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APPLICATION NUMBER:

125427Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	February 21, 2013
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
BLA #	125427
Applicant Name	Genentech, Inc.
Date of Submission	August 24, 2012
PDUFA Goal Date	February 26, 2013
Proprietary Name / Established (USAN) Name	Kadcyla/ ado-trastuzumab emtansine
Dosage Forms / Strength	100 mg and 160 mg in 15 mL and 20 mL single-use vials
Proposed Indication(s)	KADCYLA™, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy.
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Laleh Amiri-Kordestani, Gideon Blumenthal
Statistical Reviews	Qiang Xu, Shenghui Tang, Meiyu Shen
Pharmacology Toxicology Reviews	William McGuinn, Todd Palmby, John Leighton
OBP Reviews	Linan Ha, Wendy Weinberg, Kimberly Rains
ONDQA	Anne Marie Russell, Xiao-Hong Chen, Ali Al Hakim
Product Quality Microbiology	Bo Chi, Patricia Hughes, Reyes Candau-Chacon
OMPQ/NDMAB	Linda Ng
Clinical Pharmacology Review	Sarah Schrieber, Jian Wang, Pengfei Song
OPDP	Marybeth Toscano
OSI	Lauren Iacono-Connors
CDTL Review	Patricia Cortazar
OSE/DMEPA	Jibril Abdus-Samad
OSE/OMEPRM	Suzanne Robottom
IRT-QT Consultation	Satjit Brar, Kevin Kudys, Moh Ng, Qianyu Dang, Norman Stockbridge
CDRH/OIVD	Kevin Lorick

OND = Office of New Drugs
DPDP = Division of Professional Drug Promotion
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
OSI = Office of Scientific Investigations
DDRE = Division of Drug Risk Evaluation
DRISK = Division of Risk Management
CDTL = Cross-Discipline Team Leader
IRT-QT = Interdisciplinary Review Team for QT Studies
N/A = not applicable

Division Director Summary Review

1. Introduction

This Biologics License Application (BLA) for KADCYLA (ado-trastuzumab emtansine) is dated August 24, 2012, and was received on August 27, 2012. The final indication is "KADCYLA™, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy."

This review will summarize the efficacy and safety data supporting approval, the issues identified by and recommendations of each review discipline, and the risk benefit assessment.

This application was granted a priority review. An expedited review of less than four months was planned but was not possible because of manufacturing issues described below which were discovered during the review and manufacturing site inspections.

2. Background

The product and its mechanism of action are summarized in the following excerpt from the agreed-upon package insert.

> Ado-trastuzumab emtansine is a HER2-targeted antibody-drug conjugate. The antibody is the humanized anti-HER2 IgG1, trastuzumab. The small molecule cytotoxin, DM1, is a microtubule inhibitor. Upon binding to sub-domain IV of the HER2 receptor, ado-trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubule networks in the cell, which results in cell cycle arrest and apoptotic cell death. In addition, *in vitro* studies have shown that similar to trastuzumab, ado-trastuzumab emtansine inhibits HER2 receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity and inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2.

The regulatory history is summarized in the CDTL Review.

3. CMC/Device

DMA Primary Reviews

The Division of Monoclonal Antibodies (DMA) was the overall submission lead and was responsible for review of the antibody manufacturing. The DMA review dated 1/29/13 recommended approval of the BLA from a product quality perspective. Two PMR's and two PMC's were recommended but were not final at the time of this review.

The review noted that two significant issues were identified during the inspections of two manufacturing facilities. During the inspection of (b) (4), which manufactures the trastuzumab emtansine bulk drug substance, it was discovered that multiple lots of DM1 manufactured (b) (4) At the time of the inspection of (b) (4), which is one of the manufacturers of DM1, the root cause investigation was ongoing and no root cause had been identified. However, no cGMP violations were observed.

The addendum to the DMA review dated 2/6/13 finalized two pending PMC's and reviewed the response to an IR regarding modification of the post-approval stability protocol. The proposed stability protocol was deemed acceptable.

ONDQA Reviews

ONDQA was responsible for review of DM1, the linker, and the conjugation process. The review dated 1/28/13 stated that "From the small molecule DM1 perspective, this BLA is recommended for approval based on the adequate CMC information provided in the BLA and the post-marketing requirement Genentech has agreed upon (see below)."

A joint review dated 2/12/13 by OMPQ and ONDQA summarized the PMRs and PMCs recommended by OBP, ONDQA, and NDMAB. In addition, the proposed in-process testing (b) (4) and the acceptance limit was found to be acceptable by both NDMAB and ONDQA.

The Quality Team Leader's Executive Summary

The Quality Team Leader's Executive Summary provides the following recommendation and conclusion on approvability.

> The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125427 for KADCYLA (Ado-trastuzumab emtansine) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of KADCYLA (Ado-trastuzumab emtansine) is well controlled, and leads to a product that is pure and potent. The conditions used in manufacturing have been sufficiently validated and a consistent product was produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert.

The review stated that the following should be included in the approval letter:

> Under this license, you are approved to manufacture ado-trastuzumab emtansine bulk drug substance at (b) (4), and ado-trastuzumab emtansine final drug product at (b) (4). Drug product labeling and packaging will be done at Genentech Hillsboro Fill Finish Facility in Hillsboro, OR.
>
> The trade name for ado-trastuzumab emtansine is KADCYLA.
>
> The expiration date for ado-trastuzumab emtansine drug product, 160mg/vial, shall be 36 months at 2-8°C. The expiration date for ado-trastuzumab emtansine drug product, 100mg/vial, will be 24 months at 2-8°C.
>
> The expiration date for ado-trastuzumab emtansine drug substance shall be (b) (4). A cumulative expiry study supported holding drug substance (b) (4)
>
> The expiration date for trastuzumab intermediate is (b) (4).
>
> We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of the drug substance and drug product under 21 CFR 601.12. Data supporting extension of the expiration dating period should be submitted to the BLA Annual Report.
>
> Consistent with 21 CFR 601.12, Genentech must inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved application.

However, the review summarized the following significant manufacturing concerns that were identified during the review and inspections:

> ***Note: There were significant CMC concerns related to manufacture of ado-trastuzumab emtansine, both from the small molecule (DM1) and CGMP perspective. The small molecule concern relates to*** (b) (4) ***the drug substance manufacturing site. This was identified upon inspection of the*** (b) (4) ***drug substance manufacturing facility and brought back to the Agency as a review issue. Refer to reviews from ONDQA and NDMAB regarding this issue. Significant CGMP concerns include: 1) endotoxin masking effects and lack of a validated test method to measure endotoxin in final drug product stored in glass vials; 2) inadequate cleaning validation*** (b) (4) ***at the drug product facility*** (b) (4) ***Refer to reviews from BMAB regarding these CGMP issues.***

Product Quality Microbiology Reviews

The microbiology review of the drug substance made the following recommendation:

> The drug substance part of this application is recommended for approval from product quality microbiology perspective with the following post-market commitment:
>
> Conduct endotoxin spiking and recovery studies [redacted] (b) (4) Submit the information and study results in a CBE-30 by May 31, 2013.

The microbiology review of the drug product made the following recommendation on approvability:

> The Drug Product Section for BLA 125427 was reviewed and is recommended for approval from a CMC sterility assurance and microbiology product quality perspective with the following post-marketing commitments:
>
> 1. Transfer the methodology for validated dye ingress testing developed by Genentech to [redacted] (b) (4). Confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method by February 28, 2013 and report changes to the Agency in the 2014 Annual Report.
> 2. Conduct controlled studies to assess the risk of endotoxin masking [redacted] (b) (4) using endotoxin spiked trastuzumab emtansine drug product [redacted] (b) (4) and submit results and updated specifications to the Agency by March 29, 2013 as a PAS.
> 3. If endotoxin masking is observed in the drug product [redacted] (b) (4), develop an alternative method to quantitate endotoxin in the finished trastuzumab emtansine drug product [redacted] (b) (4) using routine production conditions. Any change in the analytical methods should be approved by the Agency before implementation. Submit protocol to the Agency by September 30, 2013 as a PAS.
> 4. Dedicate [redacted] (b) (4) for trastuzumab emtansine DP manufacture and submit results from sterilization validation and 3 media fill simulations to the Agency by June 30, 2013 as a CBE-0.
> 5. Conduct cleaning verification [redacted] (b) (4) and report the updated [redacted] (b) (4) procedures to the Agency in the 2014 Annual Report.

An addendum dated 2/12/13 reviewed cleaning verification results of the [redacted] (b) (4) drug product contract manufacturer for T-DM1. The review concluded [redacted] (b) (4)

The Team Leader Microbiology Product Assessment made the following recommendation for approvability:

> …The BLA sections were assessed from a microbial control, sterility assurance and microbiology product quality perspective. The BLA, as amended, is recommended for approval from a microbiology product quality perspective. Six post-marketing commitments (PMCs) should be communicated to the sponsor. The PMCs are as follows.
>
> 1. Conduct endotoxin spiking and recovery studies [redacted] Submit the final report as a Changes Being Effected in 30 days Supplement (CBE-30). The final report should be submitted by 05/13.
>
> 2. Transfer the methodology for validated dye ingress method developed by Genentech to [redacted]. Conduct a study to confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method and provide a final report in the 2014 annual report.
>
> 3. Conduct a study to assess the risk of endotoxin masking [redacted] using endotoxin spiked ado-trastuzumab emtansine drug product [redacted] Submit a final report that includes updated specifications as a Prior Approval Supplement. 29-Mar-2013 as a PAS. The final report should be submitted by 03/13.
>
> 4. If endotoxin masking is observed in the drug product [redacted], develop an alternative method to quantitate endotoxin in the finished ado-trastuzumab emtansine drug product [redacted] using routine production conditions. Any change in the analytical methods should be approved by the Agency before implementation. Submit protocol to the Agency by 30-June-2013 as a PAS.
>
> 5. [redacted] for ado-trastuzumab emtansine drug product manufacture and submit results from sterilization validation and 3 media fill simulations to the Agency by 30-June- 2013 as a CBE-0.
>
> 6. Conduct cleaning verification [redacted] until [redacted] is implemented and report the updated [redacted] procedures to the Agency in the 2014 Annual Report.

TB-EER

The TB-EER provided the following summary of the [redacted] issue:

> For a review of CGMP issues associated with the 11/2/12 IR response, please see the primary review of 2/12/13 by …, ONDQA, available in DARRTS. This review was

cleared through …, OMPQ/DGMPA/NDMAB and documents NDMAB's review of (b) (4) concerns highlighted in IR responses.

NDMAB has evaluated (b) (4) concerns through inspectional coverage and follow up discussions with the sponsor and CMO's (IR and teleconference). During these discussions, Genentech's initial responses, investigations (b) (4) and proposals (b) (4) were inadequate. The Agency determined that incorporating pre-marketing requirements and commitments into the action letter would generate adequate control of the observed (b) (4). These PMRs/PMCs (b) (4) have been drafted for inclusion in the action letter and have been agreed to by the sponsor.

As a result of these commitments, NDMAB is able to make a recommendation that the manufacturing facilities for DM1 should be considered acceptable provided that Genentech and (b) (4) continue to address issues (b) (4)

OMPQ/DGMPA/NDMAB recommendation:

After evaluation of the inspections in support of this supplement and Genentech's concurrence with the PMRs/PMCs proposed by the Agency, there are no pending or ongoing compliance actions that prevent approval of this BLA.

The manufacturing issues identified in the CMC and Microbiology reviews and in the TB-EER are being managed by PMRs and PMCs. I concur with the recommendations for approval.

4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology BLA Review and Evaluation stated that "There are no non-clinical findings of unacceptable toxicity that would prevent the approval of trastuzumab emtansine for this indication."

The Pharmacology/Toxicology Supervisor secondary review concurred with the primary reviewer's recommendation for approval and provided the following summary and evaluation (b) (4) of Kadcyla during manufacturing of the drug product.

During review of the BLA submission, members of the review team in the Division of Good Manufacturing Practice Assessment (DGMPA) within the Office of Compliance determined that the manufacturing contractor for the Kadcyla drug product has been using manufacturing equipment (b) (4) The reviewer in DGMPA … requested a consult from the Pharmacology/Toxicology review team to determine if the proposed limits (b) (4) in the Kadcyla drug product were acceptable.

(b) (4) In response to an information request from the review team, the Applicant submitted two proposed (b) (4). One was conducted by a third party consultant and the other by the manufacturer of (b) (4). Both ADE calculations were based on clinical data from administration of (b) (4). The proposed ADEs (b) (4) were (b) (4) Additional information submitted to the BLA in response to this information request included cleaning verification/validation data gathered in 2010 (b) (4)

From a Pharmacology/Toxicology perspective, the greatest concern (b) (4) in the Kadcyla drug product is (b) (4) Therefore, it would be more appropriate to evaluate (b) (4) in the Kadcyla drug product (b) (4) (b) (4)

Kadcyla is administered once every three weeks. The indicated patient population has HER2-positive metastatic breast cancer. The median duration of survival of patients treated with Kadcyla in the randomized clinical trial was 30.9 months and the median age of patients was 53 years (ranged from 24-85 years). The median duration of treatment with Kadcyla was 5.7 months. In teleconferences between the Applicant and the review team held during the review cycle for this BLA, the Applicant stated that cleaning verification/validation data will be collected (b) (4)

(b) (4)

Therefore, from a Pharmacology/Toxicology perspective, the proposed limit (b) (4) in the Kadcyla drug product is acceptable.

(b) (4) In response to another information request from the review team, the Applicant submitted cleaning verification/validation data (b) (4)

(b) (4) Therefore, from a Pharmacology/Toxicology perspective, the amount (b) (4) of ado-trastuzumab emtansine drug product is acceptable.

The tertiary pharmacology/toxicology review concurred with the analysis regarding risks (b) (4) and the conclusion that Kadcyla may be approved. No additional nonclinical studies are needed to support the proposed indication.

I concur with the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review stated that this BLA is considered acceptable from a clinical pharmacology perspective and provided the following summary of the clinical pharmacology.

> Trastuzumab emtansine (T-DM1, xxx-trastuzumab emtansine) is a HER-2-directed antibody-drug conjugate (ADC) consisting of trastuzumab, a humanized anti-HER2 IgG1 isotype monoclonal antibody, emtansine (DM1), an anti-microtubule agent derived from maytansine, and SMCC, a linker molecule used to conjugate DM1 to trastuzumab.
>
> *Mechanism of Action*: The mechanism of action of T-DM1 consists of a multi-step process. T-DM1 binds to HER2 then undergoes receptor-mediated internalization, which results in the intracellular release of DM1 and subsequently cell death.
>
> *Efficacy:* The proposed indication is for the treatment of patients with HER2-positive, (b) (4) metastatic breast cancer who have received prior treatment with trastuzumab and a taxane. One phase 3 randomized (1:1), open-label, active-control trial was conducted to support the proposed indication at a dose of 3.6 mg/kg T-DM1 given as an intravenous infusion over 30 minutes once every three weeks. Overall survival (OS) and progression free survival (PFS) were significantly longer in the T-DM1 arm compared to the active control arm (lapatinib plus capecitabine).
>
> *Exposure-Response (Efficacy and Safety):* After accounting for baseline risk factors, the exposure-response analysis demonstrated that increases in T-DM1 exposures are related with better efficacy (OS, PFS, and objective response rate (ORR)). Exposure-response relationships for safety identified an inverse trend for Grade 3 or worse hepatotoxicity, but no significant exposure-response relationships were identified for thrombocytopenia.
>
> Pharmacokinetics (PK): Data on the PK of T-DM1, total antibody, and DM is available from one phase 1 trial, four phase 2 trials, and one phase 3 trial. A population PK analysis estimated the T-DM1 clearance and terminal elimination half-life as 0.68 L/day and ~4 days, respectively; inter-individual variability of CL is 19.1%. T-DM1 accumulation was not observed following multiple dosing. No dose adjustments are required for significant covariates (sum of longest diameter of target lesions by RECIST, albumin, HER2 ECD concentrations, baseline trastuzumab concentrations, AST, and body weight). Based on the population PK analysis, as well as analysis of Grade 3 or greater adverse drug reactions and dose modifications, dose adjustments are not needed for mild or moderate renal impairment. The influence of hepatic impairment on the PK of T-DM1 or DM1 has not been determined. In vitro studies indicate that DM1, the cytotoxic component of T-DM1, is metabolized mainly by

> CYP3A4. Concomitant use of strong CYP3A4 inhibitors with T-DM1 should be avoided due to the potential for an increase in DM1 exposure and toxicity.
>
> Immunogenicity: With the immunogenicity assays used, the overall incidence of positive anti-therapeutic antibody (ATA) to T-DM1 was determined to be 5.3% in the studies included in the BLA. The presence of T-DM1 in patient serum at the time of ATA sampling can interfere with the ability of this assay to detect anti-KADCYLA antibodies. As a result, data may not accurately reflect the true incidence of anti-T-DM1 antibody development. In addition, neutralizing activity of anti-T-DM1 antibodies has not been assessed.
>
> QT: No large changes in the mean QT interval (i.e., >20 ms) were detected at the proposed T-DM1 dosing regimen.

The review recommended one PMR and one PMC.

I concur with the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The design of the randomized trial that supports approval and the efficacy results are summarized in the following excerpt from the agreed-upon package insert.

> The efficacy of KADCYLA was evaluated in a randomized, multicenter, open-label trial of 991 patients with HER2-positive, unresectable locally advanced or metastatic breast cancer. Prior taxane and trastuzumab-based therapy was required before trial enrollment. Patients with only prior adjuvant therapy were required to have disease recurrence during or within six months of completing adjuvant therapy. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 determined at a central laboratory. Patients were randomly allocated (1:1) to receive lapatinib plus capecitabine or KADCYLA. Randomization was stratified by world region (United States, Western Europe, other), number of prior chemotherapy regimens for unresectable locally advanced or metastatic disease (0–1, >1) and visceral versus non-visceral disease as determined by the investigators.
>
> KADCYLA was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Lapatinib was administered at 1250 mg/day orally once per day of a 21-day cycle and capecitabine was administered at 1000 mg/m^2 orally twice daily on Days 1−14 of a 21-

day cycle. Patients were treated with KADCYLA or lapatinib plus capecitabine until progression of disease, withdrawal of consent, or unacceptable toxicity. At the time of the primary analysis, median time on study drug was 5.7 months (range: 0–28.4) for KADCYLA, 4.9 months (range: 0–30.8) for lapatinib, and 4.8 months (range: 0–30.4) for capecitabine.

The co-primary efficacy endpoints of the study were progression-free survival (PFS) based on tumor response assessments by an independent review committee (IRC), and overall survival (OS). PFS was defined as the time from the date of randomization to the date of disease progression or death from any cause (whichever occurred earlier). Overall survival was defined as the time from the date of randomization to the date of death from any cause. Additional endpoints included PFS (based on investigator tumor response assessments), objective response rate (ORR), duration of response and time to symptom progression.

Patient demographics and baseline tumor characteristics were balanced between treatment arms. All patients had metastatic disease at study entry. The median age was approximately 53 years (range 24-84 years), 74% were White, 18% were Asian and 5% were Black. All but 5 patients were women. Twenty-seven percent of patients were enrolled in United States, 32% in Europe and 16% in Asia. Tumor prognostic characteristics including hormone receptor status (positive: 55%, negative: 43%), presence of visceral disease (68%) and non-visceral disease only (33%) and the number of metastatic sites (< 3: 61%, ≥ 3: 37%) were similar in the study arms.

The majority of patients (88%) had received prior systemic treatment in the metastatic setting. Twelve percent of patients had prior treatment only in the neoadjuvant or adjuvant setting and had disease relapse within 6 months of treatment. All but one patient received trastuzumab prior to study entry; approximately 85% of patients received prior trastuzumab in the metastatic setting. Over 99% percent of patients had received a taxane, and 61% of patients had received an anthracycline prior to study entry. Overall, patients received a median of 3 systemic agents in the metastatic setting. Among patients with hormone receptor-positive tumors, 44.4% received prior adjuvant hormonal therapy and 44.8% received hormonal therapy for locally advanced/metastatic disease.

The randomized trial demonstrated a statistically significant improvement in IRC-assessed PFS in the KADCYLA-treated group compared with the lapatinib plus capecitabine-treated group [hazard ratio (HR) = 0.65, 95% CI: 0.55, 0.77, $p < 0.0001$], and an increase in median PFS of 3.2 months (median PFS of 9.6 months in the KADCYLA-treated group vs. 6.4 months in the lapatinib plus capecitabine group). See Table 8 and Figure 1. The results for investigator-assessed PFS were similar to those observed for IRC-assessed PFS.

At the time of PFS analysis, 223 patients had died. More deaths occurred in the lapatinib plus capecitabine arm (26%) compared with the KADCYLA arm (19%), however the results of this interim OS analysis did not meet the pre-specified stopping boundary for statistical significance. At the time of the second interim OS analysis, 331 events had occurred. The co-primary endpoint of OS was met; OS was significantly improved in patients receiving KADCYLA (HR = 0.68, 95% CI: 0.55, 0.85, p = 0.0006). This result crossed the pre-specified efficacy stopping boundary (HR = 0.73 or p = 0.0037). The median duration of survival was 30.9 months in the KADCYLA arm vs. 25.1 months in the lapatinib plus capecitabine arm. See Table 8 and Figure 2.

A treatment benefit with KADCYLA in terms of PFS and OS was observed in patient subgroups based on stratification factors, key baseline demographic and disease characteristics, and prior treatments. In the subgroup of patients with hormone receptor-negative disease (n=426), the hazard ratios for PFS and OS were 0.56 (95% CI: 0.44, 0.72) and 0.75 (95% CI: 0.54, 1.03), respectively. In the subgroup of patients with hormone receptor-positive disease (n=545), the hazard ratios for PFS and OS were 0.72 (95% CI: 0.58, 0.91) and 0.62 (95% CI: 0.46, 0.85), respectively. In the subgroup of patients with non-measurable disease (n=205), based on IRC assessments, the hazard ratios for PFS and OS were 0.91 (95% CI: 0.59, 1.42) and 0.96 (95% CI: 0.54, 1.68), respectively; in patients with measurable disease the hazard ratios were 0.62 (95% CI: 0.52, 0.75) and 0.65 (95% CI: 0.51, 0.82), respectively. The PFS and OS hazard ratios in patients who were younger than 65 years old (n=853) were 0.62 (95% CI: 0.52, 0.74) and 0.66 (95% CI: 0.52, 0.83), respectively. In patients ≥ 65 years old (n=138), the hazard ratios for PFS and OS were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively.

Table 8 Summary of Efficacy from Study 1

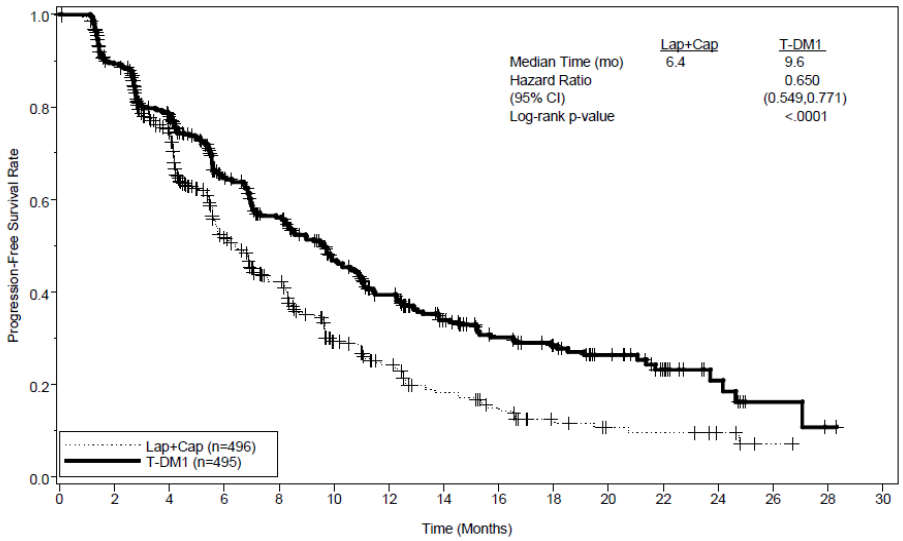
	KADCYLA N= 495	Lapatinib +Capecitabine N= 496
Progression-Free Survival (independent review)		
Number (%) of patients with event	265 (53.5%)	304 (61.3%)
Median duration of PFS (months)	9.6	6.4
Hazard Ratio (stratified*)	0.650	
95% CI for Hazard Ratio	(0.549, 0.771)	
p-value (Log-Rank test, stratified*)	<0.0001	
**Overall Survival ** **		
Number (%) of patients who died	149 (30.1%)	182 (36.7%)
Median duration of survival (months)	30.9	25.1
Hazard Ratio (stratified*)	0.682	
95% CI for Hazard Ratio	(0.548, 0.849)	
p-value (Log-Rank test*)	0.0006	
Objective Response Rate (independent review)		
Patients with measurable disease	397	389
Number of patients with OR (%)	173 (43.6%)	120 (30.8%)
Difference (95% CI)	12.7% (6.0, 19.4)	
Duration of Objective Response (months)		
Number of patients with OR	173	120
Median duration (95% CI)	12.6 (8.4, 20.8)	6.5 (5.5, 7.2)

PFS: progression-free survival; OR: objective response

* Stratified by world region (United States, Western Europe, other), number of prior chemotherapeutic regimens for locally advanced or metastatic disease (0-1 vs. >1), and visceral vs. non-visceral disease.

** The second interim analysis for OS was conducted when 331 events were observed and the results are presented in this table.

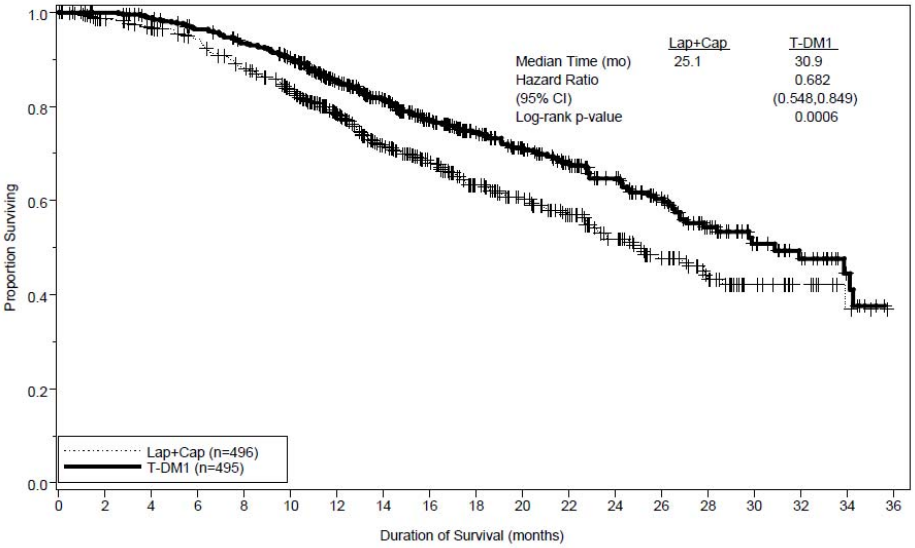
Figure 1 Kaplan-Meier Curve of IRC-Assessed Progression-Free Survival for Study 1



Number at Risk:																
Lap+Cap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

T-DM1: ado-trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine; IRC: independent review committee.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

Figure 2 Kaplan-Meier Curve of Overall Survival for Study 1



Number at Risk:																		
Lap+Cap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

T-DM1: ado-trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

8. Safety

The safety findings are summarized in the following excerpt from the agreed-upon package insert.

> In clinical trials, KADCYLA has been evaluated as single-agent in 884 patients with HER2-positive metastatic breast cancer. The most common (frequency ≥ 25%) adverse drug reactions (ADRs) seen in 884 patients treated with KADCYLA were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation.
>
> The ADRs described in Table 6 were identified in patients with HER2-positive metastatic breast cancer treated in a randomized trial (Study 1) *[see Clinical Studies (14.1)]*. Patients were randomized to receive KADCYLA or lapatinib plus capecitabine. The median duration of study treatment was 7.6 months for patients in the KADCYLA-treated group and 5.5 months and 5.3 months for patients treated with lapatinib and capecitabine, respectively. Two hundred and eleven (43.1%) patients experienced ≥ Grade 3 adverse events in the KADCYLA-treated group compared with 289 (59.2%) patients in the lapatinib plus capecitabine-treated group. Dose adjustments for KADCYLA were permitted *[see Dosage and Administration (2.2)]*. Thirty-two patients (6.5%) discontinued KADCYLA due to an adverse event, compared with 41 patients (8.4%) who discontinued lapatinib, and 51 patients (10.5%) who discontinued capecitabine due to an adverse event. The most common adverse events leading to KADCYLA withdrawal were thrombocytopenia and increased transaminases. Eighty patients (16.3%) treated with KADCYLA had adverse events leading to dose reductions. The most frequent adverse events leading to dose reduction of KADCYLA (in ≥ 1% of patients) included thrombocytopenia, increased transaminases, and peripheral neuropathy. Adverse events that led to dose delays occurred in 116 (23.7%) of KADCYLA treated patients. The most frequent adverse events leading to a dose delay of KADCYLA (in ≥ 1% of patients) were neutropenia, thrombocytopenia, leukopenia, fatigue, increased transaminases and pyrexia.
>
> Table 6 reports the ADRs that occurred in patients in the KADCYLA-treated group (n=490) of the randomized trial (Study 1). Selected laboratory abnormalities are shown in Table 7. The most common ADRs seen with KADCYLA in the randomized trial (frequency > 25%) were nausea, fatigue, musculoskeletal pain, thrombocytopenia, increased transaminases, headache, and constipation. The most common NCI–CTCAE (version 3) ≥ Grade 3 ADRs (frequency >2%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue.

Table 6 Summary of Adverse Drug Reactions Occurring in Patients on the KADCYLA Treatment Arm in the Randomized Trial (Study 1)

Adverse Drug Reactions (MedDRA) System Organ Class	KADCYLA (3.6 mg/kg) n=490 Frequency rate %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488 Frequency rate %	
	All grades (%)	Grade 3 – 4 (%)	All grades (%)	Grade 3 – 4 (%)
Blood and Lymphatic System Disorders				
Neutropenia	6.7	2.0	9.0	4.3
Anemia	14.3	4.1	10.5	2.5
Thrombocytopenia	31.2	14.5	3.3	0.4
Cardiac Disorders				
Left ventricular dysfunction	1.8	0.2	3.3	0.4
Eye Disorders				
Lacrimation increased	3.3	0	2.5	0
Dry eye	3.9	0	3.1	0
Vision blurred	4.5	0	0.8	0
Conjunctivitis	3.9	0	2.3	0
Gastrointestinal Disorders				
Dyspepsia	9.2	0	11.5	0.4
Stomatitis	14.1	0.2	32.6	2.5
Dry Mouth	16.7	0	4.9	0.2
Abdominal pain	18.6	0.8	17.6	1.6
Vomiting	19.2	0.8	29.9	4.5
Diarrhea	24.1	1.6	79.7	20.7
Constipation	26.5	0.4	11.1	0
Nausea	39.8	0.8	45.1	2.5
General Disorders and Administration				
Peripheral edema	7.1	0	8.2	0.2
Chills	7.6	0	3.1	0
Pyrexia	18.6	0.2	8.4	0.4
Asthenia	17.8	0.4	17.6	1.6
Fatigue	36.3	2.5	28.3	3.5
Hepatobiliary Disorders				
Nodular regenerative hyperplasia*	0.4	ND	0	0
Portal hypertension*	0.4	0.2	0	0
Immune System Disorders				
Drug hypersensitivity	2.2	0	0.8	0
Injury, Poisoning, and Procedural				

Adverse Drug Reactions (MedDRA) System Organ Class	KADCYLA (3.6 mg/kg) n=490 Frequency rate %		Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2) n=488 Frequency rate %	
	All grades (%)	Grade 3 – 4 (%)	All grades (%)	Grade 3 – 4 (%)
Infusion-related reaction	1.4	0	0.2	0
Infections and Infestations				
Urinary tract infection	9.4	0.6	3.9	0
Investigations				
Blood alkaline phosphatase increased	4.7	0.4	3.7	0.4
Increased transaminases	28.8	8.0	14.3	2.5
Metabolism and Nutrition Disorders				
Hypokalemia	10.2	2.7	9.4	4.7
Musculoskeletal and Connective Tissue Disorders				
Myalgia	14.1	0.6	3.7	0
Arthralgia	19.2	0.6	8.4	0
Musculoskeletal pain	36.1	1.8	30.5	1.4
Nervous System Disorders				
Dysgeusia	8.0	0	4.1	0.2
Dizziness	10.2	0.4	10.7	0.2
Peripheral neuropathy	21.2	2.2	13.5	0.2
Headache	28.2	0.8	14.5	0.8
Psychiatric Disorders				
Insomnia	12.0	0.4	8.6	0.2
Respiratory, Thoracic, and Mediastinal Disorders				
Pneumonitis	1.2	0	0	0
Dyspnea	12.0	0.8	8.0	0.4
Cough	18.2	0.2	13.1	0.2
Epistaxis	22.5	0.2	8.4	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	5.5	0.2	9.2	0
Rash	11.6	0	27.5	1.8
Vascular Disorders				
Hypertension	5.1	1.2	2.3	0.4

* Nodular Regenerative Hyperplasia and Portal Hypertension occurred in the same patient.

ND = Not determined

Table 7 Selected Laboratory Abnormalities

Parameter	KADCYLA (3.6 mg/kg)			Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2)		
	All Grade %	Grade 3 %	Grade 4 %	All Grade %	Grade 3 %	Grade 4 %
Increased bilirubin	17	<1	0	57	2	0
Increased AST	98	7	<1	65	3	0
Increased ALT	82	5	<1	54	3	0
Decreased platelet count	83	14	3	21	<1	<1
Decreased hemoglobin	60	4	1	64	3	<1
Decreased neutrophils	39	3	<1	38	6	2
Decreased potassium	33	3	0	31	6	<1

Immunogenicity: A total of 836 patients from six clinical studies were tested at multiple time points for anti-therapeutic antibody (ATA) responses to KADCYLA. Following dosing, 5.3% (44/836) of patients tested positive for anti-KADCYLA antibodies at one or more post-dose time points. The presence of KADCYLA in patient serum at the time of ATA sampling may interfere with the ability of this assay to detect anti-KADCYLA antibodies. As a result, data may not accurately reflect the true incidence of anti-KADCYLA antibody development. In addition, neutralizing activity of anti-KADCYLA antibodies has not been assessed.

Warnings and Precautions: Eight warnings and precautions are for safety issues and one is regarding HER2 testing.

Hepatotoxicity: Hepatotoxicity, predominantly in the form of asymptomatic, transient increases in the concentrations of serum transaminases, was observed in clinical trials. Serious hepatobiliary disorders, including at least two fatal cases of severe drug-induced liver injury and associated hepatic encephalopathy, were reported. Some of the observed cases may have been confounded by comorbidities and/or concomitant medications with known hepatotoxic potential. Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies (3 cases out of 884 treated patients).

Left Ventricular Dysfunction: Patients treated with KADCYLA are at increased risk of developing left ventricular dysfunction. A decrease of LVEF to < 40% has been observed in patients treated with KADCYLA. In the randomized trial, left ventricular dysfunction occurred in 1.8% of patients in the KADCYLA-treated group and 3.3% of patients in the lapatinib plus capecitabine-treated group.

Embryo-Fetal Toxicity: KADCYLA can cause fetal harm when administered to a pregnant woman. Treatment with trastuzumab, the antibody component of KADCYLA, during pregnancy in the postmarketing setting has resulted in oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. DM1, the cytotoxic component of KADCYLA, can be expected to cause embryo-fetal toxicity based on its mechanism of action.

Pulmonary Toxicity: Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome have been reported in clinical trials with KADCYLA. Pneumonitis at an incidence of 0.8% (7 out of 884 treated patients) has been reported, with one case of grade 3 pneumonitis. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions. In the randomized trial, the overall frequency of pneumonitis was 1.2%.

Infusion-Related Reactions, Hypersensitivity Reactions: Infusion-related reactions, characterized by one or more of the following symptoms − flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia have been reported in clinical trials of KADCYLA. In the randomized trial, the overall frequency of IRRs in patients treated with KADCYLA was 1.4%. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. One case of a serious, allergic/anaphylactic-like reaction was observed in clinical trials of single-agent KADCYLA.

Thrombocytopenia: Thrombocytopenia was reported in clinical trials of KADCYLA (103 of 884 treated patients with ≥ Grade 3; 283 of 884 treated patients with any Grade). The majority of these patients had Grade 1 or 2 events (< LLN to ≥ 50,000/mm^3) with the nadir occurring by day 8 and generally improving to Grade 0 or 1 (≥ 75,000 /mm^3) by the next scheduled dose. In clinical trials of KADCYLA, the incidence and severity of thrombocytopenia were higher in Asian patients. Independent of race, the incidence of severe hemorrhagic events in patients treated with KADCYLA was low. In the randomized trial, the overall frequency of thrombocytopenia was 31.2% in the KADCYLA-treated group and 3.3% in the lapatinib plus capecitabine-treated group. The incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated group and 0.4% in the lapatinib plus capecitabine-treated group. In Asian patients, the incidence of ≥ Grade 3 thrombocytopenia was 45.1% in the KADCYLA-treated group and 1.3% in the lapatinib plus capecitabine-treated group.

Neurotoxicity: Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of KADCYLA (14 of 884 treated patients with ≥ Grade 3; 196 of 884 treated patients with any Grade). In the randomized trial, the overall frequency of peripheral neuropathy was 21.2% in the KADCYLA-treated group and 13.5% in the lapatinib plus capecitabine-treated group. The incidence of ≥ Grade 3 peripheral neuropathy was 2.2% in the KADCYLA-treated group and 0.2% in the lapatinib plus capecitabine-treated group.

Extravasation: Reactions secondary to extravasation were observed in clinical trials. These reactions, observed more frequently within 24 hours of infusion, were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site.

Boxed Warning: There is a boxed warning for hepatotoxicity, cardiac toxicity, and embryo-fetal toxicity.

9. Advisory Committee Meeting

The application was not referred to a meeting of the Oncologic Drugs Advisory Committee because outside expertise was not necessary; there were no controversial clinical issues that would benefit from advisory committee discussion.

10. Pediatrics

PeRC agreed with a full waiver of the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable to conduct.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- USAN name: The original USAN name of trastuzumab emtansine was revised to ado-trastuzumab emtansine to eliminate potential confusion with trastuzumab.
- Proprietary name: The proprietary name of Kadcyla was found to be acceptable.
- Physician labeling: agreement has been reached on the physician labeling.
- Carton and immediate container labels: Agreement has been reached on carton and container labels.
- Patient labeling/Medication guide: N/A

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The recommendation for full approval is based on statistically significant and clinically meaningful improvements in the co-primary efficacy endpoints of progression-free survival (PFS) and overall survival in patients receiving ado-trastuzumab emtansine compared to those receiving lapatinib plus capecitabine. The hazard ratio for PFS was 0.65 (95% CI: 0.55, 0.77), $p < 0.0001$. The median PFS was 9.6 and 6.4 months for

patients in the ado-trastuzumab emtansine and lapatinib plus capecitabine arms, respectively. At the time of the second interim OS analysis, a statistically significant improvement in OS was observed in patients receiving ado-trastuzumab emtansine compared to those receiving lapatinib plus capecitabine [HR 0.68 (95% CI: 0.55, 0.85), p = 0.0006]. The median OS was 30.9 and 25.1 months in the ado-trastuzumab emtansine and the lapatinib plus capecitabine arms, respectively.

The most common (> 25%) adverse reactions observed in patients receiving ado-trastuzumab emtansine were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation. The most common adverse events leading to ado-trastuzumab emtansine withdrawal were thrombocytopenia and increased transaminases. The most common (> 2%) Grade 3 – 4 adverse reactions were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue. Serious hepatobiliary disorders, including at least two fatal cases of severe drug-induced liver injury and associated hepatic encephalopathy, have been reported in clinical trials with ado-trastuzumab emtansine. Other significant adverse reactions include left ventricular dysfunction, interstitial lung disease, and infusion-associated reactions. Given the clinically significant improvements in PFS and OS, the risk benefit profile is favorable.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  Because of a signal of a serious risk of embryo-fetal toxicity, postmarketing requirement 1 is for a pregnancy registry. PMR's 2-4 are intended assess a signal of a serious risk of increased toxicity due to a variable antibody drug ratio and to identify unexpected serious risks of increased toxicity (b) (4) PMR 5 is for a trial to assess a signal of a serious risk of increased toxicity in patients with hepatic impairment.

Postmarketing Requirements

1. Establish a Pregnancy Registry to collect and analyze information for 10 years on pregnancy complications and birth outcomes in women with breast cancer exposed to ado-trastuzumab-emtansine within 6 months of conception or during pregnancy. Submit yearly interim reports, which may be included in your annual reports, on the cumulative findings and analyses from the Pregnancy Registry.

Draft Protocol Submission:	03/13
Final Protocol Submission:	05/13
Interim Report #1:	05/14
Interim Report #2:	05/15

Interim Report #3:	05/16
Interim Report #4:	05/17
Interim Report #5:	05/18
Interim Report #6:	05/19
Interim Report #7:	05/20
Interim Report #8:	05/21
Interim Report #9:	05/22
Study Completion:	05/23
Final Report Submission:	05/24

2. Perform a multivariate characterization study to support the implementation (b) (4) of *trans*-succinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) (b) (4) during manufacture of T-DM1.

Final Protocol Submission:	03/13
Study Completion:	05/13
Final Report Submission:	06/13

3. Develop and validate an iCIEF method to use as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data.

Final Protocol Submission:	05/13
Study Completion:	11/13
Final Report Submission:	12/13

4. Provide quarterly reports on the status of any (b) (4) These reports should include, at a minimum, a summary of the root cause analyses, associated corrective actions, and disposition of all affected DM1 batches. Also, provide the disposition of any potentially affected finished product batches using these affected DM1 batches. Submit an interim report documenting that the manufacturing processes have been appropriately controlled at the manufacturing facilities according to Genentech's evaluation. The interim report should include a request for follow-up inspection(s). Submit a final report with a statement concerning the follow-up performed on the (b) (4) issues during the course of the FDA inspection(s), an update on whether there have been any further instances of (b) (4) and a proposal to prevent (b) (4) managed by each site's quality system.

Quarterly Report #1:	05/13
Quarterly Report #2:	08/13
Quarterly Report #3:	11/13
Quarterly Report #4:	02/14

Interim Report: 04/14
Quarterly Report #5: 05/14
Quarterly Report #6: 08/14
Quarterly Report #7: 11/14
Quarterly Report #8: 02/15
Final Report Submission: 04/15

5. Conduct a clinical trial to evaluate the impact of hepatic impairment on the pharmacokinetics of Kadcyla (ado-trastuzumab emtansine conjugate), total trastuzumab, and DM1-containing catabolites. Based on the results of this trial, update the approved KADCYLA labeling with recommendations for appropriate use of KADCYLA in patients with hepatic impairment.

Trial Completion: 06/14
Final Report Submission: 06/15

Postmarketing Commitments

6. Transfer the methodology for validated dye ingress testing developed by Genentech to (b) (4) Conduct a study to confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method and provide a final report in the 2014 annual report.

Study Completion: 03/13
Final Report Submission: 04/14

7. Conduct a study to assess the risk of endotoxin masking (b) (4) using endotoxin spiked ado-trastuzumab emtansine drug product (b) (4) Submit a final report that includes updated specifications as a Prior Approval Supplement.

Final Report Submission: 03/13

8. If endotoxin masking is observed in the drug product (b) (4), develop an alternative method to quantitate endotoxin in the finished ado-trastuzumab emtansine drug product (b) (4) using routine production conditions. Submit a final report on any changes in the analytical methods as a Prior Approval Supplement.

Final Protocol Submission: 09/13
Final Report Submission: 12/13

9. Dedicate (b) (4) for ado-trastuzumab emtansine drug product manufacture and submit a final report of the results from sterilization validation and 3 media fill simulations as a Changes Being Effected Supplement (CBE-0).

Final Report Submission: 06/13

10. Conduct cleaning verification [redacted] until use of [redacted] is implemented and report the updated [redacted] procedures in the 2014 Annual Report.

    Study completion: 06/13
    Final Report Submission: 04/14

11. Conduct endotoxin spiking and recovery studies [redacted] Submit the final report as a Changes Being Effected in 30 days Supplement (CBE-30).

    Final Report Submission: 05/13

12. Develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ado-trastuzumab emtansine, including procedures for accurate detection of neutralizing antibodies to ado-trastuzumab emtansine in the presence of ado-trastuzumab emtansine levels that are expected to be present in the serum or plasma at the time of patient sampling. The assay final report will be submitted as a Prior Approval Supplement by June, 2015.

    Final Report Submission (Assay and Methodology) Date: 06/15

13. Reassess release and stability specifications for ado-trastuzumab emtansine drug substance and drug product through the end of February 2015. Submit the final report as a Changes Being Effected-30 Supplement (CBE-30).

    Final Report Submission: 05/15

14. Provide a material compatibility assessment [redacted] Provide a toxicological risk assessment [redacted] If significant

[redacted] are identified during these assessments, initiate action to mitigate the source(s) of risk to product quality.

Material Compatibility Assessment Completion:	04/13
[redacted] Assessment and Toxicological Risk Assessment:	05/13
Final Report Submission:	06/13

15. Conduct ado-trastuzumab emtansine conjugate exposure-response analyses for progression-free survival, final overall survival, and safety utilizing data from trial BO25734/TDM4997 (TH3RESA). The results of the exposure-response analyses from both TH3RESA and BO21977/TDM4370g (EMILIA) will be used to determine whether a postmarketing trial is needed to optimize the dose in patients with metastatic breast cancer patients who have lower exposure to ado-trastuzumab emtansine conjugate at the approved dose (3.6 mg/kg q3w). Submit a final report of the exposure-response analyses based on TH3RESA and EMILIA.

Trial Completion:	06/16
Final Report Submission:	12/16

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/s/

ROBERT L JUSTICE
02/21/2013