeta - No PLR Format Issues

Importance: High
Josephine,

Regarding the Filing Communication Letter sent to you on June 26th, the purpose of this email is to communicate to you that there were no PLR format deficiencies identified in the review of the proposed PI.

Kind Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
06/28/2013

From: Tilley, Amy
Sent: Wednesday, June 26, 2013 4:34 PM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: *Time Sensitive* sBLA 125409 51 - Safety IR due July 2nd

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, July 02, 2013 3:00 PM
Flag Status: Red
Josephine,

Below is the safety information request for Perjeta sBLA 125409 51. Please respond by **no later than 3 pm on 7-2-13.**

Please provide further information for Patient #3580 on Protocol BO22280 who developed pneumonitis in the neoadjuvant setting. Provide clinical course including how the diagnosis of pneumonitis and attribution to docetaxel were made.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
06/26/2013



BLA 125409/51

FILING COMMUNICATION

Genentech, Inc.
Attention: Josephine Ing
Sr. Scientist, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Ing:

Please refer to your Supplemental Biologics License Application (sBLA) dated April 30, 2013, received May 1, 2013, submitted under section 351(a) of the Public Health Service Act for Perjeta® (pertuzumab).

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Priority**. Therefore, the user fee goal date is October 31, 2013.

We are reviewing your supplemental application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. The PLR format issues will be sent in a separate information request. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 10, 2013.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your supplement. Following a review of the supplement, we will advise you in writing of any action we have taken and request additional information if needed.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list

each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
06/26/2013

From: Fagbami, Modupe
Sent: Wednesday, June 19, 2013 10:31 AM
To: 'ing.josephine@gene.com'
Cc: Tilley, Amy; Alebachew, Elleni; Venugopal, Rajesh
Subject: sBLA 125409-51 Perjeta- Clinical IR
Importance: High

Hi Josephine,

Below is a Clinical Information Request for sBLA 125409-51 Perjeta.

Please send information for patients 2743, 3853 and 4006 regarding recovery of their LVEF. Please provide LVEF value and dates for LVEF assessment.

Send your response to the above Clinical IR **on or before COB, Wednesday, June 26, 2013.**

Please reply all when you are responding to this IR.

Kindly let me know if you have any questions.

Thanks

Modupe O. Fagbami (Sent on behalf of Amy Tilley)

RPM

Division of Oncology Products 1

Office of Hematology and Oncology Products

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 2108

Silver Spring, Maryland 20993

Phone: 301-796-1348

Fax: 301-796-9845

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/s/

MODUPE O FAGBAMI
06/19/2013

From: Tilley, Amy
Sent: Monday, June 17, 2013 5:58 PM
To: 'Josephine Ing'
Subject: sBLA 125409-51 Perjeta - Clinical Information Request

Follow Up Flag: Follow up
Due By: Friday, June 21, 2013 1:00 PM
Flag Status: Red
Josephine,

Below is a Clinical Information Request for sBLA 125409-51 Perjeta.

You have reported that in your audit of 3 sites, there were major findings involving non-compliance with GCP.

Please specify what these major findings were and what corrective and preventive actions were undertaken.

We request your response to the above Clinical Information Request as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
06/17/2013

From: Tilley, Amy
Sent: Friday, June 14, 2013 10:14 AM
To: 'Josephine Ing'
Cc: Alebachew, Elleni; Fagbami, Modupe; Venugopal, Rajesh
Subject: sBLA 125409-51 Perjeta- Clinical (Safety) IR
Josephine,

Below is the Clinical Information Request for sBLA 125409-51 Perjeta.

1. Why are there 157 rows that are blank in the AEEXT database?
2. Please provide more information for patient 4009/116807 with a diagnosis of lung infiltration (interstitial infiltration of lung). Please provide details regarding clinical presentation, work up and clinical course until resolution of AE.
3. Please provide more information for patient 3078/116801 (primary biliary cirrhosis). Please provide details regarding clinical presentation, work up, and clinical course.

We respectfully request your response to the above Clinical IR **no later than 10 am on Friday, June 21, 2013 or sooner.**

As I will be attending a seminar Tuesday through Thursday of next week please reply to all when responding.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
06/14/2013

From: Tilley, Amy
Sent: Tuesday, June 11, 2013 5:24 PM
To: 'Josephine Ing'
Subject: sBLA 125409-51 - Statistical Information Request

Follow Up Flag: Follow up
Due By: Friday, June 28, 2013 12:00 AM
Flag Status: Flagged
Josephine,

Reference is made to the sBLA125409 submitted on 01 May 2013. The following requests are for the pivotal study WO20697. Please respond **by June 28, 2013**.

1. Please perform a re-randomization test for pCR per three definitions, i.e., bpCR, tpCR, and GBG pCR. Submit the SAS or R program with the re-randomization test report.
2. We have identified the following 21 patients with DCIS/LCIS data missing for pCR assessment (dataset: EFEXEFF). Please clarify the reason for data missing.

Patient IDs:

2367, 4401, 2500, 2505, 2510, 2513, 2514, 2515, 2516, 2581, 3803,
3804, 3843, 3845, 3846, 3882, 3525, 3940, 4060, 2982, 2486

3. Please submit individual patient stratification data used in the IVRS randomization system.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
06/11/2013

Tilley, Amy

From: Tilley, Amy
Sent: Monday, June 10, 2013 4:22 PM
To: 'Josephine Ing'
Subject: *URGENT* sBLA 125409-51 Perjeta - OSI Information Request
Importance: High
Follow Up Flag: Follow up
Due By: Friday, June 14, 2013 12:00 AM
Flag Status: Flagged

Josephine,

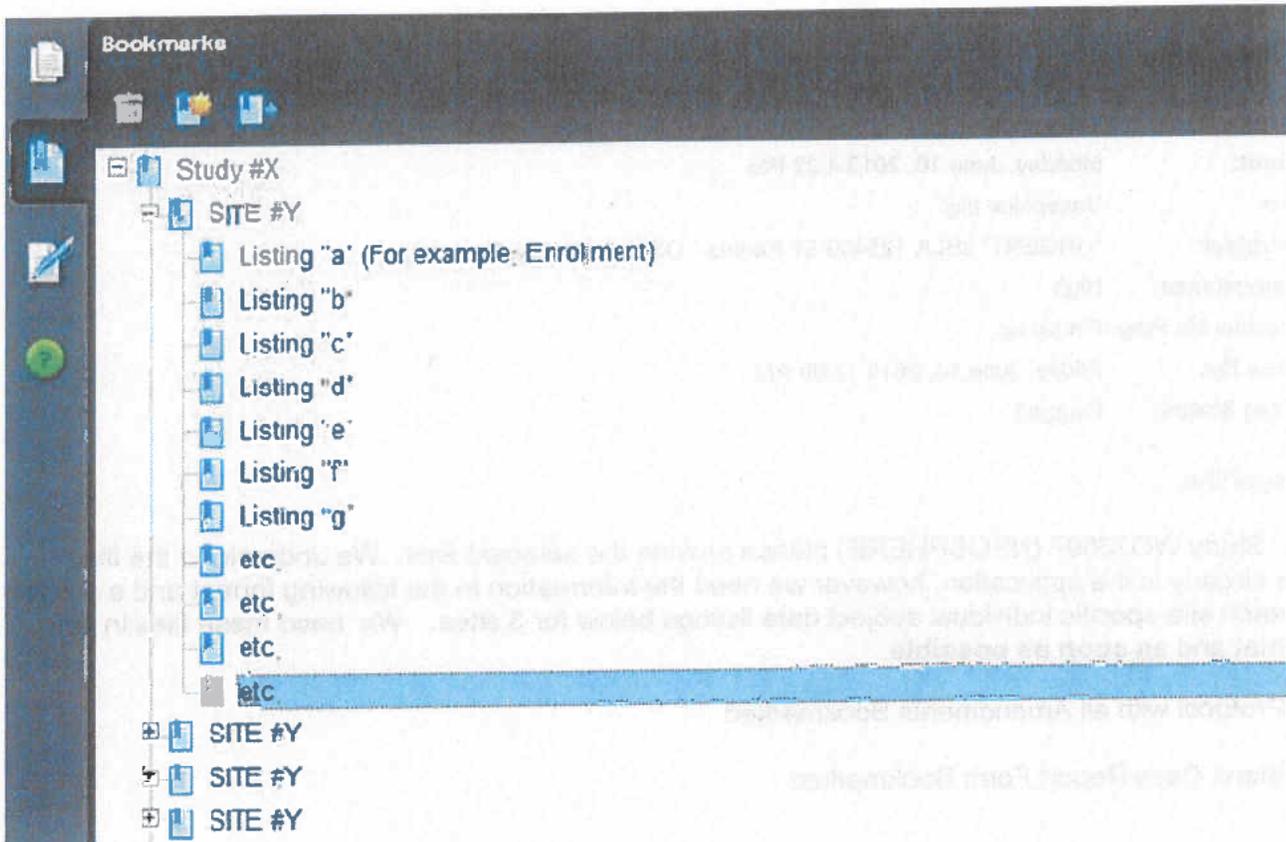
For Study WO20697 (NEOSPHERE) please provide the selected files. We understand the files are already in the application, however we need the information in the following format and a subset of each site-specific individual subject data listings below for 3 sites. We need these files in pdf format and **as soon as possible**.

1. Protocol with all Amendments Bookmarked
2. Blank Case Report Form Bookmarked
3. Data listings organized by Site (see below): For the following sites-
 - 116798 (Dr. Luca Gianni)
 - 116801 (Dr. Tadeusz Pienkowski)
 - 116814 (Dr. Ana Lluch Hernandez)

Site-Specific Individual subject data listings as follows:

- Randomization
- Protocol Deviations (Major and Minor)
- Demographic Data
- Individual Efficacy Response Data (Pathologic Response Assessment)
- Adverse Events/Serious Adverse Events
- Listing of individual Laboratory Measurements
- Compliance and drug concentration data
- Con Meds
- Disposition of all Subjects

Site-specific individual subject Data Listings for requested Sites only. Organized by site as illustrated here.



Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
06/10/2013

From: Tilley, Amy
Sent: Friday, June 07, 2013 11:00 AM
To: 'Josephine Ing'
Subject: *Urgent* sBLA 125409-51 Perjeta - Need Contact Info for the following Foreign Sites

Importance: High

Follow Up Flag: Follow up
Due By: Monday, June 10, 2013 12:00 PM
Flag Status: Flagged

Attachments: Picture (Metafile)
[Josephine,](#)

We are in need of the telephone numbers and email addresses for the POC's at the following foreign sites:

Site # (Name,Address, Phone number, email, fax#)	Protocol ID
116798 (Dr LUCA GIANNI, ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI, MILANO, Italy)	WO20697
116801 (Dr TADEUSZ PIENKOWSKI, CENTRUM ONKOLOGII - INST.IM. MARIII SKLODOWSKIEJ-CURIE, WARSZAWA, Poland)	WO20697
116814 (Dr ANA LLUCH HERNANDEZ , HOSPITAL CLINICO UNIVERSITARIO DE VALENCIA, VALENCIA , Spain)	WO20697

We respectfully request this information as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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Appears this way on original

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/s/

AMY R TILLEY
06/07/2013

From: Tilley, Amy
Sent: Monday, June 03, 2013 5:43 PM
To: 'Josephine Ing'
Subject: sBLA 125409-051 Perjeta - Clinical Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Friday, June 07, 2013 12:00 AM
Flag Status: Flagged
[Josephine,](#)

Please submit complete information regarding Patient 1747 death . We need detailed information on the hospital admission including clinical diagnosis, treatment, laboratory and cardiac assessment during hospitalization.

Please provide information on all cases of hepatotoxicity seen patients treated with Pertuzumab across all of your Pertuzumab clinical trials.

We respectfully request your response to this email as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
06/03/2013

From: Tilley, Amy
Sent: Tuesday, May 21, 2013 4:30 PM
To: 'Josephine Ing'
Subject: RE: sBLA 125409/051 Perjeta – Revised PAS Acknowledgement Letter

Attachments: Corrected sBLA 125409–51 Perjeta PAS [Efficacy] – Ack Ltr.pdf
Josephine,

Please disregard the previously emailed Prior Approval Supplement Acknowledgement Letter for sBLA 125409/051 Perjeta.

Attached is the revised letter containing the corrected filing date.

My apologies for any confusion this may have caused.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

From: Josephine Ing [mailto:ing.josephine@gene.com]
Sent: Tuesday, May 21, 2013 11:24 AM
To: Tilley, Amy
Subject: Re: sBLA 125409/051 Perjeta - PAS Acknowledgement Letter

Dear Amy

Thank you for sending an electronic copy of this letter. I confirm that the USPI has been submitted in SPL format. I will look into submitting Form FDA 3674, "Certification of Compliance".

Also, I'd like to clarify whether the filing date should be June 30, 2013 in accordance with 21 CFR 601.2 (a) unless you notify us within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review. Please advise.

Thanks
Josephine

On Tue, May 21, 2013 at 7:35 AM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:
Josephine,

Below is a courtesy copy of the Prior Approval Supplement Acknowledgement Letter for the sBLA 125409/051 Perjeta. An official letter is forth coming in the mail.

Kind Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ [301.796.3994](tel:301.796.3994) (phone) • [301.796.9845](tel:301.796.9845) (fax) | ✉ amy.tilley@fda.hhs.gov

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--Margaret Mead, The Wagon and the Star

--

Josephine Ing | Product Development Regulatory | Genentech, Inc. | ☎p: (650) 225-2330 |
✉m: (b) (6)



BLA 125409/051

**PRIOR APPROVAL SUPPLEMENT -
ACKNOWLEDGEMENT**

Genentech, Inc.
Attention: Josephine Ing
Sr. Scientist, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Ing:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: 125409/051

PRODUCT NAME: Perjeta® (pertuzumab)

DATE OF SUBMISSION: April 30, 2013

DATE OF RECEIPT: May 1, 2013

US LICENSE NUMBER: 1048

This supplemental application proposes the following change to expand the use of pertuzumab to support the following proposed indication: *Perjeta is indicated for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin, and cyclophosphamide (FEC) or carboplatin.*

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 30, 2013 in accordance with 21 CFR 601.2(a).

CONTENT OF LABELING

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **BLA**

125409/051 submitted on April 30, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

If you have questions, call me at (301) 796-3994.

Amy R. Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY R TILLEY
05/21/2013

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/s/

AMY R TILLEY
05/21/2013

From: Tilley, Amy
Sent: Tuesday, May 21, 2013 2:15 PM
To: 'Josephine Ing'
Subject: sBLA 125409 Perjeta - Clinical IR sent 5-21-13

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, May 28, 2013 12:00 PM
Flag Status: Flagged
[Josephine,](#)

[Below is a Clinical Information Request which we ask you to respond to by **no later than May 28, 2013.**](#)

- Patient 2367: Some sections of the CRF pathological response missing. Please provide this information.
- Patient 2486 appears to have a pCR according to the datasets. However, the CRF states a gross tumor size of 30.0 (page 468). Also, it is unclear if this patient had residual DCIS. Please clarify.
- Patient 2514 has a different CRF version than the annotated CRF. We cannot find the microscopic assessment of the primary tumor. Also, the histology type of tumor data is missing; we need to know if the patient had residual DCIS.
- Patient 3803 appears to have a pCR according to the datasets. However, the CRF states a gross tumor size of 24. Please clarify.
- Patient 3882 appears to have a pCR according to the datasets. However, the CRF states a gross tumor size of 17 (page 468). Please clarify.
- Patient 3940 appears to have a pCR according to the datasets. However, the CRF states a gross tumor size of 33 (page 468). Please clarify.
- Patient 4406 primary tumor microscopic assessment data cannot be found in the CRF, however EFEXEFF dataset EFVAL notes there is "Distinct single nodule". Please clarify where in the CRF this information is captured.

[Please confirm receipt of this email.](#)

[Regards.](#)

[Amy Tilley](#)

[Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,](#)

CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

📞 301.796.3994 (phone) • 301.796.9845 (fax) | ✉️ amy.tilley@fda.hhs.gov

*Never doubt that a small group of thoughtful, committed people can change the world; indeed,
it's the only thing that ever has.*

--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
05/21/2013

From: Tilley, Amy
Sent: Thursday, May 16, 2013 10:09 AM
To: 'Josephine Ing'
Subject: sBLA 125409-51 Perjeta - ODAC in Sept 2013

Importance: High
Josephine,

This email is to notify you of the FDA's plan to bring Genentech to an ODAC in September 2013 regarding the sBLA 125409-51 for Perjeta.

Please note that the plan to bring you to ODAC is **NOT** public and should **NOT** be disclosed until the FR publishes.

At a later date you will receive a letter informing you of your deadlines for the ODAC.

Please confirm receipt of this email.

Thanks.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
05/16/2013

From: Tilley, Amy
Sent: Wednesday, May 15, 2013 5:26 PM
To: 'Josephine Ing'
Subject: *Time Sensitive* sBLA 125409-51 Perjeta - Clinical IR

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, May 21, 2013 12:00 AM
Flag Status: Flagged
Josephine,

Below is the Clinical Information Request which we are requesting your response to **no later than May 21, 2013.**

- 1) Please clarify why the proposed label does not have a safety table with the NeoSphere data.
- 2) We could not find the death narratives from the NeoSphere trial. If you have already submitted these narratives, please let us know their location.
- 3) Please provide a rationale for assuming the applicability of the foreign data to the US population. This is a requirement for completing the filing of your application.

Please confirm receipt of this email.

Thanks.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
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/s/

AMY R TILLEY
05/15/2013

From: Tilley, Amy
Sent: Monday, May 13, 2013 6:18 PM
To: 'Josephine Ing'
Cc: Cottrell, Christy L.
Subject: sBLA 125409/51 - Stat Information Request

Follow Up Flag: Follow up
Due By: Wednesday, May 22, 2013 12:00 AM
Flag Status: Flagged
Josephine,

Below is the Statistical Information Request.

Reference is made to the sBLA 125409 SE1 submitted on 01 May 2013. The following request is for the pivotal study WO20697. Please respond by May 23, 2013.

- 1. Provide a summary of changes for each SAP amendment.**
- 2. Provide the randomization program code.**

Since I will be out of the office on May 23rd please reply to all when responding to this email.

Kindly confirm receipt of this email.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
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/s/

AMY R TILLEY
05/14/2013