

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125427Orig1s000

OTHER REVIEW(S)

CDRH/OIR Inter-Center Consult

From: Lorick, Kevin
To: BLA 125427 Record
Through: Lisa Skarupa, Regulatory Project Manager, CDER
Subject: CDRH/OIR Consult concerning KADCYLA™ drug label (BLA125427).

Background:

CDER is currently reviewing KADCYLA™ (ado-trastuzumab emtansine or TDM-1) for the (b) (4) treatment of metastatic breast cancer for patients who have failed therapy that includes trastuzumab and a taxane. The drug targets the HER2 protein and following internalization kills the HER2-overexpressing cells through the cytotoxic action of the emtansine moiety. From the Drug sponsor:

“Ado-trastuzumab emtansine is a novel antibody–drug conjugate specifically designed for the treatment of HER2-positive cancer. It is composed of the potent cytotoxic agent DM1 (a thiol-containing maytansinoid anti-microtubule agent) conjugated to trastuzumab via a linker molecule. Ado-trastuzumab emtansine binds to HER2 with an affinity similar to that of trastuzumab; such binding is required for its anti-tumor activity. It is hypothesized that after binding to HER2, ado-trastuzumab emtansine undergoes receptor-mediated internalization, followed by intracellular release of DM1 and subsequent cytotoxicity (19). A number of clinical studies have shown that ado-trastuzumab emtansine is effective and safe in treatment of HER2-positive breast cancer patients (20, 21, 22, 23). “

As such, the protein is not expected to be effective in patients who do not express higher than normal levels of HER2 protein. The EMILIA clinical trial studied the effect of TDM-1 in patients who had been tested for the presence of HER2 by both IHC and FISH. OIR reviewed the HER2 testing devices and the proposed labeling of ado-trastuzumab emtansine in regard to HER2 testing during review of PMA supplements P980018/S016 and P04005/S009. CDRH consulted due to the change of label to the medical devices and the change in the tested population.

CDRH/OIVD Review Team:

Kevin L. Lorick, Lead Reviewer OIR/DIHD/Pathology and Cytology
Meijuan Li, Mathematical Statistician, OSB
Yun-Fu Hu, Associate Director OIR/DIHD/ Pathology and Cytology
Reena Philip, Deputy Division Director, OIR/DIHD
Maria M. Chan Division Director, OIR/DIHD

Review:

CDRH believes that the Dako pharmDX™ HER2 FISH test and Dako HercepTest™ IHC test are appropriate as companion diagnostic devices for the determination of eligibility of breast cancer patients to receive TDM-1, as described in the EMILIA trial. CDRH originally had concerns that all of the patients were not originally screened with the Dako pharmDX™ test. Because the pharmDX™ test was used after a number of

patients (246 in the US cohort) were selected using the Abbott PathVysion® kit, some patients were excluded from the trial prior to testing with the Dako kit. Therefore it is possible that some patients who were excluded from the trial based upon the Vysis results would have been included based upon the pharmDX™ results. However, with the level of agreement between the two FISH tests, along with the fact that all of these were in the smaller population (there is a larger 737 patient cohort from Europe tested exclusively with pharmDX FISH) this should be acceptable.

Additionally, the Sponsor has not recorded the source of the tested tissue. It is therefore not clear whether these tests for the EMILIA study population will confirm the original HER2-positive status of their tumors or if they will determine if the progressive disease will respond to the new treatment. We caution that claims of benefit may be overstated if patients have developed progressive disease while on anti-HER2 therapy because they have lost expression of the protein. Because this information was not required at the beginning of the study, CDRH accepts that the study population consists of any breast cancer patient with progressive disease following trastuzumab/taxane therapy who has ever shown HER2 positive status in their breast tumors.

While HER2 gene amplification in breast cancer is highly correlated with protein expression, CDRH believes that insufficient data is present (8/991 patients in the EMILIA trial were FISH positive (HER2/CEN17 \geq 2.0 but IHC negative (0, 1+)) to label the pharmDX™ FISH device as a stand-alone test without providing a clear explanation of the risks involved in diagnosing a patient as HER2 positive or negative based solely on FISH results alone.

While some benefit to patients may have been observed in this trial based upon FISH data alone, the data is limited. As described above 8 of 991 patients would not be eligible for Herceptin® based upon the testing algorithm provided and so should not have been eligible for ado-trastuzumab emtansine treatment. Of these 8 patients, only 5 were given ado-trastuzumab emtansine. CDRH believes that should either the drug or device Sponsor wish to make claims about general use of FISH testing for determining pertuzumab eligibility a larger study observing only this population (FISH positive/IHC negative) should be conducted.

However, these patients were included in the trial according to the criteria set by the drug Sponsor. CDRH believes that some clarification should be added to the HER2 testing portion of the ado-trastuzumab emtansine drug label. This should indicate that IHC provides clear demonstration of HER2 protein overexpression while FISH testing provides indirect evidence of overexpression in breast cancers only (this indication for use). The Sponsor proposed using wording similar to what CDRH approved for HER2 testing on the PERJETA™ label. The Sponsor's new wording is consistent with previous labels for anti-HER2 therapy and reflects accepted practice for HER2 IHC and FISH scoring.

With this in mind, CDRH has approved the following label, as discussed with CDER on

January 10, 2013 at an internal labeling meeting and January 24, 2013 via email:

“5.8 HER2 Testing

Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for KADCYLA™ therapy because these are the only patients studied for whom benefit has been shown [see Indications and Usage (1), Clinical Studies (14.1)]. In the randomized study (Study 1), patients with breast cancer were required to have evidence of HER2 overexpression defined as 3+ IHC by Dako HercepTest™ or evidence of overexpression defined as FISH amplification ratio ≥ 2.0 by Dako HER2 FISH pharmDx™ test kit. Only limited data were available for patients whose breast cancer was positive by FISH and 0 or 1+ by IHC.

Assessment of HER2 status should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of sub-optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.”

Signed: _____

Kevin L. Lorick, Ph.D.
Lead Reviewer
CDRH/OIR/DIHD/PACB

Concur: _____

Yun-Fu Hu, Ph.D.
Chief
Pathology and Cytology Branch
CDRH/OIR/DIHD

Division Concur: _____

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/s/

LISA M SKARUPA
01/31/2013



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
301-796-4242

FINAL LABEL AND LABELING REVIEW-Amendment

Date: January 16, 2013

Reviewer: Kimberly Rains, Pharm. D.
Office of Biotechnology Products

Through: Linan Ha, Ph.D.
Division of Monoclonal Antibodies

Kathleen Clouse, Ph.D.
Director
Division of Monoclonal Antibodies

Application: BLA 125427

Product: Kadcyla (trastuzumab ematansine)

Applicant: Genentech, Inc.

Submission Date(s): August 27, 2012, January 4, 2013, January 18, 2013, January 30, 2013

Executive Summary

The carton and container labels for Kadcyla (trastuzumab ematansine) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, USP 35/NF 30 (12/1/12-5/1/13). Labeling deficiencies were identified, mitigated, and resolved. Comments are listed in the conclusions section. The container and carton labels submitted on January 30, 2013 are acceptable.

Background and Summary Description

BLA 125427, Kadcyla (trastuzumab ematansine) is indicated for the treatment of patients with HER2-positive, (b) (4) metastatic breast cancer who have received prior treatment with trastuzumab and a taxane.

Materials Reviewed:

100 mg and 160 mg vial and carton label

Sequence 0000, 0004, 0073, 0085

<<http://cberedweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea681052cdd>

***only the 100 mg strength shown below**

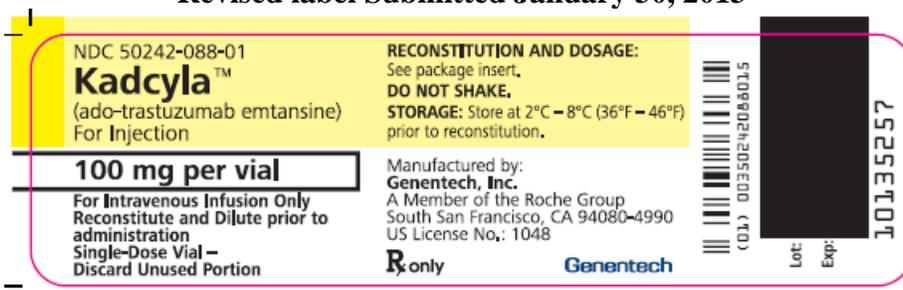
Start of Sponsor Material



Revised label submitted January 7, 2013



Revised label Submitted January 30, 2013



End of Sponsor Material

Subpart G-Labeling Standards Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. Conforms

(2) The name, address, and license number of manufacturer; Conforms

(3) The lot number or other lot identification; Conforms

(4) The expiration date; Conforms

(5) The recommended individual dose, for multiple dose containers. Not applicable. Single dose container

(6) The statement: “Rx only” for prescription biologicals. Conforms

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. Not applicable.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. Not applicable. Container is enclosed in a package.

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. Not applicable. Full label

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. Not applicable. Container label present

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation per CMC visual inspection.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35];

C. 21 CFR 201.5 Drugs; adequate directions for use; Conforms

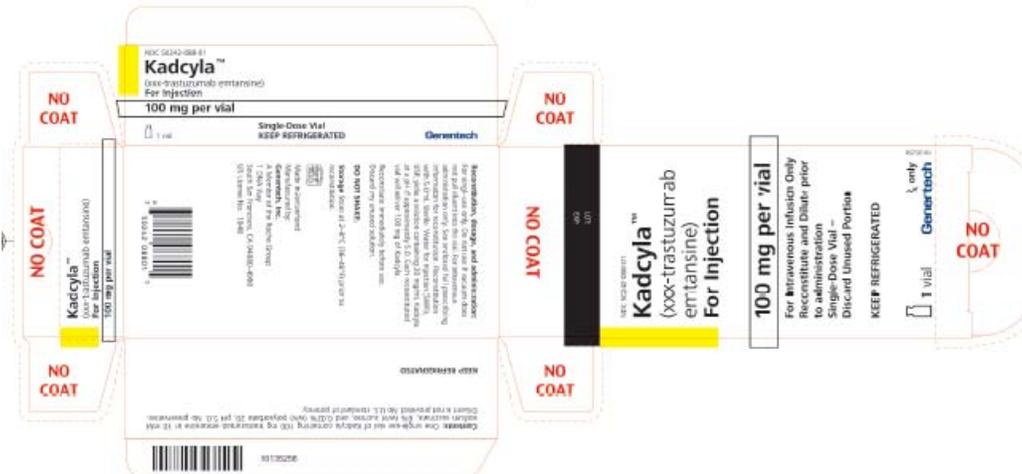
- D. 21 CFR 201.6 Drugs; misleading statements; Conforms
- E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] Conforms
- F. 21 CFR 201.15 Drugs; prominence of required label statements; Conforms
- G. 21 CFR 201.17 Drugs; location of expiration date; Conforms
- H. 21 CFR 201.25 Bar code; Conforms
- I. 21 CFR 201.50 Statement of identity; Conforms
- J. 21 CFR 201.51 Declaration of net quantity of contents; Conforms
- K. 21 CFR 201.55 Statement of dosage; Conforms
- L. 21 CFR 201.100 Prescription drugs for human use; Conforms

Start of Sponsor Material

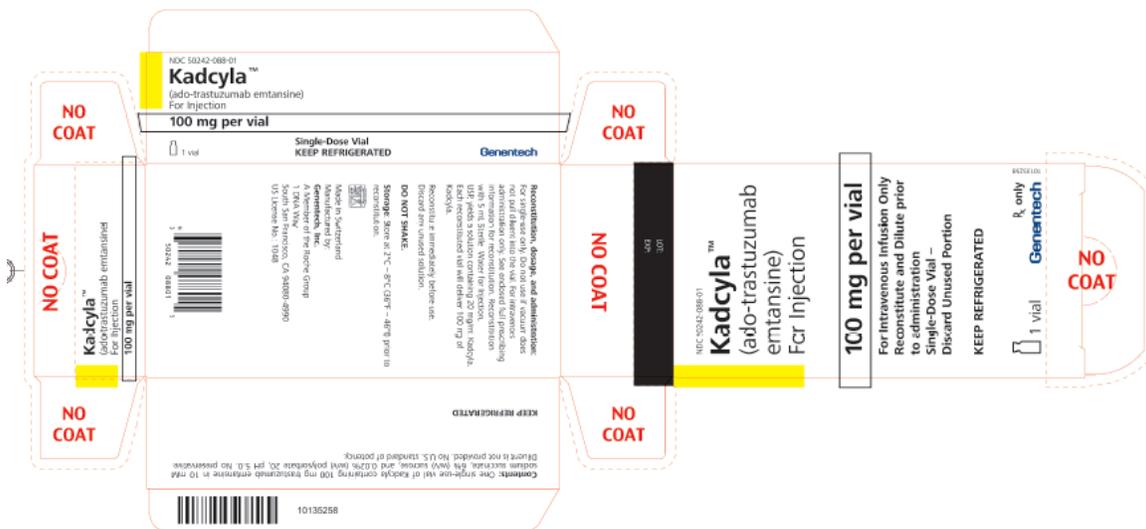
(b) (4)



Revised label submitted January 7, 2013



Revised label submitted January 30, 2013



End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label

- a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. Conforms
- b) The name, addresses, and license number of manufacturer; Conforms
- c) The lot number or other lot identification; Conforms
- d) The expiration date; Conforms

- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”. **Does not conform.** Revise ^{(b) (4)} [redacted] to read “No preservative.”
- f) The number of containers, if more than one; Conforms
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; Conforms
- h) The recommended storage temperature; Conforms
- i) The words “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; Conforms
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; Not applicable. Single-dose container.
- k) The route of administration recommended, or reference to such directions in and enclosed circular; **Does not Conform**
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; Conforms
- m) The type and calculated amount of antibiotics added during manufacture; Conforms
- n) The inactive ingredients when a safety factor or reference to enclosed circular containing appropriate information; Conforms
- o) The adjuvant, if present; Not applicable.
- p) The source of the product when a factor in safe administration; Not applicable.
- q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the

method of inactivation, or reference to an enclosed circular containing appropriate information; Not applicable

- r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency”; Conforms
- s) The statement “Rx only” for prescription biologicals; Conforms

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*]

- a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.
- b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.
- c) Legible type. All items required to be on the container label and package label shall be in legible type. “Legible type” is type of a size and character which can be read with ease when held in a good light and with normal vision.
Not applicable.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; Not applicable

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”, “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. Not applicable

E. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter; Conforms

- F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] Conforms.
- G. 21 CFR 201.5 Drugs; adequate directions for use; Conforms
- H. 21 CFR 201.6 Drugs; misleading statements; Conforms
- I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence]. Conforms
- J. 21 CFR 201.15 Drugs; prominence of required label statements; Conforms
- K. 21 CFR 201.17 Drugs; location of expiration date; Conforms
- L. 21 CFR 201.25 Bar code label requirements; Conforms
- M. 21 CFR 201.50 Statement of identity; Conforms
- N. 21 CFR 201.51 Declaration of net quantity of contents; Conforms
- O. 21 CFR 201.55 Statement of dosage; Conforms
- P. 21 CFR 201.100 Prescription drugs for human use; Conforms

Conclusions

Revised labels were submitted on January 7, 2013 and included several revisions that were not requested by OBP. The revisions were addressed by DMEPA. The applicant revised and resubmitted labels to address DMEPA’s concerns on January 30, 2013. The labels are acceptable.

III. Container and Container Labels

1. Add the dosage form, For Injection, to appear below the proper name, trastuzumab emtansine. *See recommended format below. **Change made with January 7, 2012 submission. Acceptable.**
2. Add the route of administration including the method, “For Intravenous Infusion Only” to appear below the strength presentation. *See

3. recommended format below. **Change made with January 7, 2012 submission. Acceptable.**
4. Add the following statements to the primary panel, “Single-Dose Vial –
5. Discard Unused Portion”. **Change made with January 7, 2012 submission. Acceptable.**

IV. Carton Label

1. Per 610.61(e), revise the statement, (b) (4)
[REDACTED] to “No preservative.” **Change made with January 7, 2012 submission. Acceptable.**

*Recommended format

Kadcyla
(trastuzumab emtansine)
For Injection
xxx mg per vial
For Intravenous Infusion Only

Reconstitute and Dilute prior to administration
Single-Dose Vial – Discard Unused Portion

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/s/

KIMBERLY M RAINS
02/12/2013

LINAN HA
02/12/2013

KATHLEEN A CLOUSE STREBEL
02/12/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Prescription Drug Promotion (DPDP)

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

Memorandum

Date: January 14, 2013

To: Lisa Skarupa, Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
OPDP

Subject: OPDP comments on draft product labeling for Kadcylla (trastuzumab emtansine) (TDM1) injection
BLA 125427

In response to your consult request dated September 6, 2012, OPDP has reviewed the draft labeling (Package Insert [PI] and carton and container labels) for Kadcylla injection. OPDP's comments are based on the proposed, substantially complete version of the PI and on the carton and container labels submitted by the applicant, available in the EDR at \\Cbsap58\M\eCTD_Submissions\STN125427.

OPDP has no comments on the carton and container labels.

If you have any questions about OPDP's comments on the PI, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov.

Section	Statement from draft	Comment
<ul style="list-style-type: none">• Highlights, Indications and Usage	Kadcyla is a HER2- targeted antibody....	Please consider removing the word "targeted" in the PI, to be consistent with other labels (e.g., Herceptin and Adcetris) and to avoid misuse of this term in promotion
<ul style="list-style-type: none">• Clinical Pharmacology	Xxx-trastuzumab emtansine is a HER2- targeted antibody drug-conjugate.	
<ul style="list-style-type: none">• Highlights, Warnings and	The highlights section does not include all of the warnings and precautions.	Please include all of the warnings and precautions

<p>Precautions</p>		<p>from the full prescribing information (see Herceptin PI).</p>
<ul style="list-style-type: none"> • 5 Warnings and Precautions 	<p>5.1 Hepatotoxicity- Some of the observed cases may have been confounded by comorbidities and/or concomitant medications with known hepatotoxic potential.</p>	<p>This statement minimizes hepatotoxicity associated with Kadcyra. Please consider providing the number of patients for which this is true or removing this statement.</p>
<ul style="list-style-type: none"> • 12 Clinical Pharmacology 	<p>12.1 Mechanism of Action- The small molecule cytoxin, DM1, is a (b) (4) microtubule inhibitor</p>	<p>(b) (4) We recommend removing the term (b) (4)</p>
<ul style="list-style-type: none"> • 14 Clinical Studies 	<p>Additional endpoints included PFS (based on investigator tumor response assessments), objective response rate (ORR), duration of response and time to symptom progression.</p>	<p>Please consider including PFS based on investigator assessments and time to symptom progression results in Table 8 if they are secondary endpoints and mentioned in section 14.</p>
<ul style="list-style-type: none"> • 14 Clinical Studies 	<p>(b) (4)</p>	<p>(b) (4)</p>

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/s/

MARYBETH TOSCANO
01/14/2013

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

Label and Labeling Review

Date: December 21, 2012

Reviewer: Jibril Abdus-Samad, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD, MPH
Division of Medication Error Prevention and Analysis

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

Drug Name and Strengths: Kadcyla (Trastuzumab Emtansine) for Injection
100 mg per vial and 160 mg per vial

Application Type/Number: BLA 125427

Applicant: Genentech, Inc.

OSE RCM #: 2012-2037

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

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Kadcyła (Trastuzumab Emtansine), BLA 125427, for areas of vulnerability that could lead to medication errors.

Additionally, this review evaluates the Applicant's proposed plan for minimizing nonproprietary name confusion between the proposed Kadcyła (Trastuzumab Emtansine) and currently marketed Herceptin (Trastuzumab). The Applicant proposed this plan because of the Agency's concern of potential confusion between the currently marketed Herceptin (Trastuzumab) and the proposed product Kadcyła (Trastuzumab Emtansine) due to similarity of the nonproprietary names (the nonproprietary names for both products contain "Trastuzumab").

1.1 REGULATORY HISTORY

On July 11, 2012, there was a multi-disciplinary team meeting to discuss the concerns noted in the IND regarding nonproprietary name confusion between Kadcyła (Trastuzumab Emtansine) and Herceptin (Trastuzumab). On August 24, 2012, the Applicant submitted the BLA for Kadcyła (Trastuzumab Emtansine). The Applicant was not informed of the concerns with the nonproprietary names prior to the submission of the BLA. Following initial discussion with the review team, it appeared a nonproprietary name change was not possible, therefore DMEPA requested the Applicant conduct a Human Factors (HF) Assessment of their labels and labeling and create an educational program for healthcare practitioners (HCP) to minimize potential confusion among these products. The Division of Oncology Products I (DOP1) sent these requests to the Applicant on September 9, 2012 (Appendix B). DMEPA and DOP1 held a teleconference with the Applicant on September 28, 2012 (Appendix C) to discuss DMEPA's comments regarding potential nonproprietary name confusion. On October 11, 2012, the Applicant submitted a response to our request for HF Study and education plan. Additionally, during the review of the BLA, we were informed of actual errors that occurred in clinical trials between Trastuzumab Emtansine and Trastuzumab.

1.2 PRODUCT INFORMATION

Kadcyła (Trastuzumab Emtansine) is an antibody-drug conjugate, which is a monoclonal antibody (Trastuzumab) attached to a highly potent cytotoxic agent (Emtansine). The Trastuzumab allows for specific attachment to the cancer cell receptor, and once attached the Emtansine enters the cell. Trastuzumab (without Emtansine) is currently marketed as Herceptin with multiple indications (please refer to Table 1 for detailed comparison of product characteristics for Kadcyła and Herceptin).

The following product information is provided in the August 24, 2012 submission.

- Non-proprietary name: Trastuzumab Emtansine
- Indication of use: Single agent for use in HER2 positive (b) (4) metastatic breast cancer
- Route of administration: Intravenous infusion

- Dosage form: Lyophilized powder
- Strengths: 100 mg per vial and 160 mg per vial
- Dose: 3.6 mg/kg every 3 weeks infused over 30 to 90 minutes
 - Dose reductions for symptomatic adverse events: 3 mg/kg and 2.4 mg/kg
- How supplied: Single use vials
- Storage: Room temperature
- Container and Closure Systems: Glass vial

Table 1: Comparison of Kadcyla vs. Herceptin

Product Characteristics	Kadcyla (Trastuzumab Emtansine) BLA 125427 <i>pending</i>	Herceptin (Trastuzumab) BLA 103792 <i>approved</i>
Indication(s)	Single agent, is indicated for the treatment of patients with HER2 +, ^{(b) (4)} metastatic breast cancer who have received prior treatment with trastuzumab and a taxane	<ul style="list-style-type: none"> - Adjuvant treatment of HER2 overexpressing node + or node – breast cancer, as part of a treatment regimen consisting of doxo, cyclo, and either paclitaxel or docetaxel OR with docetaxel and carboplatin - Metastatic breast cancer in combination with Paclitaxel for first line treatment of HER@ overexpressing metastatic breast cancer OR a single agent for treatment of HER2 overexpressing breast cancer in patient who have received one more chemotherapy regimens - In combination with Cisplatin and Capecitabine or 5-FU for the treatment of patients with HER2 overexpressing metagastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.
Patient population	Adults	Adults
Dose and frequency	3.6 mg/kg every 3 weeks (21-day cycle)	<ul style="list-style-type: none"> - Adjuvant Breast Cancer treatment: initial dose of 4 mg/kg then 2 mg/kg for 12 to 18 weeks then continue at 6 mg/kg every 3 weeks - Adjuvant Breast Cancer: single agent within 3 weeks following completion of multi-modality anthracycline: initial dose of 8 mg/kg then 6 mg/kg every three weeks - Metastatic Treatment Breast Cancer: alone or in combination with Paclitaxel at initial dose 4 mg/kg then once weekly dose of 2 mg/kg - Metastatic Gastric Cancer: initial dose of 8 mg/kg as a 90 minute intravenous infusion followed by 6 mg/kg every 3 weeks

Table 1: Comparison of Kadcyla vs. Herceptin

Product Characteristics	Kadcyla (Trastuzumab Emtansine) BLA 125427 <i>pending</i>	Herceptin (Trastuzumab) BLA 103792 <i>approved</i>
Dose modifications	For symptomatic adverse events: - first dose reduction: 3 mg/kg - second dose reduction: 2.4 mg/kg Specific modifications to withhold doses for Hepatotoxicity, Thrombocytopenia, decreased Left Ventricular Ejection Fraction (LVEF)	- Decrease rate of infusion - withhold for 4 weeks if >16% absolute decrease in LVEF for pre-treatment or below institutional limits of normal and >10% absolute decrease in LVEF
Route of administration	Intravenous infusion, first time over 90 minutes, then over 30 minutes	Intravenous infusion, first time over 90 minutes then over 60 minutes or 30 minutes depending on reaction
Reconstitution directions	Reconstitute with 5 mL Sterile Water for Injection (SWFI) for 100 mg vial or 8 mL of SWFI for 160 mg vial to 20 mg/mL concentration, swirl vial, dilute calculated dose with 250 mL of (b) (4) 0.9% sodium chloride	Reconstitute with 20 mL of BWFI (for multi-dose) or 20 mL of SWFI (for allergy to benzyl alcohol) for single use solution, sit for 5 minutes, dilute calculated dose with 250 mL of 0.9% sodium chloride
Strength	100 mg/vial and 160 mg/vial; after reconstitution 100 mg/5 mL (20 mg/mL) or 160 mg/8 mL (20 mg/mL)	440 mg/vial, after reconstitution 440 mg/20 mL (21 mg/mL)
Dosage form	Single use vial of lyophilized powder	Multi-dose vial of lyophilized powder and vial of diluent
Storage	Refrigerator, after reconstitution can be stored in refrigerator (b) (4)	Refrigerator, after reconstitution can be stored for 28 days if reconstituted with BWFI, if SWFI, discard after 24 hours

2 METHODS AND MATERIALS REVIEWED

2.1 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed proprietary name requests for Trastuzumab Emtansine. OSE Reviews 2010-2591 (dated May 11, 2011), 2011-4188 (dated April 26, 2012) for the IND 071072, and 2012-2017 (November 6, 2012) for BLA 125427 discussed the potential for confusion of the nonproprietary names Trastuzumab Emtansine and Trastuzumab. Concerns with confusion between the nonproprietary names ultimately led to the July 11, 2012 multi-disciplinary meeting and subsequent information requests to the Applicant (see Section 1.1 of this review).

2.2 LITERATURE SEARCH

The PubMed search conducted on October 24, 2012 concerning Kadcyła yielded zero actions or cases.

2.3 LABELS AND LABELING

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

- Container Labels submitted August 24, 2012 (Appendix D)
- Carton Labeling submitted August 24, 2012 (Appendix E)
- Insert Labeling submitted August 24, 2012

2.4 HUMAN FACTORS STUDY REQUEST AND PLAN

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the Applicant's response to Human Factors Study request and education plan submitted October 11, 2012.

2.5 CLINICAL TRIAL MEDICATION ERROR REPORTS

The BLA submission described medication errors between Trastuzumab Emtansine and Trastuzumab in clinical trials . DMEPA was notified of these errors after contacting the Applicant to determine how they would differentiate these products because of our initial concerns. We requested the errors be submitted for review. The medication errors cases from the clinical trials describe 4 patients who were supposed to receive Herceptin (Trastuzumab) 6 mg/kg but received Kadcyła (Trastuzumab Emtansine) 6 mg/kg (overdose-maximum single dose is 3.6 mg/kg) in error, and 1 patient who was supposed to receive Perjeta (Pertuzumab) 420 mg but received Kadcyła 420 mg (4.6 mg/kg) in error. The adverse events in all these cases appear to be Grade 2 thrombocytopenia, which resolved without treatment, and increased liver transaminases. However, one case resulted in a patient death. It is possible that the medication error played a role in the patient's death but we are uncertain. Only one case mentioned causality and it was stated as "due to pharmacy error".

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

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

3.1 CLINICAL TRIAL MEDICATION ERRORS

Unfortunately, the clinical trial medication error reports lack details with regard to causality and descriptions of the product labels. Typically, clinical trial labels are simple with regard to graphics, colors, and differentiation as compared to marketed drug labels. However, without the images of a physical description, we cannot assess if these errors were in part related to incorrect product selection because of visual similarity of the labels and labeling or confusion with the nonproprietary names.

There were apparently numerous names used to designate the Trastuzumab Emtansine (trastuzumab-MCC-DM1, PRO132365, RO5304020, Trastuzumab-SMCC-DM1, Tmab-MCCDM1, T-MCC-DM1, Herceptin-DM1, Herceptin-SMCC-DM1, Herceptin-MCC-DM1, and Hu Tmab-MCC-DM1) in clinical trials prior to INN recommending Trastuzumab Emtansine in February 2011. The use of the nonproprietary name Trastuzumab Emtansine into clinical trials was a gradual process.

Despite the lack of information concerning all contributing factors to the errors, these clinical trial errors are concerning because product confusion occurred in such a controlled environment of use. Based on our experience with wrong drug errors with other marketed products, similar nonproprietary names and overlapping product characteristics increase the risk of wrong drug errors. Thus, we remained concerned with the similarity of the non-proprietary names.

3.2 APPLICANTS PROPOSALS TO MITIGATE ERRORS BETWEEN HERCEPTIN AND KADCYLA

The Applicant responded to DMEPA's request for a HF study with a plan to mitigate the medication error issues rather than conducting a HF study. The Applicant's response included a formative evaluation, prepared by an expert in pharmaceutical risk management, that included subject matter authorities (SMAs) representing physicians, pharmacists and nurses. The SMAs provided viewpoints from the hospital in-patient and out-patient settings, infusion suite setting, pharmacy setting, physician office setting, electronic medical records (EMR), quality and regulatory perspectives. The objectives of the formative evaluation were the following:

- Gain a comprehensive understanding of the existing end-to-end workflow process from the point of prescription through post-infusion patient monitoring and reimbursement
- Identify and evaluate potential Kadcyla – Herceptin medication confusion issues
- Develop awareness tactics and a communication plan intended to promote education of identified medication confusion points

Based on the Applicant's evaluation, they developed the following strategies to minimize the risk:

1. Differences in the visual presentation of Kadcyła and Herceptin
2. Proposed labeling and warning statements for Kadcyła
3. Proposed educational programs and materials. This plan included:



3.2.1 Differences in the Visual Presentation of Kadcyła and Herceptin

The Applicant proposed differences in the visual presentation of the labels and labeling to minimize the risk of nonproprietary name confusion. The container label and carton labeling for Kadcyła are designed differently than Herceptin with regard to graphical layout. These types of labeling revisions will not impact name misinterpretation during prescribing, transcription, or order entry. Additionally, the proposed labels and labeling can be improved upon to prevent wrong drug confusion between Kadcyła and Herceptin and also wrong strength confusion between Kadcyła 100 mg and 160 mg vials.

Deficiencies noted include:

- The purple background color surrounding the 160 mg strength is too similar to Herceptin.
- The yellow color surrounding the name and other information on the upper portion of the container label is more prominent than the strengths. The carton labeling does not contain the same yellow block and thus provides adequate differentiation of strength. Thus, revising the container label to match the carton labeling should help prevent wrong selection errors if the vial happens to be stored outside of the carton.
- The container label and carton labeling are missing important information from the principal display panel which includes the dosage form, a statement that Kadcyła require reconstitution and dilution prior to use and a statement to discard unused portion.

3.2.2 Proposed Labeling and Warning Statements

The Applicant proposed labeling changes in the Dosage and Administration section of the insert labeling to warn against inappropriate product substitution between Trastuzumab Emtansine and Trastuzumab. The proposed labeling and warning statements may help to inform HCPs about the risk of substitution. However, the insert labeling is not available at the time the medication order is transcribed or filled. Since the clinical team is creating a boxed warning for toxicities, it would be beneficial to include a warning to prevent substitution for or with Herceptin (Trastuzumab). The addition of a boxed warning may prove beneficial, similar to other product pairs in which there are wrong drug errors between the original formulation and a newer formulation (e.g., Amphotericin B and Amphotericin B Lipid, Doxorubicin HCl and Doxorubicin HCl Liposome, Paclitaxel and Paclitaxel Protein-Bound Particles).

3.2.3 Education Program and Materials

The proposed education plan and materials are intended to be executed (b) (4). The education plan may provide awareness of the potential nonproprietary name confusion. However, there is no way to ensure all HCPs receive the education plan materials. Additionally, without continued education throughout the product life-cycle, awareness may decrease over time. Furthermore, the Applicant must also expand the education plan to include the following:

- Add pharmacy technician education because pharmacy technicians perform chemotherapeutic product compounding and may be less likely than the pharmacist to understand the differences between Trastuzumab and Trastuzumab Emtansine.
- Emphasize use of proprietary name because some hospitals or clinics encourage the use of nonproprietary names during prescribing and dispensing²

3.2.4 Nonproprietary Name Change

The Applicant noted that it was important to change the nonproprietary name. Internally, DMEPA also considered other methods of differentiating the nonproprietary names of Kadcyra and Herceptin and discussed these methods during team meetings consisting of DMEPA, DOP1, Office of New Drug Quality and Assessment (ONDQA), Office of Biotechnology Products (OBP), Division of Monoclonal Antibodies (DMA), and Office of Chief Counsel (OCC) on November 15, 2012 and November 20, 2012. More superficially, we discussed keeping the nonproprietary name (b) (4)

Additionally, we considered the use of a prefix to improve differentiation. (b) (4)

² Kloth, Dwight D. Guide to the Prevention of Chemotherapy Medication Errors: Strategies to Prevent Chemotherapy Errors. Clinical Oncology News. Edition 2 2009. Pgs 107-114

(b) (4)

After discussing the options, the team concluded that distinguishing the first word of the nonproprietary name for Kadcyła ([xxx]-trastuzumab emtansine) from Herceptin (trastuzumab) will minimize medication errors by preventing a patient from receiving a product different than what was intended to be prescribed.

To monitor post-marketing errors and confusion between Kadcyła and Herceptin, a post marketing commitment (PMC) should be considered. This PMC should request the Applicant submit any reports of medication errors to the Agency as 15 day expedited reports.

In summary, we believe the most effective way to decrease nonproprietary name confusion and the risk of wrong drug errors is to use a non-sensical prefix to modify the nonproprietary name because label and labeling differentiation, warning statements, and an education program alone will not prevent nonproprietary name confusion. This is consistent with the Applicant's suggestion to add a prefix to "Trastuzumab Emtansine" to differentiate it from "Trastuzumab". The Applicant cited the prefix used in the product Zaltrap (Ziv-Aflibercept) to avoid nonproprietary name confusion with Eylea (Aflibercept).

3.3 IN-LINE FILTER USE

The use of an in-line filter during administration of Kadcyła is dependent on the intravenous bag solution used for dilution. More specifically, an in-line filter is (b) (4) required for 0.9% Sodium Chloride. This is uncommon for the use of an in-line filter during administration to be determined by the intravenous bag fluid used for dilution and thus, there is a risk of healthcare practitioners administering Kadcyła in 0.9% Sodium Chloride without an inline filter.

Upon discussion with DMA, we learned dilution of Kadcyła with 0.9% Sodium Chloride produces visible particle formation, (b) (4) Subsequent to an information request from DMA, the Applicant submitted compatibility data for both types of solutions. The team will incorporate a recommendation to use of an in-line filter during Kadcyła administration regardless of the solution used for dilution in the insert labeling.

4 RECOMMENDATIONS

Based on this review, we recommend the following. If you have questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

4.1 COMMENTS TO THE DIVISION

A. Post Marketing Commitment

We request the Applicant submit reports of medication error to the Agency as 15-day expedited reports.

B. Boxed Warning

Add the statement, *Do Not Substitute for or with Trastuzumab*, to the black box warning of the insert labeling. This is similar to information that appears on the labels of other products such as Amphotericin, Abraxane, Doxil, and Marqibo that have similar risk of confusion as seen with this product.

C. Highlights of Prescribing, Product Title

Revise the product title from, [REDACTED] (b) (4) to read, *For Injection, for intravenous* [REDACTED] (b) (4). Because this product is a dry solid that requires reconstitution, the appropriate dosage form is *for injection* per United States Pharmacopeia definitions.

D. Section 2.2 – Dose Modifications

Clarify what adverse events require dose reduction in Table 1-Recommended Dose Reductions Schedule for Adverse Events.

E. Section 2.3, Preparation for Administration and Section 16.2, [REDACTED] (b) (4)

Replace the symbol, - , with the word, to.

F. Section 2.3 Preparation for Administration

Include the concentration of the reconstituted Kadcyła solution (20 mg/mL) in the *Reconstitution* steps.

G. Highlights of Prescribing Information – Dosage Forms and Strengths, Section 3 – Dosage Forms and Strengths, Section 16 – How Supplied

Revise the strength presentation to read *xxx mg per vial*.

4.2 COMMENTS TO THE APPLICANT

A. General Comments

1. Your proposed education plan should be revised to include Pharmacy Technicians:

Pharmacy technicians compound chemotherapeutic products and may be less likely than pharmacists, nurse and practitioners to understand the differences between Trastuzumab and Trastuzumab Emtansine.

Therefore, it is essential to include this group in your education plan.

2. Revise the purple color used in the 160 mg strength container label and carton labeling to a different color. This purple color is similar to color used on Herceptin (trastuzumab). It is imperative that these products are distinguished.

B. Container Label

1. Revise the strength, xxx mg, to read, xxx mg per vial.
2. Add the dosage form, For Injection, to appear below the nonproprietary name, trastuzumab emtansine.
3. Add a statement that conveys reconstitution and dilution are required prior to use.
4. Revise the single-use vial statement to read “Single-Dose Vial – Discard Unused Portion”. Thus, the principal display panel should appear as:

Kadcyla
(trastuzumab emtansine)
For Injection

xxx mg per vial
For Intravenous Infusion Only

Reconstitute and Dilute prior to administration
Single-Dose Vial – Discard Unused Portion

C. Carton Labeling

1. See Comments B1 through B4.
2. Revise the statement, [REDACTED] ^{(b) (4)} to read as, Do not use if vacuum does not pull diluent into the vial.
3. Replace the abbreviation, *IV*, with the word, *intravenous*.
4. Delete recommendations [REDACTED] ^{(b) (4)}
5. Per 610.61(e), revise the statement, [REDACTED] ^{(b) (4)} to “No preservative.”

APPENDICES

Appendix A

OSE Reviews (AERS)

Abdus-Samad, Jibril. OSE Review 2012-2017: Proprietary Name Review for Kadcyła,
November 6, 2012

Tobenkin, Anne. OSE Review 2011-4188: Proprietary Name Review for Kadcyła,
April 26, 2012

Tobenkin, Anne. OSE Review 2010-2591: Proprietary Name Review for (b) (4),
May 11, 2011

Appendix B: Comments to the Applicant sent September 9, 2012

Our evaluation of the introduction of the proposed product, Kadcyła (Herceptin Trastuzumab) to the market identified that there is potential for error between the currently marketed Herceptin (Trastuzumab) and your proposed product due to the similarity in the established names as well as the numerous product overlaps. Both products have similar established names (Trastuzumab) making them likely to be stored next to one another in the pharmacy and certain hospitals or clinics may encourage the use of established names during prescribing and dispensing³. Additionally, both are oncology products, both are prepared and diluted in 250 mL bags and administered over the same rates (30, 60 or 90 minutes) and with the same frequency of administration (every 3 weeks). Additionally, both would be prescribed (Oncologists) and utilized in similar settings (infusion or cancer centers) for similar patients (women with breast cancer).

If Herceptin and Kadcyła were confused patients may experience overdose or underdose making the product either toxic or less-effective, depending on the direction of the error. Considering all the overlapping product characteristics and the possible adverse events that would ensue due to the error, we recommend that you conduct a Human Factors Study to evaluate this risk and identify other failures that may occur with the use of Kadcyła. Practitioners must be able to differentiate the two products. The formative study should evaluate the best approaches to ensure visual differentiation between the product's labels and labeling, as well as testing various statements on the labels to identify what approach best communicates to practitioners that the products are different and should not be substituted for one another. The labels, labeling and warning statements should be targeted at all practitioners who participate in the drug use process including: technicians, pharmacists, nurses and prescribers. The final prototype should be validated to ensure the risk of product mix-ups are mitigated at all points in the use system.

Please submit the Human Factors validation study protocol as well as the results of the formative study and design history for our review prior to initiating the study to ensure that all steps in the drug use process that may be particularly prone to failures, such as technician selection and drug verifications, are included.

In addition, we recommend you implement educational programs/materials to educate the prescribers about the differences between the two products and work with hospitals and vendors to ensure they utilize appropriate steps and systems to enable differentiation between the two products throughout the use process (including data entry and drug label printing).

³ Kloth, Dwight D. Guide to the Prevention of Chemotherapy Medication Errors: Strategies to Prevent Chemotherapy Errors. Clinical Oncology News. Edition 2 2009. Pgs 107-114.

Appendix C: Memorandum of Meeting Minutes from 9/28/2012 Teleconference with Applicant

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 28, 2012
TIME: 12:00 PM (EST)
APPLICATION: BLA 125427
DRUG NAME: Kadcyla (Trastuzumab emtansine)
TYPE OF MEETING: T-con
MEETING RECORDER: Frances Fahnbulleh

FDA ATTENDEES:

Office of Surveillance and Epidemiology

Todd Bridges (Team Leader, DMEPA)
Jibril Abdus-Samad (Safety Evaluator, DMEPA)
Lubna Merchant (Team Leader, DMEPA)
Anne Tobenkin (Safety Evaluator, DMEPA)
Frances Fahnbulleh (Safety Project Manager, OSE)

Division of Oncology Products 1

Gideon Blumenthal (Medical Officer, DOP1)
Laleh Amiri Kordestani (Medical Officer, DOP1)
Lisa Skarupa (Project Manager, DOP1)

EXTERNAL CONSTITUENT ATTENDEES:

Genentech, Inc.

Erica Evans (Project Development Regulatory-Program Management)
Monica Shah (Regulatory Management)
William Berglind (US Commercial Regulatory)
Kathy Francissen (CMC Regulatory)

BACKGROUND:

The proposed product, Kadcyla (Trastuzumab Emtansine), a drug-antibody conjugate, shares a component of the established name with the currently marketed product, Herceptin (Trastuzumab). DMEPA is concerned that the "Emtansine" component of the established name will be overlooked and will not convey to practitioners that this product is a different entity. If these two products are confused, an error could lead to patients receiving twice the recommended dose of Trastuzumab Emtansine.

DMEPA met with ONDQA on July 11, 2012, and decided that the Applicant would be asked to perform Human Factor Studies.

These comments were conveyed in an IR sent to the Applicant on 9/9/12. The Applicant requested this t-con to further discuss the issues.

MEETING PURPOSE:

- To discuss the issue of the established name, Trastuzumab Emtansine, and the potential for confusion/medication error with Trastuzumab (Tradename-Herceptin).

- To discuss the recommendation for a Human Factors Study

Applicant questions for T-con discussion:

1) The USAN/INN approved established name is for T-DM1 is trastuzumab emtansine. In the first sentence of the "Comments to the Applicant" received Sept 7 2012, the Agency makes reference to Kadcylla (**Herceptin Trastuzumab**). Can the Agency confirm that the reference to Herceptin Trastuzumab in this context was a typographical error?

Discussion: The Agency confirmed that this was a typographical error.

2) The USAN/INN approved established name trastuzumab emtansine was included in a previous request for review of a proprietary name (KADCLYA) as submitted to IND 71072 as S0604 (Oct 31 2011). Following review of this submission, we gained conditional acceptance of the name KADCYLA on April 27 2012. We would appreciate if the Agency could help us understand why the recommendation that for the conduct a Human Factors Study was not made following this initial review of the proprietary name request?

Discussion: The agency apologized for the delay in conveying this; this was recognized earlier in the name review process, however we were having internal discussion on how to best address this issue, since this is a unique case with these established names.

3) Can the Agency advise us on the required timing for submission and review of the information requested in the Comments to the Applicant sent Sept 7 2012 (i.e., Human Factors validation study protocol as well as results of formative study) as it relates to review and potential approval of KADCYLA under BLA125427? Specifically,
a) Will the Agency require the results of a Human Factor study to be submitted and reviewed by the FDA as part of the initial BLA review and approval process?

Discussion: FDA will review Genentech's proposed plan and give feedback in a follow up t-con. FDA's goal is not to hold up the approval of this application.

b) Further to 3a above, can the Agency advise us on how the information gained from a Human Factor study could impact the labeling of Kadcylla?

Discussion: Human Factors Study will help determine best approaches to ensure visual differentiation between the products and allow for testing of various statements to determine which statements best communicate to practitioners that the products are different and should not be substituted for one another.

c) In addition, can the Agency comment on the potential for FDA to request a change in the established name for trastuzumab emtansine akin to that recently requested for Zaltrap as reviewed under BLA 125418?

Discussion: The Applicant asked if a change in the established name is an acceptable proposal. FDA stated the proposal will be discussed and a response provided to the Applicant.

4) The similarity between the established names for Kadcylla and Herceptin has been recognized by the Sponsor and plans to mitigate the risk of medication errors between the two products have been ongoing in preparation for the potential launch of Kadcylla. Genentech plans to outline the risk mitigation steps we have planned or implemented to date in our response to the Sept 7, 2012 Information Request. In the meantime, any guidance the FDA can share with us on the conduct of Human Factors studies for a therapeutic agent (versus a medical device) would be much appreciated.

Agreements:

Applicant will submit their proposed plan to reduce the potential for medication errors, which will include education of stakeholders, and container label and carton labeling that demonstrate distinct differences between Kadcylla and Herceptin; as well as computer drop-down menu assessments. Target date: Oct. 5th or week of Oct. 8th, 2012.

FDA Internal Plan of Action:

DMEPA will review the Applicant's submission and determine the feasibility of the Applicant including a prefix with the established name. Following internal discussions, a follow up T-con will be set up with the Applicant to discuss the FDA's recommendations.

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

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

/s/

JIBRIL ABDUS-SAMAD
12/21/2012

TODD D BRIDGES
12/21/2012

CAROL A HOLQUIST on behalf of KELLIE A TAYLOR
12/21/2012
Signing on behalf of Kellie Taylor

CAROL A HOLQUIST
12/21/2012

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

BLA	125427
Generic Name	Trastuzumab-MCC-DM1 (T-DM1)
Sponsor	Genentech, Inc.
Indication	HER2-Positive locally advanced or metastatic breast cancer (MBC)
Dosage Form	IV infusion
Drug Class	Antibody-Drug Conjugate
Therapeutic Dosing Regimen	3.6 mg/kg q3week (q3w)
Duration of Therapeutic Use	Till tolerated or until disease progression
Maximum Tolerated Dose	3.6 mg/kg q3w or 2.4 mg/kg qw
Submission Number and Date	SDN 001/27 Aug 2012
Review Division	DOP1

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes in mean QTc intervals (i.e. >20 ms) were detected following the treatment of T-DM1 administered by i.v. infusion every 3 weeks at a dose of 3.6 mg/kg. The largest upper bound of the 2-sided 90% CI for the mean QTc change from baseline was 7.73 ms observed 60 minutes post-dose on Day 1 of Cycle 3.

T-DM1 is a novel antibody-drug conjugate (ADC) that provides targeted delivery of a cytotoxic agent (DM1) to HER2-positive breast cancer cells. It was not possible to conduct a placebo-controlled thorough QT study in healthy patients. This was a Phase 2, single-arm, open-label study in which all patients received single-agent T-DM1 through Cycle 3 Day 1. T-DM1 was administered by IV infusion every 3 weeks at a dose of 3.6 mg/kg and fifty patients received a single-agent T-DM1. Therefore, the threshold for regulatory concern for QT prolongation in the thorough QT/QTc Study defined in ICH E14 is not applicable in this study.

No suprathreshold doses were tested in patients. The therapeutic dose (3.6 mg/kg intravenous infusion administered every three weeks) produces mean T-DM1 (trastuzumab ematansine conjugate) C_{max} values of 83.4 ug/ml after Cycle 1 and 85.0 ug/ml after Cycle 4 (which are similar to the C_{max} values observed in this current study).

As the half-life of the trastuzumab conjugate is 4 days, dosing every three weeks is not expected to yield accumulation. The evaluation of QT was conducted at day 1 of treatment and at presumed steady-state PK of T-DM1 during the third cycle.

T-DM1 undergoes catabolism via proteolysis in cellular lysosomes. Therefore, it is expected that there is no significant involvement of human CYP enzymes in the elimination of T-DM1. No formal drug-drug interaction studies have been conducted with T-DM1 (or trastuzumab itself). Data from the Phase III pivotal clinical trial, demonstrate that concomitant administration of CYP3A inhibitors, CYP3A inducers or Pgp inhibitors with T-DM1 does not result in any noticeable change in the pharmacokinetics of the trastuzumab emtansine conjugate, total trastuzumab, or DM1. No formal studies of T-DM1 in patients with renal impairment have been conducted and a study in patients with hepatic impairment is ongoing. Other intrinsic factors (e.g., age, gender or race) and extrinsic factors (e.g., drug interactions, food effect), have been explored as potential factors of PK variability, with no significant differences in exposure with these factors. No supratherapeutic doses have been tested in patients and the highest dose tested was 4.8 mg/kg in a q3w regimen.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

12.2 PHARMACODYNAMICS

The effect of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was established in an open-label, single arm study in 51 evaluable patients with HER2-positive metastatic breast cancer. The observed upper limit of the 90% two-sided confidence interval for the largest mean effect of KADCYLA on the baseline adjusted QTcF interval was below 10 ms.

2.2 QT-IRT'S PROPOSED LABEL

QT-IRT has the following label recommendations which are suggestions only. We defer final labeling decisions to the review division.

12.6 Cardiac Electrophysiology

The effect of multiple doses of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open label, single arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study.

3 BACKGROUND

3.1 PRODUCT INFORMATION

T-DM1 is a novel antibody-drug conjugate (ADC) that provide targeted delivery of a cytotoxic agent (DM1) to HER2-positive breast cancer cells.

3.2 MARKET APPROVAL STATUS

T-DM1 is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

A hERG assay was negative. A single-dose cardiovascular safety study in cynomolgus monkeys showed no toxicity findings.

3.4 PREVIOUS CLINICAL EXPERIENCE

There have not been cardiovascular safety findings of note to date.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 71,072. The sponsor submitted the study report TDM4688g for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase II, Open-Label Study to Evaluate Corrected QT Interval Effects of Trastuzumab-MCC-DM1 (T-DM1) in Patients with HER2-Positive Recurrent Locally Advanced or Metastatic Breast Cancer and to Evaluate the Safety and Tolerability of Combined T-DM1 and Pertuzumab in Patients with Early Disease Progression While Receiving T-DM1 Alone

4.2.2 Protocol Number

TDM4688g

4.2.3 Study Dates

Initiation Date: 14 July 2009

Completion Date: 21 October 2010

4.2.4 Objectives

Primary objective:

- To evaluate the effect of T-DM1 on the duration of corrected QT (QTc) interval as measured by the change from baseline to selected timepoints after the T-DM1 infusion in mean duration of the QTc interval as calculated using Fridericia's correction (QTcF)

Secondary objectives:

- To evaluate the effect of T-DM1 on the duration of QTc interval as measured by the change from baseline to selected timepoints after the T-DM1 infusion in mean duration of the QTc interval as calculated using Bazett's correction (QTcB)
- To investigate the effect of T-DM1 on heart rate, QT interval, PR interval, and QRS duration
- To assess the incidence of selected cardiac events (ventricular arrhythmia, left ventricular)
- To further characterize the pharmacokinetic (PK) profile of T-DM1 as a single agent in patients with HER2-positive recurrent locally advanced or metastatic breast cancer.
- To further characterize the safety and tolerability of T-DM1 as a single agent in patients with HER2-positive recurrent locally advanced or metastatic breast cancer
- To further evaluate the development of anti-therapeutic antibodies (ATA) to T-DM1
- To describe the safety and tolerability of combined T-DM1 and pertuzumab when administered once every 3 weeks in patients with HER2-positive recurrent locally advanced or metastatic breast cancer who experience early progressive disease, defined as progressive disease occurring in patients who have received up to 6 cycles of T-DM1 monotherapy

4.2.5 Study Description

4.2.5.1 Design

This was a multicenter, single-arm, open-label study in which all patients received single-agent T-DM1 through Cycle 3 Day 1. Patients who demonstrated progressive disease at the tumor assessment after receiving T-DM1 at Cycle 3 and who completed the ECG and PK assessments required during Cycles 1–3 were eligible to receive combined T-DM1 and pertuzumab starting at Cycle 4 Day 1. Patients who were determined to have progressive disease on single-agent T-DM1 between Cycle 4 and Cycle 7 were eligible to receive combined T-DM1 and pertuzumab. Patients who had progressive disease on single-agent T-DM1 after Cycle 7 were not eligible to receive combined T-DM1 and pertuzumab and were discontinued from the study.

4.2.5.2 Controls

No placebo and no positive (moxifloxacin) controls in this study.

4.2.5.3 Blinding

This is an open-label study.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

T-DM1 administered by IV infusion every 3 weeks at a dose of 3.6 mg/kg. T-DM1 doses may be reduced to as low as 2.4 mg/kg according to the dose-modification guidelines for hematologic or hepatotoxicity proposed by the sponsor.

Pertuzumab was administered at a loading dose of 840 mg IV on Cycle 4 Day 1 (if progressive disease is determined before Cycle 4) or on Day 1 of any subsequent cycle until Cycle 7 Day 1 (if progressive disease was determined at the end of Cycle 6), followed by 420 mg IV no more frequently than every 3 weeks in subsequent cycles.

4.2.6.2 Sponsor’s Justification for Doses

In the Phase I study, the maximum tolerated dose (MTD) of T-DM1 administered by IV infusion every 3 weeks was 3.6 mg/kg. This treatment schedule was well tolerated and associated with significant clinical activity in other Phase II studies and was the dose regimen selected for use in the present study.

The dose of pertuzumab was based on clinical safety and PK data across a range of studies. A preliminary analysis of data from a Phase Ib/II study of the combination of T-DM1 and pertuzumab (TDM4373g) confirmed that the standard Phase II dose and schedule of each agent (T-DM1 and pertuzumab) could be safely combined.

Reviewer’s Comment: The dose selected for the study is acceptable based on the risk for thrombocytopenia (seen at higher doses of 4.8 mg/kg in an every 3-week regimen). As stipulated in the currently proposed label, the dose used in the assessment of QT represents the maximum therapeutic dose.

4.2.6.3 Instructions with Regard to Meals

There are no instructions with regards to meals.

Reviewers Comment: T-DM1 is administered by IV infusion so food effects are not anticipated.

4.2.6.4 ECG and PK Assessments

Triplicate ECG assessments were performed at Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 3 Day 1 for all enrolled patients. All ECGs assessments and PK blood samples were to be collected at approximately the same time of the day (preferably ± 30 minutes) and at least 1 hour postprandially. For timepoints when ECGs, blood draws, and treatment administration were scheduled, the ECG measurement was to be performed first, followed by the blood draw for PK and laboratory assessments, and then treatment administration.

Study Day(s)	-1 (Prior to Day 1 of Cycle 1)	1 (Cycles 1 Day 1, Day 8 and Cycle 3, Day 1)
Intervention	No treatment	One (1) IV infusion at a dose of 3.6 mg/kg (In Cycle 1, the first T-DM1 dose was administered as a 90-minute infusion; subsequent cycles were 30-minute infusions.)
12-Lead ECGs	The screening ECG was	Cycle 1 Day 1, 30 and 15 minutes

	obtained between Day -21 and Day -3.	pre-dose; Cycle 1 Day 1, 15 and 60 minutes post-dose; Cycle 1 Day 8; and Cycle 3 Day 1, 15 minutes pre-dose and 15 and 60 minutes post-dose.
PK Samples for drug*	None collected	Pre-dose, within 15 minutes post-infusion (at C _{max}) and 1 hour post dose and anytime on days 8 and 15 in cycles 1 and 3. Pre-dose blood samples were also collected prior to dosing in Cycle 4.

*Analytes include serum T-DM1, total trastuzumab (i.e., the sum of conjugate T-DM1 and unconjugated trastuzumab), and DM1.

Reviewer's Comment: The PK and ECG assessments are adequate to capture QT at peak concentrations of T-DM1 and other analytes (maximum concentration achieved at end of infusion). The assessments of ECGs and PK were conducted on the Days 1 and 8 of the first cycle and on Day 1 of third cycle (after continuous administration, one cycle is 21 days). As the half-life of T-DM1 is 3.9 days, the evaluation of QT was conducted after the first dose and presumed steady-state PK of T-DM1 during the third cycle.

4.2.6.5 Baseline

The sponsor used the average of the QTc intervals collected at 30 and 15 minutes prior to T-DM1 administration on Cycle 1 Day 1 as baseline values.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Fifty patients enrolled this Phase II study to ensure at least 45 ECG-evaluable patients. With 45 ECG-evaluable patients, assuming an estimated standard deviation of 20 ms for mean QTcF at each time point, the two-sided 90% CI for the baseline-adjusted QTcF at each post-baseline time point will be within 7 ms of the observed difference.

Approximately 10–15 patients are predicted to experience PD before completing 6 cycles of T-DM1 monotherapy and be eligible to receive combined T-DM1 and pertuzumab.

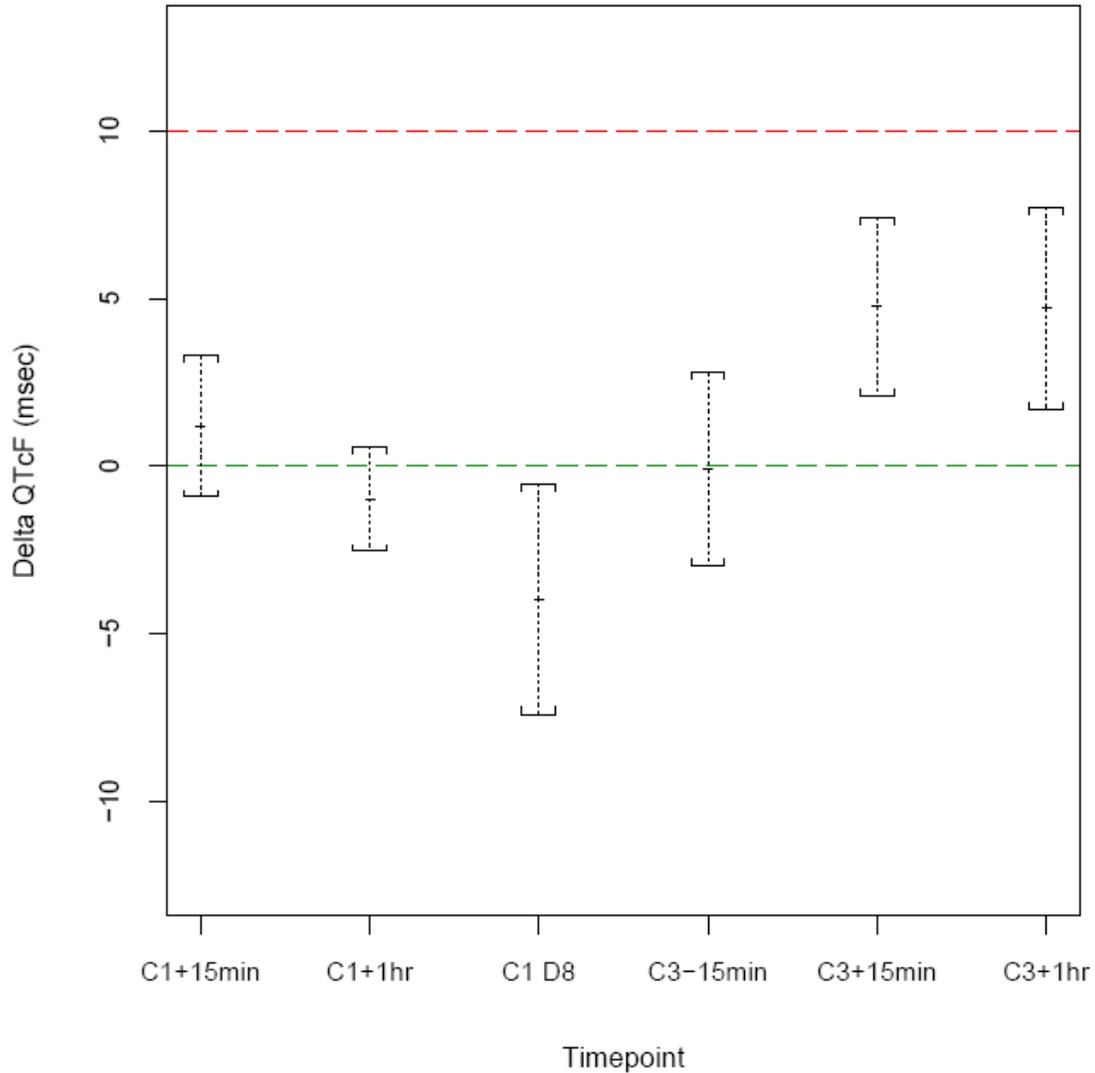
4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the baseline-adjusted QTcF interval at each post-baseline time point. Baseline-adjusted QTcF is defined as the change in QTcF from baseline to each post-baseline time point. Baseline time points are the ECGs obtained 30 minutes and 15 minutes prior to T-DM1 infusion on Cycle 1, Day 1 (C1D1). All remaining six ECG

collection time points, i.e., two on C1D1 (15 minutes and 60 minutes) after the T-DM1 infusion, one on Cycle 1 Day 8 (C1D8), and three on Cycle 3 Day 1 (C3D1) (-15 minutes, 15 minutes and 60 minutes), are considered to be post-baseline time points. Figure 1 presents the sponsor's mean baseline adjusted QTcF and 90% 2-sided Confidence Intervals.

Figure 1: Sponsor Results of Mean Baseline – Adjusted Average QTcF Interval and 90% Two-Sided Confidence Intervals



Source: Clinical Study Report No., Section 11.4.1, Figure 3, Pg 72/1195

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. We used SAS Proc Mean Procedure to analyze QTcF.

4.2.8.2.2 Assay Sensitivity

There is no positive-control group in the study.

4.2.8.2.3 Categorical Analysis

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

4.2.8.3 Safety Analysis

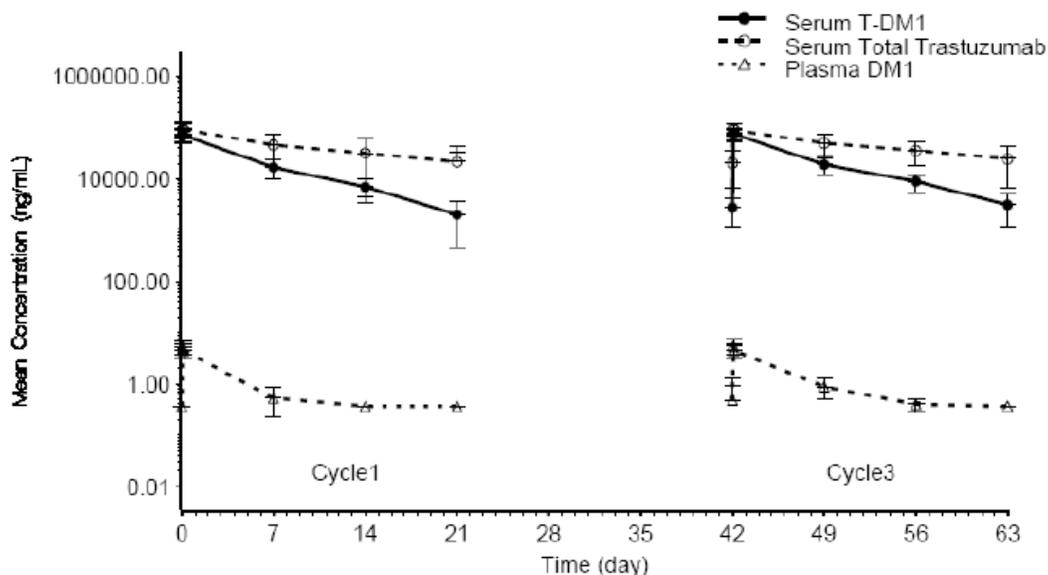
Few cardiovascular adverse events are described; none seem to be adverse reactions or evidence of a proarrhythmic effect.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The sponsor reported the estimated average (SD) C_{max} for TDM-1 to be 75.6 ng/mL (21.9 ng/mL) and 80.7 ng/mL (18.1 ng/mL) for Cycle 1 and Cycle 3, respectively. Maximum concentrations were observed at the end of the TDM-1 infusion (90 min). For total trastuzumab and DM1 analytes, similar C_{max} values were observed with each cycle. The mean drug concentration-time profiles of each analyte, after T-DM1 administration, are illustrated in Figure 2 and the PK results are presented in Table 1.

Figure 2: Mean (SD) T-DM1, Total Trastuzumab and DM1 Concentration-Time Profile following 3.6 mg/kg T-DM1 administration during Cycle 1 and Cycle 3



(Source: Report No ICSR TDM4688g, pages 84)

Table 1: Descriptive Statistics of TDM-1, Total Trastuzumab and DM1 PK Concentrations

Analyte	Cycle	Cmax (ug/mL)		AUC0-inf (day*ug/mL)		T1/2 (day)	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
T-DM1	1	51	75.6 (21.9)	51	431 (126)	51	4.02 (0.938)
	3	47	80.7 (18.1)	47	475* (150)	47	4.46 (0.926)
Total trastuzumab	1	51	95.5 (32.3)	51	1420 (1390)	51	10.3 (6.81)
	3	47	98.6 (26.1)	47	958* (394)	47	12 (6.24)
DM1	1	51	5.42** (1.62)	NA	NA	NA	NA
	3	46	5.46** (1.87)	NA	NA	NA	NA

*AUC last **in ng/mL

(Source: Adapted from Report No ICSR TDM4688g, pages 213-219)

4.2.8.4.2 Exposure-Response Analysis

The sponsor examined the relationship between QTcF as a function of T-DM1, total trastuzumab and DM-1 concentrations using a linear mixed effects modeling approach, with Δ QTc as dependent variable and corresponding analyte concentrations as predictors and subjects as random effect. The models were also tested to determine whether the model parameters varied by cycle.

For T-DM1, the best fit model incorporated random effects on both slope and intercept, with a same slope and different intercept for each cycle. The results of the model are presented in Table 2 and a plot of Δ QTcF vs. T-DM1 concentration, by cycle, is illustrated in Figure 3. The model was re-estimated with DM1 and total trastuzumab concentrations replacing conjugated T-DM1 as the predictor variable. Parameter estimates from the final model using DM1 and total trastuzumab as predictor variables are summarized in Table 3.

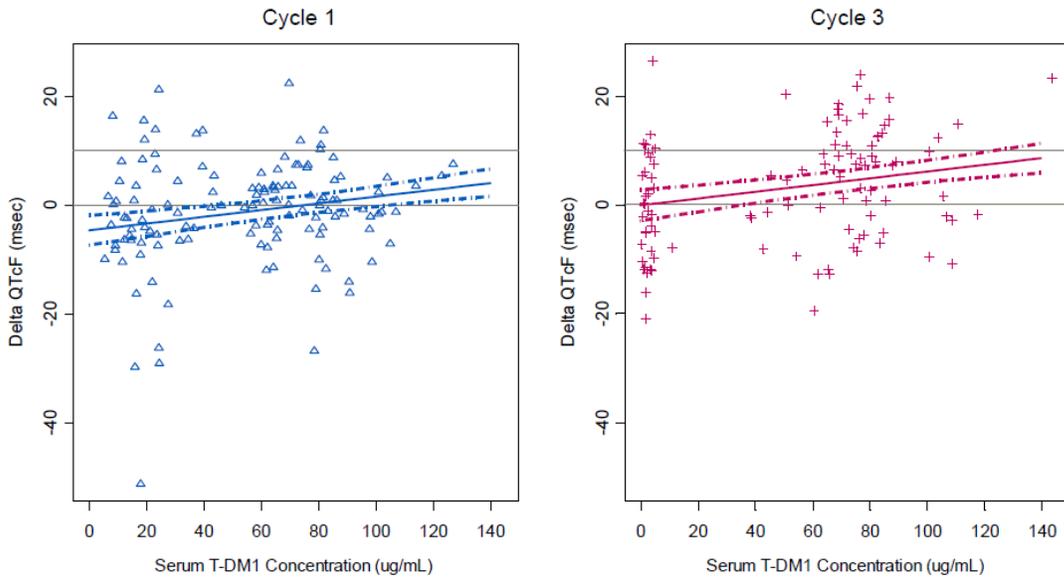
The sponsor concluded there appears to be a trend between T-DM1 drug concentration and its effect on QT interval and, at the observed concentration ranges of T-DM1, DM1, and total trastuzumab, there is reasonable assurance that the true increase in mean baseline-adjusted average QTcF is not > 5 ms.

Table 2: Final Parameter Estimates for the Linear Mixed-Effects model of T-DM1 vs. Δ QTcF

Parameter	Parameter Estimate	SE	CV%	95% CI (SE Derived)
Intercept for Cycle 1 (ms)	-4.6	1.7	37%	-7.9, -1.3
BSV (ms)	7.9			
Difference in intercept, Cycle 3 vs. Cycle 1	4.5	1.1	24%	3.3, 6.7
Slope (ms/[μ g/mL])	0.062	0.018	29%	
BSV (ms/[μ g/mL])	0.046			
Residual variability (ms)	8.3			

(Source: Report No ICSR TDM4688g, page 97)

Figure 3: Delta QTcF vs. T-DM1 Concentrations Stratified by Cycle



(Source: Report No ICSR TDM4688g, page 98)

Table 3: Final Parameter Estimates for the Linear Mixed-Effects model of Total Trastuzumab (top) and DM1 (bottom) vs. $\Delta QTcF$

Total Trastuzumab

Parameter	Parameter Estimate	SE	CV%	95% CI (SE Derived)
Intercept for Cycle 1 (ms)	-5.3	1.7	32%	-8.6, -2.0
BSV (ms)	5.0			
Difference in Intercept Cycle 3 vs. Cycle 1	4.7	1.2	26%	2.3, 7.1
Slope (ms/[μ g/mL])	0.054	0.017	31%	0.021, 0.087
BSV (ms/[μ g/mL])				
Residual variability (ms)	8.6			

DM1

Parameter	Parameter Estimate	SE	CV%	95% CI (SE Derived)
Intercept for Cycle 1 (ms)	-3.7	1.6	43%	-6.8, -0.6
BSV (ms)	8.0			
Difference in Intercept Cycle 3 vs. Cycle 1	3.9	1.1	28%	1.7, 6.1
Slope (ms/[ng/mL])	0.76	0.25	33%	0.27, 1.25
BSV (ms/[ng/mL])	0.85			
Residual variability (ms)	8.2			

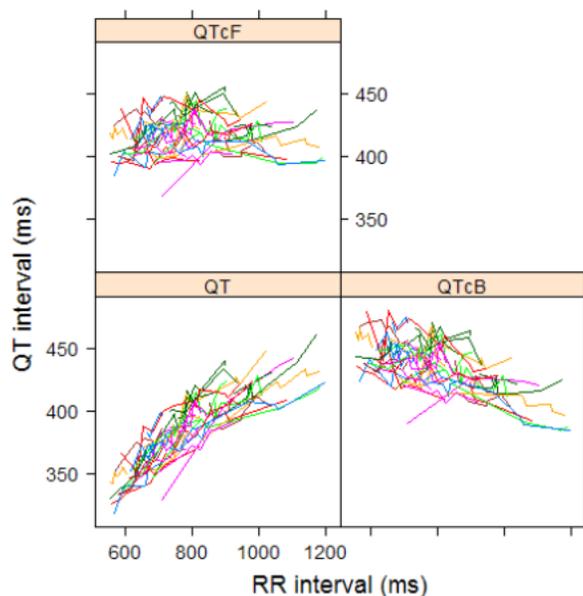
Reviewer's Analysis: The sponsor's analysis yielded a positive relationship between T-DM1 concentration and $\Delta QTcF$, the shallow slope suggests that we would not expect QT prolongation at therapeutic concentrations. The same conclusion can be made for total trastuzumab and DM1. According to the FDA analysis (pooling data for cycle 1 and 3), a significant trend was observed between T-DM1 concentration and $\Delta QTcF$ (slope p-value <0.05). The same results were observed for total trastuzumab and DM1 (data not shown). A plot of ΔQTc vs. T-DM1 concentrations generated from the FDA analysis is presented in Figure 6.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals. The relationship between different correction methods and RR is presented in Figure 4. QTcF was chosen as the correction method for the study.

Figure 4: QT, QTcB, and QTcF, vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used SAS PROC Mean procedure to analyze QTcF effect. Since this is a single arm study, there are no placebo and positive-control groups. The analysis is listed in Table 4. The largest upper bound of the 2-sided 90% CI for T-DM1 is 7.7 ms.

Table 4: Analysis Results for QTcF with 2-Sided 90% Confidence Intervals for T-DM1

Time Points	N	Mean	Standard Error	95% LB	95% UB
Cycle 1 – Day 1 15 Min Post	44	1.18	1.26	-0.94	3.29
Cycle 1 – Day 1 60 Min Post	45	-0.99	0.93	-2.56	0.57
Cycle 1 – Day 8 Exp-Dosing	41	-4.21	2.14	-7.81	-0.61
Cycle 3 – Day 1 15 Min Pre	35	-0.11	1.71	-3.00	2.77
Cycle 3 – Day 1 15 Min Post	36	4.67	1.63	1.92	7.41
Cycle 3 – Day 1 60 Min Post	37	4.71	1.79	1.70	7.73

5.2.1.2 Assay Sensitivity Analysis

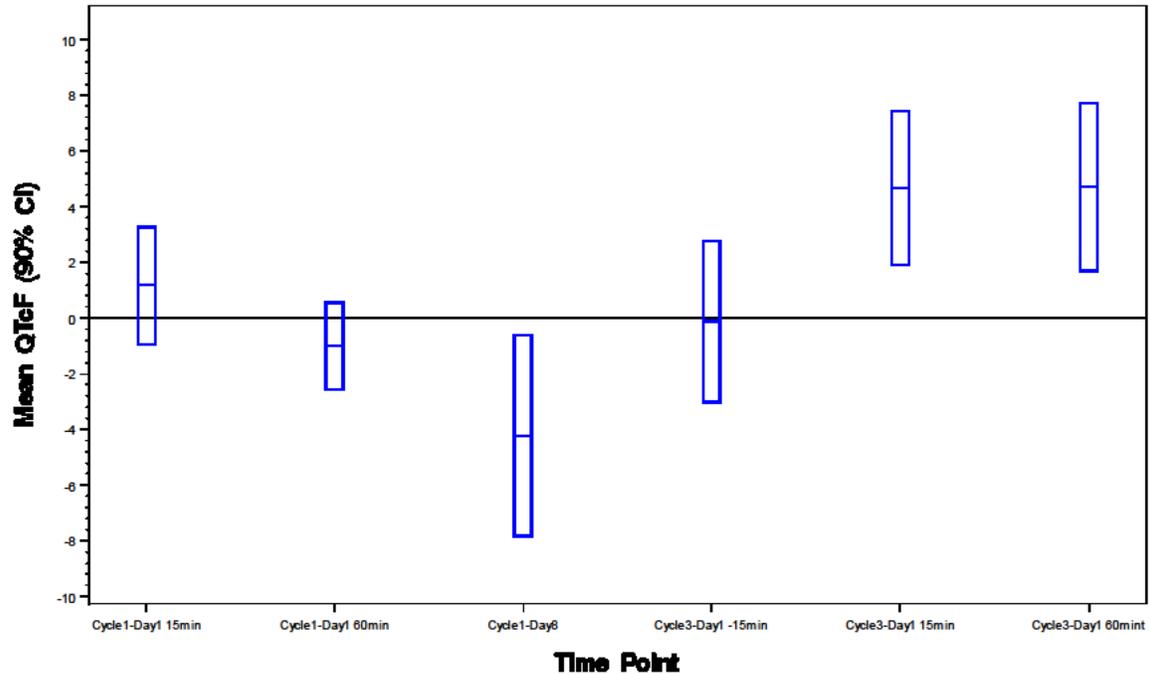
There is no positive-control group in the study.

5.2.1.3 Graph of Δ QTcF Over Time

The following figure displays the time profile for QTcF for T-DM1 group.

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Figure 5: Mean and 90% CI for QTcF Time Course for T-DM1



5.2.1.4 Categorical Analysis

Table 5 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms and no subject's change from baseline was above 30 ms.

Table 5: Categorical Analysis for QTcF for T-DM1

Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
46	44 (95.7%)	2 (4.3%)

5.2.2 HR Analysis

The statistical reviewer used SAS PROC Mean procedure to analyze HR effect. The analysis is listed in Table 6. The largest upper bound of the 2-sided 90% CI for T-DM1 is 7.2 ms. Table 7 presents the categorical analysis of HR. Eight subjects who experienced HR interval greater than 100 bpm was in T-DM1 group.

Table 6: Analysis Results for HR with 2-Sided 90% Confidence Intervals for T-DM1

Time Point	N	Mean	Standard Error	95% LB	95% UB
Cycle 1 – Day 1 15 Min Post	44	2.93	1.24	0.84	5.02
Cycle 1 – Day 1 60 Min Post	45	4.37	1.17	2.40	6.34
Cycle 1 – Day 8 Exp-Dosing	41	5.02	1.29	2.85	7.20
Cycle 3 – Day 1 15 Min Pre	35	4.12	1.34	1.85	6.38
Cycle 3 – Day 1 15 Min Post	36	0.83	1.29	-1.35	3.01
Cycle 3 – Day 1 60 Min Post	37	2.39	1.29	0.22	4.56

Table 7: Categorical Analysis for HR for T-DM1

Total N	HR <100 bpm	HR >=100 bpm
46	38 (82.6%)	8 (17.4%)

5.2.3 PR Analysis

The statistical reviewer used SAS PROC Mean procedure to analyze PR effect. The analysis results are listed in Table 8. The largest upper bound of the 2-sided 90% CI for T-DM1 is 9.6 ms. Table 9 presents the categorical analysis of PR. Three subjects who experienced PR interval greater than 200 ms were in T-DM1 group.

Table 8: Analysis Results for PR with 2-Sided 90% Confidence Intervals for T-DM1

Time Point	N	Mean	Standard Error	95% LB	95% UB
Cycle 1 – Day 1 15 Min Post	44	2.30	1.13	0.39	4.20
Cycle 1 – Day 1 60 Min Post	45	2.48	1.30	0.29	4.67
Cycle 1 – Day 8 Exp-Dosing	41	-0.60	1.70	-3.47	2.26
Cycle 3 – Day 1 15 Min Pre	35	1.85	1.86	-1.30	5.00
Cycle 3 – Day 1 15 Min Post	36	6.82	1.66	4.02	9.62
Cycle 3 – Day 1 60 Min Post	37	5.31	1.42	2.91	7.71

Table 9: Categorical Analysis for PR for T-DM1

Total N	PR < 200 ms	PR >=200 ms
46	43 (93.5%)	3 (6.5%)

5.2.4 QRS Analysis

The statistical reviewer used SAS PROC Mean procedure to analyze QRS effect. The analysis results are listed in Table 10. The largest upper bound of the 2-sided 90% CI for T-DM1 is 3.04 ms, respectively. No subject who experienced QRS interval greater than 110 ms was in T-DM1 group.

Table 10: Analysis Results for QRS with 2-Sided 90% Confidence Intervals for T-DM1

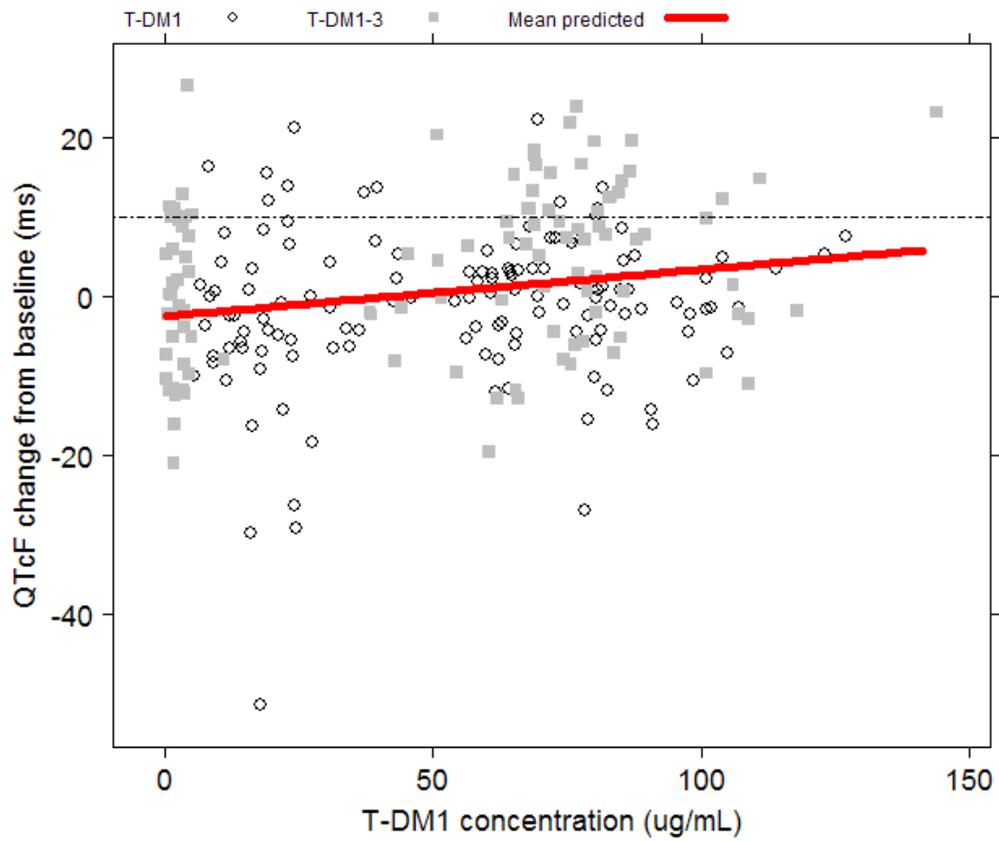
Time Point	N	Mean	Standard Error	95% LB	95% UB
Cycle 1 – Day 1 15 Min Post	44	1.23	0.47	0.44	2.02
Cycle 1 – Day 1 60 Min Post	45	0.41	0.45	-0.34	1.17
Cycle 1 – Day 8 Exp-Dosing	41	1.10	0.76	-0.19	2.39
Cycle 3 – Day 1 15 Min Pre	35	0.45	0.77	-0.84	1.75
Cycle 3 – Day 1 15 Min Post	36	1.90	0.68	0.75	3.04
Cycle 3 – Day 1 60 Min Post	37	1.47	0.62	0.42	2.51

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated previously in Figure 2.

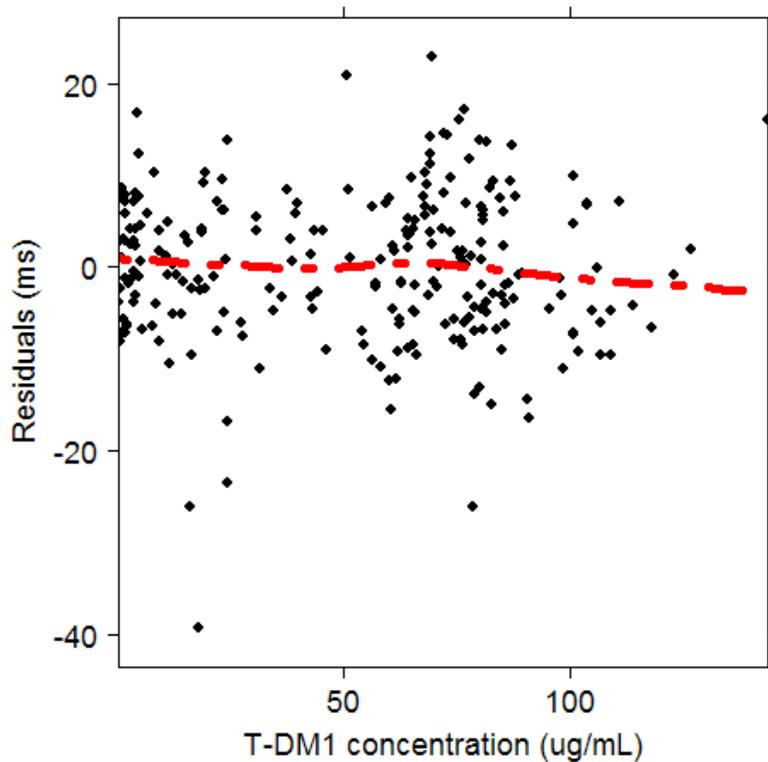
The reviewer analyzed the data via pooling the observations from both Cycles 1 and 3. The relationship between Δ QTcF and T-DM1 concentrations is visualized in Figure 6 with a significant exposure-response relationship being observed. Independent review yielded a positive and significant relationship between T-DM1 plasma concentrations and Δ QTcF with a positive slope of 0.059 ms per ug/mL (95%CI: 0.030 – 0.087, p-value = <0.0001). Of note, statistically significant but shallow exposure-response relationships were observed for both DM1 and total trastuzumab concentrations.

Figure 6: Δ QTcF vs. T-DM1 concentration



Residuals analysis for the linear model yielded an adequate fit (Figure 7)

**Figure 7: Δ QTcF vs. T-DM1 Concentration (Residuals vs. T-DM1 concentration)
– Reviewer’s Analysis**



The relationship between Δ QTcF and T-DM1 concentrations was investigated by linear mixed-effects modeling.

The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

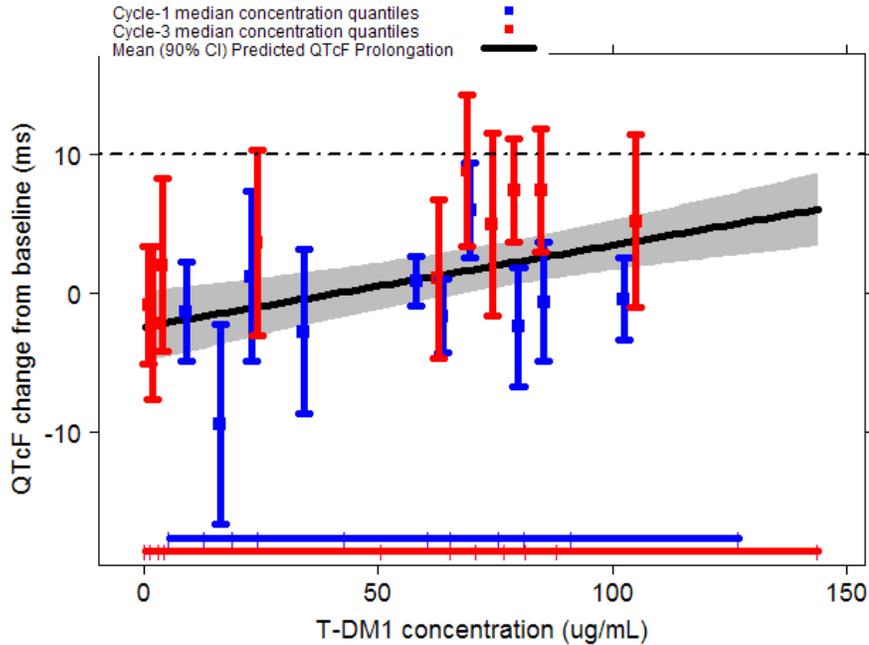
Table 11 summarizes the results of the T-DM1 concentration- Δ QTcF analyses. Model 1 was used for further analysis since the model with an intercept was found to fit the data best.

Table 11: Exposure-response Analysis of T-DM1 Associated Δ QTcF Prolongation

Parameter	Estimate	p-value	IIV (CV%)
<i>Model 1: $dQTcF = Intercept + slope * T-DM1 \text{ Concentration}$</i>			
Intercept (ms)	-2.46 (-5.03; 0.11)	0.1145	7.26
Slope (ms per ug/mL)	0.0588 (0.0304; 0.0872)	<0.0001	0
Residual Variability (ms)	8.73		
<i>Model 2: $dQTcF = Intercept + slope * T-DM1 \text{ Concentration (Fixed Intercept)}$</i>			
Intercept (ms)	0		7.53
Slope (ms per ug/mL)	0.0378 (0.0165; 0.0591)	0.0072	0
Residual Variability (ms)	8.76		
<i>Model 3: $dQTcF = slope * T-DM1 \text{ Concentration (No Intercept)}$</i>			
Slope (ms per ug/mL)	0.0264 (0.00494; 0.0478)	0.0449	0.05
Residual Variability (ms)	9.79		

The goodness-of-fit plot in Figure 8 shows the observed median-quantile T-DM1 concentrations and associated mean Δ QTcF (90% CI) together with the mean (90% CI) predicted Δ QTcF.

Figure 8: Δ QTcF vs. T-DM1 concentration, linear model prediction– Reviewer’s Analysis

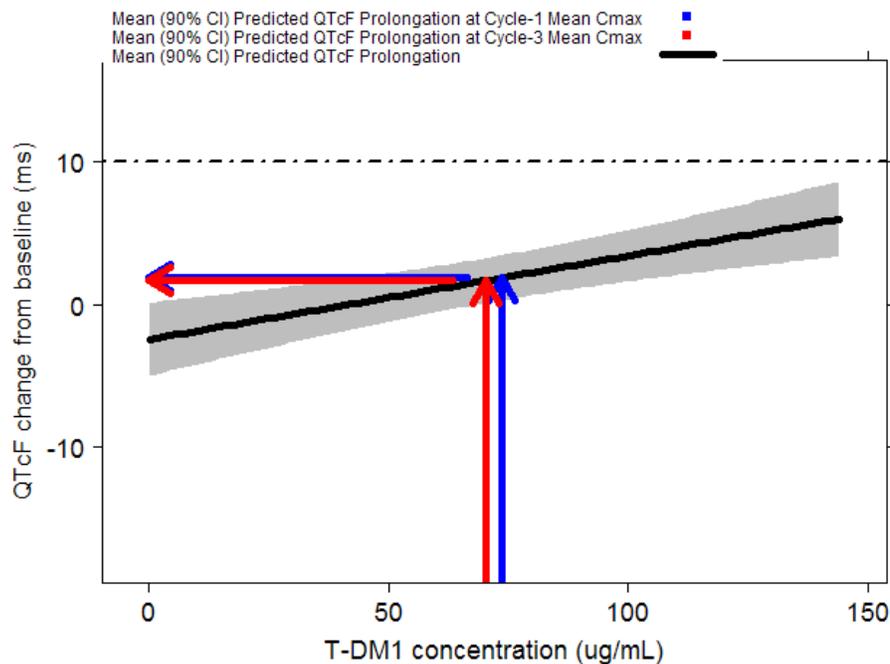


The predicted Δ QTcF at the geometric mean peak T-DM1 concentrations can be found in Table 12 and graphically in Figure 9.

Table 12: Predicted Δ QTcF Interval at Geometric Mean Peak T-DM1 Concentration Using Model 1, By Cycle

Treatment	Geometric Cmax (ug/mL)	Predicted Δ QTcF (ms)	90% Confidence Interval
Cycle-1	73.7 ug/mL	1.87	(0.286; 3.46)
Cycle-3	70.5 ug/mL	1.68	(0.099; 3.27)

Figure 9: Δ QTcF vs. T-DM1 concentration, linear model prediction– Reviewer’s Analysis



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	3.6 mg/kg every 3-week regimen	
Maximum tolerated dose	3.6 mg/kg in an every 3-week regimen (3.6 mg/kg in 21-day cycle) or 2.4 mg/kg in an every week regimen (cumulative dose of 7.2 mg/kg in 21-day cycle)	
Principal adverse events	<p>The most common adverse drug reactions (frequency > 25%) with KADCYLA (n=884 treated patients) were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation.</p> <p>Dose limiting adverse events: thrombocytopenia is the dose limiting toxicity</p>	
Maximum dose tested	Single Dose	4.8 mg/kg in every 3-week regimen; 2.9 mg/kg in every week regimen
	Multiple Dose	q3w regimen: every 21-days (Cycle); qw regimen: every week x 3 doses in 21-day cycle
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Mean (%CV) Cmax and AUC of trastuzumab emtansine conjugate:</p> <p>Cycle 1 Cmax @ 4.8 mg/kg: 130 (± SD 7.7; %CV 5.9) µg/mL</p> <p>Cycle 1 AUC @ 4.8 mg/kg: 673 (± SD 12.2; %CV 1.8) day*µg /mL</p>
	Multiple Dose	No accumulation of trastuzumab emtansine conjugate and DM1 following multiple dose; similar exposures as Cycle 1 after multiple doses and steady state achieved within Cycle 1; Modest accumulation of total trastuzumab analyte is expected.
Range of linear PK	<p>Linear PK in dose range 2.4 mg/kg – 4.8mg/kg; At doses less than/equal to 1.2 mg/kg nonlinear PK with faster clearance.</p> <p>Non-linearity in trastuzumab emtansine pharmacokinetics was observed at doses of ≤ 1.2 mg/kg (mean CL: 21.1 to 27.8 mL/day/kg). At doses of ≥ 2.4 mg/kg, clearance was slower (mean CL: 7.1 to 12.7 mL/day/kg). Assessment of dose linearity was limited by the small number of patients evaluated, especially at doses below 2.4 mg/kg q3w.</p>	
Accumulation at steady state	<p>In TDM4370g/BO21977 (EMILIA: Phase III study following 3.6 mg/kg trastuzumab emtansine administration in an every q3w regimen) no accumulation of trastuzumab emtansine conjugate and DM1 was observed. Modest accumulation of total trastuzumab expected based on half-life.</p> <p><u>Trastuzumab ematansine conjugate:</u></p> <p>Cycle 1 Cmax: 83.4 (± SD 16.5; %CV 19.7) µg/mL</p> <p>Cycle 1 AUC: 489 (± SD 122; %CV 25) day*µg/mL</p> <p>Cycle 4 Cmax 85.0 (± SD 33.4; %CV 39.3) µg/mL</p> <p>Cycle 4 AUC: 475 (± SD 127; %CV 26.7) day*µg/mL</p> <p><u>Total Trastuzumab:</u></p> <p>Cycle 1 Cmax : 86.3 (± SD 20.1; %CV 23.2) µg/mL</p> <p>Cycle 1 AUC: 816 (± SD 422; %CV 51.7) day*µg/mL</p>	

	<p>Cycle 4 Cmax: 87.4 (\pm SD 30.7; %CV 35.2) μg/mL</p> <p>Cycle 4 AUC: 604 (\pmSD 166; %CV 27.5) day*μg/mL</p> <p><u>DM1:</u></p> <p>Cycle 1 Cmax: 4.61 (\pm SD 1.61; %CV 35.0) ng/mL</p> <p>Cycle 4 Cmax: 5.13 (\pm SD 4.09; %CV 79.9) ng/mL</p>	
Metabolites	<p><u>Include listing of all metabolites and activity</u></p> <p>Trastuzumab emtansine is expected to undergo catabolism by means of proteolysis in cellular lysosomes, with no significant involvement of cytochrome (CYP) enzymes. Catabolites including Lys-MCC-DM1, MCC-DM1 and DM1 are detected at low levels in human plasma. Across clinical studies, mean maximum DM1 concentrations in Cycle 1 following trastuzumab emtansine administration were consistently low and averaged approximately 6 ng/mL.</p> <p>In vitro metabolism studies in human liver microsomes suggest that DM1, a component of trastuzumab emtansine, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5.</p> <p>Preclinical pharmacology experiments suggest that DM1 containing catabolites like Lys-MCC-DM1 are active.</p> <p>Trastuzumab emtansine (T-DM1), DM1-methyl (capped DM1), and DM1 potently inhibited proliferation of SK BR 3 cells treated for 5 days. IC50 values for T-DM1 and DM1 methyl were 0.02 and 0.016 nM, respectively, while the value for DM1 was 0.4 nM, approximately 20 fold lower. DM1 has a free sulfhydryl group for conjugation purposes. However, this moiety is expected to react with other SH-containing molecules, such as glutathione or albumin, potentially resulting in reduced availability and lower potency. Evidence of this was shown by the greater potency of DM1-methyl compared to DM1. The catabolic products of T-DM1 measured intracellularly, Lys-MCC-DM1 and MCC-DM1, were also assessed in proliferation assays. Both DM1 and DM1 methyl were significantly more potent and exhibited maximal anti proliferative activity at concentrations between 0.1–10 nM (0.07–7 ng/mL). In contrast, Lys-MCC-DM1 tested at 10 nM (11 ng/mL) had no anti-proliferative activity in SK-BR-3 cells. Similarly, MCC-DM1 exhibited no anti proliferative activity at the highest concentration tested (10 nM, 9.6 ng/mL). In patients, the maximum concentrations detected in plasma did not exceed 6 ng/mL and 122 ng/mL for Lys-MCC-DM1, and MCC-DM1, respectively. To date, DM1 concentrations across Phase II and Phase III studies have not exceeded 60 ng/mL</p>	
Absorption	Absolute/ Relative Bioavailability	Not applicable; administered as an intravenous infusion
	Tmax	<p>Maximum concentration for trastuzumab emtansine conjugate achieved at end of infusion</p> <p>Both DM1 and MCC-DM1 appear to have maximum concentration at end of infusion. Lys-MCC-DM1 appears to have a lag time for formation.</p>

		Mean ± SD (Min-Max)		
Cycle	Time points	DM1 (ng/mL)	MCC-DM1 (ng/mL)	Lys-MCC-DM1 (ng/mL)
1	Predose	<0.737	<1.90	<1.08
	1 hour postinfusion	5.32 ± 1.48 (1.89–8.75)	34.40 ± 24.39 (6.47–122)	1.35 ± 0.133 (1.25–1.45)
	Day 8	<0.737	<1.90	1.94 ± 1.30 (<1.08–6.38)
3	Predose	<0.737	<1.90	1.19 ± 0.097 (1.09–1.28)
	1 hour postinfusion	5.51 ± 1.71 (<0.737–9.72)	25.6 ± 19.5 (3.18–87.9)	1.44 ± 0.240 (1.13–1.80)
	Day 8	0.882 ± 0.378 (<0.737–1.69)	<1.90	2.08 ± 0.579 (1.11–3.07)

DM1 lower limit of quantification = 0.737 ng/mL; MCC-DM1 lower limit of quantification = 1.90 ng/mL; Lys-MCC-DM1 lower limit of quantification = 1.08 ng/mL. SD, standard deviation; T-DM1, trastuzumab emtansine.

Reference: Current Drug Metabolism, Volume 13, Number 7, September 2012, pp. 901-910(10)

Distribution	Vd/F or Vd	Based on the population PK analysis, the estimated Vc for trastuzumab emtansine conjugate is 3.127 L The Bayesian posthoc Vc from 671 patients is 3.10 L (± SD 0.468; %CV 15.0) on average
	% bound	Trastuzumab emtansine is a large molecule and therefore protein binding is not relevant. However, the DM1 component of trastuzumab emtansine is highly protein bound across species (>90% in rat, monkey and human).
Elimination	Route	<ul style="list-style-type: none"> Primary route; percent dose eliminated: Biliary route for elimination of DM1-containing catabolites (~50% of injected radioactivity recovered in bile and feces over 7-day and ~80% recovered in feces over 14-day. In nonclinical studies, catabolites of trastuzumab emtansine including DM1, Lys-MCC-DM1, and MCC-DM1 are mainly excreted in the bile with minimal elimination in urine. Other routes: Renal elimination is the minor route (less than 5% of injected radioactivity in urine).
	Terminal t _{1/2}	Based on population PK the estimated terminal half-life for trastuzumab emtansine conjugate is 3.94 days The Bayesian posthoc terminal t _{1/2} from 671 patients is 4.89 (± SD 4.40; %CV 89.9) Liter on average • Mean (%CV) for metabolites – terminal half-life not reportable for DM1 and other catabolites as concentrations majority of timepoints were not measurable.
	CL/F or CL	Based on population PK the estimated clearance for trastuzumab emtansine conjugate is 0.676 L/day The Mean Bayesian posthoc CL from 671 patients is 0.694

		(SD ± 0.178; %CV 25.6%CV) Liter/day
Intrinsic Factors	Age	No statistically significant correlation between trastuzumab emtansine conjugate clearance and subject age
	Sex	Majority of patients are females and thus not adequate data to test gender effect.
	Race	Pharmacokinetics in Asian and Korean patients appear to be similar to Caucasian patients
	Hepatic & Renal Impairment	No formal studies of trastuzumab emtansine in patients with renal and hepatic impairment have been conducted. Study in patients with hepatic impairment is ongoing.
Extrinsic Factors	Drug interactions	<p>No formal drug-drug interaction studies with trastuzumab emtansine in humans have been conducted. In vitro metabolism studies in human liver microsomes suggest that DM1, a component of trastuzumab emtansine, is metabolized mainly by CYP3A4 and, to a lesser extent, by CYP3A5. DM1 does not induce or inhibit P450-mediated metabolism in vitro at clinically relevant concentrations. Consequently, DM1 is unlikely to affect the pharmacokinetics of concomitant medications.</p> <p>Additionally, data from the Phase III pivotal clinical trial (TDM4370g/BO21977), demonstrated that concomitant administration of CYP3A inhibitors, CYP3A inducers or P-gp inhibitors with trastuzumab emtansine does not result in any noticeable change in the pharmacokinetics of either trastuzumab emtansine conjugate, total trastuzumab, or DM1.</p> <p>Preliminary PK analyses show that co-administration of docetaxel, paclitaxel, and pertuzumab do not appear to affect the pharmacokinetics of trastuzumab emtansine conjugate or DM1. Further, the pharmacokinetics of docetaxel, paclitaxel and pertuzumab are similar with or without co-administration of trastuzumab emtansine.</p>
	Food Effects	Not applicable; administered as an intravenous infusion
Expected High Clinical Exposure Scenario	No suprathreshold doses have been tested in patients; the highest dose tested was 4.8 mg/kg in q3w regimen.	

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/s/

SATJIT S BRAR
12/17/2012

KEVIN M KRUDYS
12/17/2012

MOH JEE NG
12/17/2012

QIANYU DANG
12/17/2012

NORMAN L STOCKBRIDGE
12/17/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 30, 2012

TO: Lisa Skarupa, Regulatory Project Manager
Gideon Blumenthal, Medical Officer
Division of Oncology Products 1

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

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125427

APPLICANT: Genentech, Inc.

DRUG: Trastuzumab Emtansine (T-DM1)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION(S): Treatment of Her2-positive, (b) (4) metastatic breast cancer in patients who have received prior treatment with trastuzumab and a taxane.

CONSULTATION REQUEST DATE: September 10, 2012
 INSPECTION SUMMARY GOAL DATE: November 15, 2012
 DIVISION ACTION GOAL DATE: December 31, 2012
 PDUFA DATE: February 25, 2013

I. BACKGROUND:

Genentech, Inc., seeks approval to market trastuzumab emtansine (T-DM1) as a single agent for the treatment of patients with human epidermal growth factor 2 (HER2)-positive, ^{(b) (4)} metastatic breast cancer (MBC) who have received prior treatment with trastuzumab (Herceptin; a monoclonal antibody that interferes with the HER2 receptor), and a taxane.

Trastuzumab emtansine is a novel antibody-drug conjugate that contains the humanized anti-HER2 IgG1 antibody trastuzumab and DM1, a microtubule-inhibitory maytansinoid, covalently linked through a thioether bond. Therefore, trastuzumab emtansine retains the mechanism of action of Herceptin coupled with the potent microtubule-inhibiting, cytotoxic DM1.

The application is based on the results of the pivotal Phase III study TDM4370g/BO21977 (EMILIA). The EMILIA trial was a randomized Phase 3 study comparing trastuzumab emtansine (T-DM1) with lapatinib and capecitabine in patients with HER2-positive metastatic breast cancer who had previously received trastuzumab and a taxane. EMILIA was performed from 2009-2012; it was a randomized, multicenter, open-label, active-controlled study of T-DM1 vs. Capecitabine + Lapatinib in subjects with HER2+ locally advanced or MBC. There were 991 subjects randomized 1:1 to receive either T-DM1 (495) or capecitabine/lapatinib (496) on 21-day treatment cycles. The study was conducted at 213 centers in 26 countries. This study was conducted under IND 71,072.

Four clinical sites, chosen on the basis of patient number enrolled at each site, were inspected for this BLA. Because this is an NME, the sponsor and a CRO (Independent Review Committee [IRC] for progression free survival [PFS] determination) were also inspected.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: <u>Seock Ah Im</u> , Do-Youn Oh Seoul National Uni Hospital Dept of Internal Medicine/Hema 28 Yongon-Dong, 110-744 Seoul, Republic of Korea	Protocol: TDM4370g/BO21977 (EMILIA) Site#: 163500 (Roche) S25967(Genentech) Number of Subjects: 36	November 19-23, 2012	Pending Interim classification: NAI

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#2: Jungsil Ro National Cancer Center; Medical Oncology 809 Madu 1-Dong Ilsan-GU Goyang-SI, 411-769 Kyunggi-Do, Republic of Korea	Protocol: TDM4370g/BO21977 (EMILIA) Site#: 163502 (Roche) S26016 (Genentech) Number of Subjects: 27	November 12-16, 2012	Pending Interim classification: NAI
CI#3: Soo Hyeon Lee Yonsei Uni College of Medicine; Severance Hospital; Internal Medicine 134 Shinchon-Dong, Seodaemun-GU, CPO Box 8044, 120-752 Seoul, Republic of Korea	Protocol: TDM4370g/BO21977 (EMILIA) Site#: 163504 (Roche) S25968 (Genentech) Number of Subjects: 23	November 26-30, 2012	Pending Interim classification: NAI
CI#4: Sunil Verna Sunnybrook Odette Cancer Centre 2075 Bayview Avenue T1-155 M4N 3M5 Toronto, Ontario, Canada	Protocol: TDM4370g/BO21977 (EMILIA) Site#: 163026 (Roche) S25585 (Genentech) Number of Subjects Screened/Enrolled: 49/24	October 29- November 2, 2012	Pending Interim classification: OAI
CRO: (b) (4)	Protocol: TDM4370g/BO21977 (EMILIA) Site# Records Reviewed: 163500 (Roche) 163502 (Roche) 163504 (Roche) 163026 (Roche)	(b) (4)	Pending Interim classification: VAI
Sponsor: Genentech, Inc. (member of the Roche Group) 1 DNA Way MS+241B South San Francisco, CA 94080-4990	Protocol: TDM4370g/BO21977 (EMILIA)	October 16-23, 2012	Pending Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

1. CI#1: – Seock Ah Im, Do-Youn Oh

(Site # 16350 [Roche] S25967 [Genentech])

Seoul National Uni Hospital Dept of Internal Medicine/Hema

28 Yongon-Dong, 110-744

Seoul, Republic of Korea

a. What was inspected: The site screened 47 subjects and 36 subjects were enrolled. Twelve subjects died. The study records were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents for all subjects, test article accountability, and monitoring and safety reports.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were generated by an IRC [REDACTED] ^{(b)(4)} The FDA field investigator verified that standard radiologic imaging modalities (CT/MRI/bone scans/X-rays) were performed in accordance with the protocol for each subject, reviewed by the site, and then sent for independent review. The primary efficacy endpoint data for the subjects enrolled at this site were verified during the CRO inspections. There was no evidence of under-reporting of AEs.

The FDA field investigator's very limited preliminary communication indicated that there were some minor inspectional observations, but data appear reliable. Details of these observations are not available at this time. No Form FDA 483 was issued.

c. Assessment of data integrity: The data for Dr. Seock Ah Im's site, associated with Study TDM4370g/BO21977 (EMILIA) submitted to the Agency in support of BLA 125427, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. **CI#2:** – Jungsil Ro
(Site 163502 [Roche] S26016 [Genentech])
National Cancer Center; Medical Oncology
809 Madu 1-Dong Ilsan-GU Goyang-SI, 411-769
Kyunggi-Do, Republic of Korea

- a. **What was inspected:** The site screened 31 subjects and 27 subjects were enrolled. Five subjects died. The study records were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents for all subjects, test article accountability, and monitoring and safety reports.
- b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were generated by an IRC [REDACTED] ^{(b) (4)}. The FDA field investigator verified that standard radiologic imaging modalities (CT/MRI/bone scans/X-rays) were performed in accordance with the protocol for each subject, reviewed by the site, and then sent for independent review. The primary efficacy endpoint data for the subjects enrolled at this site were verified during the CRO inspections. There was no evidence of under-reporting of AEs.

The FDA field investigator's very limited preliminary communication indicated that there were some minor inspectional observations but data appear reliable. Details of these observations are not available at this time. No Form FDA 483 was issued.

- c. **Assessment of data integrity:** The data for Dr. Jungsil Ro's site, associated with Study TDM4370g/BO21977 (EMILIA) submitted to the Agency in support of BLA 125427, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. **CI#3:** – Soo Hyeon Lee
(Site 163504 [Roche] S25968 [Genentech])
Yonsei Uni College of Medicine; Severance Hospital; Internal Medicine
134 Shinchon-Dong, Seodaemun-GU, CPO Box 8044, 120-752
Seoul, Republic of Korea

- a. **What was inspected:** The site screened 29 subjects and 23 subjects were enrolled. Nine subjects died. The study records were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record

audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents for all subjects, test article accountability, and monitoring and safety reports.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were generated by an IRC [REDACTED] ^{(b) (4)}. The FDA field investigator verified that standard radiologic imaging modalities (CT/MRI/bone scans/X-rays) were performed in accordance with the protocol for each subject, reviewed by the site, and then sent for independent review. The primary efficacy endpoint data for the subjects enrolled at this site were verified during the CRO inspections. There was no evidence of under-reporting of AEs.

The FDA field investigator's very limited preliminary communication indicated that there were some minor inspectional observations but data appear reliable. Details of these observations are not available at this time. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Soo Hyeon Lee's site, associated with Study TDM4370g/BO21977 (EMILIA) submitted to the Agency in support of BLA 125427, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- 4. CI#4:** – Sunil Verna
(Site 163026 [Roche] S25585 [Genentech])
Sunnybrook Odette
Cancer Centre
2075 Bayview Avenue
T1-155
M4N 3M5
Toronto, Ontario, Canada

- a. What was inspected:** The site screened 49 subjects and 24 subjects were enrolled. The study records of 12 study subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring and safety reports.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were generated by an IRC [REDACTED] (b)(4). The FDA field investigator verified that standard radiologic imaging modalities (CT/MRI/bone scans/X-rays) were performed in accordance with the protocol for each subject, reviewed by the site and then sent for independent review to the IRC. The primary efficacy endpoint data for the subjects enrolled at this site were verified during the CRO inspection [REDACTED] (b)(4). There was evidence of under-reporting of AEs, and the site also failed to always maintain adequate case history records. A Form FDA 483 was issued citing 2 inspectional observations.

Observation 1: Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically, not all study records in which original subject observations/data were recorded (source documentation) were maintained. The Clinical Trials Worksheets used to initially record observations/data including target lesion measurements, vital signs, subject weights, ECOG performance status, toxicities/adverse events, concomitant medications, and physician orders at each study visit were destroyed after the data were transcribed to the Clinical Trials Progress Notes for each of the 24 subjects enrolled in the study (Subjects 17251-17274).

OSI Reviewer Notes: The FDA field investigator informed that Dr. Verna agreed with the observation but indicated that he was following the "Clinical Trials SOP" for "Maintaining Rough Notes" that was in effect at his site during the conduct of this study. Therefore, the site was following an SOP that allowed for destruction of source records once data they contained were transcribed and verified. This was a systemic practice that was not corrected until October 2011. For this reason, the reliability of the data generated at this site could not be verified because the vast majority of original source records (Clinical Trials Worksheets) were disposed of after the data were transcribed to "Clinical Trials Progress Notes".

The OSI reviewer, Lauren Iacono-Connors, communicated this inspectional finding to the DOP1 Clinical Reviewer Gideon Blumenthal and CDTL Patricia Cortazar, on November 25, 2012 via email. Even though the site represented only a small percentage of study subjects randomized in this trial it was recommended that the review division conduct a sensitivity analysis to determine the effect, if any, on study outcome. Dr. Cortazar concurred. On November 26, 2012, review division statistician Dr. Qiang Xu confirmed that exclusion of this site's data did not change overall study results for primary analyses for PFS and overall survival (OS) based on ITT patients.

While there is no evidence to suggest that the data at this site are unreliable, the review division may wish to consider censoring the subjects enrolled at this site.

The FDA field investigator verified that on October 31, 2011, the Clinical Trials Breast Site Group took corrective action. These actions included the retraining of the Breast Site clinical research staff and a revised practice for maintaining source documents to ensure that all data collected are supported by source documentation in the health record and/or research records and allows for verification of clinical study information.

Observation 2: Not all adverse events (AE) experienced by subjects during their participation in the study were recorded in the AE electronic Case Report Form (eCRF) and reported to the study sponsor as required. For example,

- a. Subject #17255 - During Cycle 1 test article infusion [REDACTED]^{(b) (6)}, the Nursing Chemotherapy Administration Records reports that the subject experienced headaches and chills; however, these AEs were not recorded in the AE eCRF and reported to the sponsor.
- b. Subject #17259 – The Cycle 2 [REDACTED]^{(b) (6)} Clinical Trials Coverage Worksheet reports that the subject experienced dry cough (1 week duration), dry mouth, anorexia (4 days duration), diarrhea, fatigue (1 week duration), and fever; however, these AEs were not recorded in the AE eCRF and reported to the sponsor.
- c. Subject #17265 – The Clinical Trials Progress Note for Cycle 15 [REDACTED]^{(b) (6)} reports that the subject experienced an upper respiratory tract infection (URTI), grade 1; however, this AE was not recorded in the AE eCRF and reported to the sponsor.
- d. Subject #17270 – The Cycle 5 [REDACTED]^{(b) (6)} Clinical Trials Progress Note reports that the subject experienced vomiting, grade 3 from [REDACTED]^{(b) (6)} through [REDACTED]^{(b) (6)}; however, this AE was not recorded in the AE eCRF and reported to the sponsor.
- e. Subject #17274 – The Cycle 4 [REDACTED]^{(b) (6)} Clinical Trials Progress Note reports that the subject experienced taste changes, grade 1; nail changes, grade 1; and nausea, grade 1; however, these AEs were not recorded in the AE eCRF and reported to the sponsor in a timely manner. The AEs were not recorded in the AE eCRF until 11/1/2012.

OSI Reviewer Notes: *These inspectional observations should not importantly impact overall study data generated by this site. These AEs represent a very small percentage of AEs experienced by subjects at this site.*

- c. **Assessment of data integrity:** The reliability of the data for Dr. Sunil Verna's site, associated with Study TDM4370g/BO21977 (EMILIA) submitted to the Agency in support of BLA 125427, could not be verified based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

5. CRO: [REDACTED] (b) (4)

- a. What was inspected:** The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused primarily on assessing the integrity of the tumor response and disease progression data generated by the Independent Review Committee (IRC) for the Genentech/Roche clinical trial: TDM4370g/BO21977 (EMILIA), titled: A Randomized, Multicenter, Phase III Open-Label Study of the Efficacy and Safety of Trastuzumab-MCC-DMI vs. Capecitabine +Lapatinib in Patients with HER2-Positive Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Trastuzumab-Based Therapy. The inspection included a review of the firm's organization and personnel, training and qualification records, transfer of responsibilities, IRC Charter, financial disclosures, subject records and source documents, practices for training clinical sites, media (imaging) receipts, image qualifications and reading, handling and transferring data to the sponsor, and data assessment and validation for primary efficacy endpoint. Primary efficacy endpoints were reviewed for all applicable subjects at each of the 4 clinical sites listed above for the identified study.
- b. General observations/commentary:** Records and procedures were clear, and generally well organized. The date of disease progression for all subjects with progressed disease was compared with the data listings submitted to the application with no discrepancies identified. The primary efficacy endpoint data generated by this CRO as IRC and submitted to BLA 125427 were verifiable at the CRO site for all clinical sites. However, the FDA field investigator found that the CRO failed to follow the investigational plan and IRC Charter. The inspectional observation potentially impacts the integrity of the entire PFS efficacy endpoint data listing submitted to the application. A Form FDA 483 was issued citing failure to provide investigators with the information needed to conduct the study properly.

Observation 1: Failure to provide investigators with the information needed to conduct the study properly.

The clinical information the sponsor [Genentech] sent (on or about 02/21/2012) for the [CRO] Independent Review Committee's final review contained lists of drug-related toxicities that were specifically prohibited by the Independent Review Charter [The Charter], Version 4, Section 4.2, which states in part, "*Any information about specific toxicities of any drug, such as palmar-plantar dysesthesia, hand-foot syndrome, rash, diarrhea, or thrombocytopenia must be removed...*". In addition, although Section 4.1.2 of The Charter states in part, "*Clinical information must be redacted of all references to study medication treatment group*", the sponsor included concomitant drug information that referenced the study medications (for example, "*premedication for TDM1*",

"post-Xeloda hot flashes", and "lapatinib for anti-cancer"). The medical oncologist members of the [CRO] IRC, therefore, were not provided with the proper information they needed to make a treatment-blinded final determination of treatment response.

OSI Reviewer Notes: According to the IRC Charter for Study TDM4370g, the IRC conducted two independent assessments for determining PFS; defined as the time from randomization to the first occurrence of progression by modified RECIST or death from any cause. The first review of tumor assessment was conducted by two radiologists, with an adjudicator as needed, for primary efficacy endpoint of PFS based solely upon study-specified periodic imaging (radiologic scans; CT/MRI). The radiologists were blinded to the study subject's treatment. The second review was conducted by a medical oncologist based upon both the radiology assessment, as well as additional clinical information for each subject [clinical dossier] prepared by the sponsor [Genentech] per IRC Charter. It was this latter assessment that determined the final primary efficacy endpoint for this study.

The sponsor provided clinical data for each subject to [REDACTED] (b) (4) who then provided this information to the blinded independent medical oncologist reviewer, however, the data included Charter-specified prohibited information, resulting in subject unblinding. Further, the medical oncologist reviewers did not report that the clinical data contained extensive prohibited information. This observation was corroborated during the sponsor inspection [Genentech]. The sponsor concurred with the inspectional observation and assumes full responsibility. Genentech stated that the toxicity data was made available to the medical oncologists (blinded IRC readers) to support their review of subject radiological scans in order to determine a final assessment on disease progression and/or confirm PFS. However, the sponsor admitted that they were uncertain as to why excluded data were provided to the central IRC reader. Genentech attributed the failure to a "breakdown in internal QC processes..."

The OSI reviewer, Lauren Iacono-Connors, communicated these inspectional findings to the DOP1 Clinical Reviewer Gideon Blumenthal and CDTL Patricia Cortazar, on October 19, 2012, via email and telecom while the CRO and Sponsor inspections were still ongoing. Dr. Cortazar and Dr. Blumenthal concurred that this observation could have significant impact of the integrity of the primary efficacy endpoint data submitted in the application and that an immediate teleconference with the sponsor would be required to clarify what was done by the sponsor, and what additional information could be provided by the sponsor to better understand the impact on the primary efficacy endpoint data submitted to the application. A telecon was held between the DOP1 clinical review team, OSI, and the sponsor [Genentech] on October 23, 2012.

Genentech agreed with the observation and to provide to the Agency the following information initially via email followed by a formal submission to the BLA:

1. *A document which summarizes Genentech's assessment of the impact on the co-primary endpoint of PFS:*
 - a. *Agreement rate of 94% for PFS status between radiology and oncology assessments*
 - b. *PFS analysis based on blinded radiology read (HR=0.644)*
 - c. *Sensitivity analysis of PFS based on earlier date of either the radiology or oncology progression event (HR=0.658).*
2. *Supporting information for the above analyses.*
3. *Patient ID for those patients with disagreement between radiology and oncology on PFS status or date will be provided along with reason for disagreement.*
4. *A description of tumor and response level IRC datasets submitted in the BLA will be provided.*
5. *SAS programs for*
 - *the derivation of PFS variables based on blinded Radiology assessments*
 - *summarizing agreement rates*
 - *the two new PFS analyses.*

Dr. Cortazar informed OSI on November 25, 2012 that DOP1 “conducted several exploratory analyses and the unblinding of the IRC oncologist assessment did not impact the study results”. Therefore, while the inspectional observations are a clear and significant systemic GCP compliance violation, failure to follow the investigational plan, the observation does not importantly impact study outcome.

- c. **Assessment of data integrity:** The data generated at this site, as it pertains to Study TDM4370g/BO21977 (EMILIA) were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Notwithstanding the inspectional observations the data from this CRO submitted to the agency in support of BLA 125427 appear reliable.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

6. **Sponsor:** Genentech, Inc.
1 DNA Way MS+241B
South San Francisco, CA
94080-4990

- a. **What was inspected:** The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection covered adherence to Protocol, and review of the firm's SOPs,

monitoring reports, actions related to monitoring deficiencies, Ethics Committee/IRB approvals, completed Form FDA 1572s, communications with the sites, drug accountability, and review of data management from the clinical study sites to the submission of the BLA to the Agency. The FDA field investigator specifically audited subject records from 4 clinical study sites; Site 16350 [Roche], S25967 [Genentech] (Dr. Seock Ah Im), Site 163502 [Roche], S26016 [Genentech] (Dr. Jungsil Ro), Site 163504 [Roche], S25968 [Genentech] (Dr. Soo Hyeon Lee), and Site 163026 [Roche], S25585 [Genentech] (Dr. Sunil Verna), against the data listings submitted to BLA 125427.

- b. General observations/commentary:** Records and procedures were clear, and generally well organized. There was nothing to indicate under-reporting of AEs/SAEs. The primary efficacy endpoint data were verified for the four audited sites. Overall site monitoring appeared adequate. The Sponsor appeared to maintain adequate oversight of the study. The FDA field investigator issued a Form FDA 483 citing inspectional observations.

Observation 1: Failure to ensure that an investigation was conducted in accordance with the investigational plan and protocols as specified in the IND.

Specifically, the Independent Review Committee Charter for Protocol TDM4370g was not followed in that information about specific toxicities of any study drug was not excluded from the Clinical Data for Oncology Review even though the charter required these data to be excluded in Section 4.1.2 of the Charter.

OSI Reviewer Notes: Please refer to OSI Review Notes related to the CRO inspection summary in this report (Inspection 5). Briefly, after a thorough assessment of the impact of this inspectional observation on study data the DOP1 clinical review team has determined the observation does not importantly impact study outcome. Therefore, while the inspectional observations are a clear and significant systemic GCP compliance violation, failure to follow the investigational plan, the observation does not importantly impact study outcome.

- c. Assessment of data integrity:** The data generated at this site, as it pertains to Study TDM4370g/BO21977 (EMILIA) were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Notwithstanding the inspection observations the findings are that the data from this Sponsor submitted to the agency in support of BLA 125427 appear reliable.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Seock Ah Im, Dr. Jungsil Ro, Dr. Soo Hyeon Lee, a study CRO [REDACTED] (b) (4) and the study sponsor, Genentech, Inc., the study [TDM4370g/BO21977 (EMILIA)] data collected appear reliable based on available information. The study data generated by Dr. Sunil Verna could not be verified.

The preliminary classification for clinical investigators Dr. Seock Ah Im, Dr. Jungsil Ro, Dr. Soo Hyeon Lee, is No Action Indicated (NAI). The study sponsor [Genentech] and the CRO responsible for Independent Review Committee's (IRC) functions [REDACTED] (b) (4) were issued a Form FDA 483 citing inspectional observations and the preliminary classification for these inspections is Voluntary Action Indicated (VAI). The preliminary classification for clinical investigator Dr. Sunil Verna is OAI (Official Action Indicated).

With respect to the inspections of Genentech and [REDACTED] (b) (4), there was a systemic failure to follow the investigational plan and IRC Charter that could potentially impact the reliability of the PFS efficacy endpoints generated by the IRC. According to the IRC Charter for Study TDM4370g, the IRC conducted two independent assessments for determining PFS (defined as the time from randomization to the first occurrence of progression by modified RECIST, or death from any cause). The first review of tumor assessment was conducted by 2 radiologists, with an adjudicator as needed, for primary efficacy endpoint of PFS based solely upon study-specified periodic imaging (radiologic scans; CT/MRI). The radiologists were blinded to the study subject's treatment. The second review was conducted by a medical oncologist based upon both the radiology assessment, as well as additional clinical information for each subject prepared by the sponsor [Genentech] per IRC Charter. It was this latter assessment that determined the final primary efficacy endpoint for this study. The inspection revealed that the Sponsor provided clinical data for each subject to [REDACTED] (b) (4) who then provided this information to the "blind independent medical oncologist reviewer", however, the data included Charter-specified prohibited information, resulting in subject unblinding.

In order to clarify what was done by the Sponsor, and what additional information could be provided by the Sponsor to better understand the impact on the primary efficacy endpoint data submitted to the application a telecom was held between the DOP1 clinical review team and OSI, and the Sponsor on October 23, 2012. Genentech agreed with the observation and to provide to the Agency additional information and analyses to determine impact on the clinical endpoint. After a thorough assessment of the impact of this inspectional observation on study data the clinical review team determined the observation does not importantly impact study outcome. Therefore, while the inspectional observations are a clear and significant systemic GCP compliance violation, i.e. failure to follow the investigational plan, the observation does not importantly impact study outcome.

The inspection of Dr. Sunil Verna revealed that the site failed to retain source documentation, "Clinical Trials Worksheets", used to initially record observations/data including target lesion measurements, vital signs, subject weights, ECOG performance status, toxicities/adverse events, concomitant medications, and physician orders at each study visit. These worksheets were destroyed after the data were transcribed to the Clinical Trials Progress Notes for each of the 24 subjects enrolled in the study (Subjects 17251-17274). The site was following an SOP that allowed for destruction of source records once data they contained were transcribed and verified. This was a systemic practice that was not corrected until October 2011. For this reason, the reliability of the data generated at this site could not be verified. While there is no additional evidence to suggest that the data at this site are unreliable, the review division may wish to consider censoring the subjects enrolled at this site. The review division conducted a sensitivity analysis and informed that exclusion of this site data did not change overall study results for primary analyses for PFS and OS based on ITT patients.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data for study TDM4370g/BO21977 (EMILIA) in support of this application may be considered reliable based on available information.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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

/s/

LAUREN C IACONO-CONNORS
11/30/2012

JANICE K POHLMAN
11/30/2012

SUSAN D THOMPSON
11/30/2012

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Oncology Products 1

Application Number: BLA 125427/0000

Name of Drug: trastuzumab emtansine 100 mg and 160 mg vials (20 mg/mL)

Applicant: Genentech, Inc.

Material Reviewed:

Submission Date: August 24, 2012

Receipt Date: August 27, 2012

Submission Date of Structure Product Labeling (SPL): August 24, 2012

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the Applicant's proposed labeling.

1. White space must be present consistently before each major heading in Highlights.
2. Each summarized statement in Highlights must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. Highlights need to be consistent. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).
3. The Bolded revision date (i.e., "Revised: MM/YYYY or Month Year") at the end of Highlights needs to be modified to MM/YYYY.
4. All section headings under Table of Contents must be **bolded**.
5. A horizontal line must also be located between the TOC and the FPI.

6. Throughout the Full Prescribing Information, formatting is inconsistent to the preferred presentation for cross-references in the FPI which is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [see Warnings and Precautions (5.2)].

Recommendations

Please address the identified deficiencies/issues and re-submit labeling in two weeks. This updated version of labeling will be used for further labeling discussions.

Lisa Skarupa, RN, MSN
Regulatory Project Manager DOP1

Supervisory Comment/Concurrence:

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff

Drafted: October 16, 2012
Revised/Initialed: October 22, 2012
Finalized: October 22, 2012
Filename: RPMLabelingReview(BLA125427)
CSO LABELING REVIEW OF PLR FORMAT

Selected Requirements of Prescribing Information (SRPI)

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

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

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

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

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

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

Comment:

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

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment: *The Highlights page is inconsistently with white space.*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Only one bullet does not follow the preferred format.*

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

Selected Requirements of Prescribing Information (SRPI)

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

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

Comment:

YES

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

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

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

NO

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

Comment:

Initial U.S. Approval

YES

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

Comment:

Boxed Warning

N/A

Selected Requirements of Prescribing Information (SRPI)

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC)

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Indications and Usage

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

Comment:

Dosage Forms and Strengths

YES

Selected Requirements of Prescribing Information (SRPI)

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

Comment:

Contraindications

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

Comment:

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

Comment:

Adverse Reactions

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

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

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

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

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

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Revised date should follow preferred format of MM/YYYY at the end of HL.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

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

Comment:

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

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- NO** 32. All section headings must be **bolded** and in UPPER CASE.

Comment: TOC section headings need to be bolded, they are already in UPPER CASE.

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment: See comment below, #38.

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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

Selected Requirements of Prescribing Information (SRPI)

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

Comment: Section 8.3 cannot be omitted, must also reflect in the TABLE OF CONTENTS.

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

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: The preferred presentation for cross-references are inconsistent.

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

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

Comment:

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

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI)

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

Comment:

Adverse Reactions

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

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

Comment:

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

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

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

21 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS)
immediately following this page

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

/s/

LISA M SKARUPA
10/22/2012

ALICE KACUBA
10/22/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # BLA# 125427	NDA Supplement #: BLA Supplement # 0000	Efficacy Supplement Type SE-
Proprietary Name: KADCYLA Established/Proper Name: trastuzumab emtansine Dosage Form: sterile lyophilized single use vial, intravenous infusion Strengths: 100 mg and 160 mg vials (20mg/mL)		
Applicant: Genentech, Inc. Agent for Applicant (if applicable): NA		
Date of Application: August 27, 2012 Date of Receipt: August 27, 2012 Date clock started after UN:		
PDUFA Goal Date: February 26, 2012		Action Goal Date (if different): December 28, 2012
Filing Date: October 26, 2012		Date of Filing Meeting: Sept 19, 2012
Chemical Classification:(1,2,3 etc.)(original NDAs only) (Not applicable to BLA 125427: this product is an antibody-drug conjugate)		
Proposed indication(s)/Proposed change(s): single agent for treatment of patients with HER2-Positive Metastatic Breast Cancer		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input checked="" type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): 071072				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>		X		
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: see comment</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>			X	BLA: Genentech (b) (4)
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>			X	
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

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

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA # Companion Diagnostic Supplements –PMA#s P040005/S009 for HER2 FISH PharmDx kit P980018/S016 for HercepTest	X			The supplements have 180 days review, due Feb 20, 2013
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	This is in August 27, 2012 submission Module 5.
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	This is in the July 31, 2012 submission Module 1.
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	X			

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Request for waiver in original submission June 12, 2012
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>			X	
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU)			

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

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

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

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)			X	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): September 24, 2008	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 3 2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): Through IND 071072 SPA-1 agreement on April 28, 2011 and SPA-2 on September 13, 2012	X			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 19, 2012

BLA #: 125427/0000

PROPRIETARY NAME: Kadcyla

ESTABLISHED/PROPER NAME: trastuzumab emtansine

DOSAGE FORM/STRENGTH: Dosage Form: sterile lyophilized single use vial,
intravenous infusion Strengths: 100 mg and 160 mg vials (20mg/mL)

APPLICANT: Genentech, Inc.

PROPOSED INDICATION: a HER2-targeted antibody-drug conjugate indicated, as a single agent, for the treatment of patients with HER2-positive, (b) (4) metastatic breast cancer who have received prior treatment with trastuzumab and a taxane.

BACKGROUND: Genentech submitted BLA 125427 as a rolling review, beginning with NonClinical Module (June 12), CMC Module (July 31), and final modules, Clinical & Clinical Pharmacology (August 27, 2012). They referenced their IND 071072 which was opened on December 16, 2005 for active enrollment to study HER2 positive metastatic breast cancer. They are submitting this BLA for trastuzumab emtansine (T-DM1) (prior codes of this product were: trastuzumab-MCC-DM1, PRO132365, RO5304020, Trastuzumab-SMCC-DM1, Tmab-MCC-DM1, T-MCC-DM1, Herceptin-DM1, Herceptin-SMCC-DM1, Herceptin-MCC-DM1, Hu Tmab-MCC-DM1). For this BLA submission, Genentech uses the International Nonproprietary Name (INN) Trastuzumab emtansine as the primary name. Genentech is the Applicant for the drug trastuzumab, or Herceptin (BLA 103792). Herceptin was approved in September 25, 1998. For their new BLA, BLA 125427, (b) (4). BLA 125427 provides for Genentech's pivotal study (TDM4370g/BO21977 EMILIA trial) to support their proposed indication.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Skarupa	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Patricia Cortazar		Y
Clinical	Reviewer:	Laleh Amiri-Kordestani Gideon Blumenthal	Y Y
	TL:	Patricia Cortazar	Y

Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Sarah Schrieber	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	Qiang (Casey) Xu	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	William McGuinn	Y
	TL:	Todd Palmby	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Linan Ha	Y
	TL:	Wendy Weinberg	Y
Product Quality (CMC)	Reviewer:	Xiao Chen And Anne Marie Russell	Y Y
	TL:	Hari Sarker	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Bo Chi and Maria Candauchacon	Y Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	Y

	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	N
	TL:	Cynthia LaCivita	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers: Clinical DSI	Lauren Iacono-Connors and Janice Pohlman.	N	N
Other reviewer: CDRH	Kevin Lorick	Y	
Other attendees	Frances Fahnbulleh-OSE	Y	

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The clinical study design was acceptable, the application did not raise significant safety or efficacy

<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>issues, the application did not raise significant public health questions on the role of trastuzumab emtansine in the treatment of Her2-positive metastatic breast cancer.</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments: Review to be done by Linan Ha</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, M.D.	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	<p>filing letter; For NDAs/NDA supplements: see CST for choices)</p> <ul style="list-style-type: none"> • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input checked="" type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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/s/

LISA M SKARUPA
10/22/2012

ALICE KACUBA
10/22/2012