CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103792Orig1s5175

Trade Name: HERCEPTIN

Generic or Proper Name: trastuzumab

Sponsor: Genentech, Inc.

Approval Date: January 18, 2008

Indication: Herceptin is a HER2/neu receptor antagonist indicated for the treatment of HER2 overexpressing breast cancer.

Adjuvant Breast Cancer

- As part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of HER2-overexpressing, breast cancer.
- As a single agent, for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR negative or with one high-risk feature) or node-positive breast cancer, following multi-modality anthracycline based therapy.

Metastatic Breast Cancer

- In combination with paclitaxel is indicated for treatment of HER2-overexpressing metastatic breast cancer.
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one of more chemotherapy regimens for metastatic disease.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103792/5175

Genentech, Incorporated
Attention: Todd Rich, M.D.
Senior Director, Regulatory Affairs
1 DNA Way, MS #242
South San Francisco, CA 94080-4990

JAN 18 2008

Dear Dr. Rich:

Your request to supplement your biologics license application for trastuzumab (Herceptin) to revise the indication for use as a single agent, for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR negative or with one high-risk feature) or node-positive breast cancer, following multi-modality anthracycline based therapy has been approved.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We acknowledge that the Highlights section of the package insert currently meets the half page requirement so a waiver of this requirement is not needed at this time.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct postmarketing studies as described in your letters of January 18, 2008, as outlined below:

Postmarketing Study Commitments subject to reporting requirements of 21 CFR 601.70.

1. To provide a final clinical study report (CSR) of the safety and efficacy of 2-years of trastuzumab treatment in Study BO16348 (HERA)in order to provide a final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility. The final study report will include the primary datasets and programs for generation of analyses; analyses will include, but not be limited to the analyses described in the statistical analysis plan. The final CSR will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the final CSR will be submitted by December 31, 2009.

2. To provide updated safety information of the observation and 1-year trastuzumab arms in Study BO16348 (HERA). Interim cardiac safety updates (narratives of new primary or secondary cardiac events) will be provided on an annual basis beginning in December 2008 and continuing until the time of the final CSR, which will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the CSR will be submitted by December 31, 2009.

3. To submit a protocol for review for a prospectively and actively enrolled pregnancy registry that will collect information assessing pregnancy complications and birth outcomes in women with breast cancer exposed to a Herceptin-containing regimen prior to conception or during pregnancy. Notice of a pregnancy registry and the telephone contact number will be included in the package insert. A proposal, including a prospective protocol for FDA review will be submitted to FDA by June 30, 2008. The registry will become active by December 31, 2008, and interim reports of all data collected will be submitted on an annual basis to FDA through December 31, 2019.

4. To conduct a QT protocol according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in a minimum of 50 subjects receiving trastuzumab. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by March 31, 2009, and will be completed by 31 March, 2013. A final study report will be submitted by September 30, 2013. A supplement with revised labeling, if applicable, will be submitted by March 31, 2014.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103792. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 103792. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Commitment Protocol
- Postmarketing Study Commitment - Final Study Report
- Postmarketing Study Correspondence
- Annual Status Report of Postmarketing Study Commitments

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and

- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cder/guidance/5569fnl.htm) for further information.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 103792/5175." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

This information will be included in your biologics license application file.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Package Insert Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

LABELING

FDA APPROVED: 1-18-08

1.14.1.2 Annotated Draft Labeling Text

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HERCEPTIN® (Trastuzumab)
Intravenous Infusion
Initial U.S. Approval: 1998

WARNING
CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning

Cardiomyopathy: Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy. (5.1, 2.2)

Infusion reactions, Pulmonary toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

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

Indications and Usage, Adjuvant Treatment of Breast Cancer (1 1)	*01*/2008
Dosage and Administration, Recommended Doses and Schedules (2.1)	*01*/2008
Dosage and Administration, Dose Modifications (2.2)	*01*/2008
Warnings and Precautions, Cardiomyopathy (5 1)	*01*/2008
Warnings and Precautions, Interstitial Pneumonitis (5.4)	*01*/2008
Warnings and Precautions, Embryo-Fetal Toxicity (5.6)	*01*/2008

----------INDICATIONS AND USAGE----------

Herceptin is a HER2/neu receptor antagonist indicated for the treatment of HER2 overexpressing breast cancer (1.1, 1.2).

----------DOSAGE AND ADMINISTRATION----------

For intravenous (IV) infusion only. Do not administer as an IV push or bolus (5.2).

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.1)

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 52 weeks.
- Or, initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer (2.1)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions (as tolerated).

----------DOSAGE FORMS AND STRENGTHS----------

- Multidose vial nominally containing 440 mg Herceptin as a lyophilized, sterile powder. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Cardiomyopathy (5.1, 6.1)
- Infusion Reactions (5.2, 6.1)
- Pulmonary Toxicity (5.4, 6.1)
- Exacerbation of Chemotherapy-Induced Neutropenia (5.3, 6.1)
- HER2 testing should be performed by laboratories with demonstrated proficiency. (5.5)
- May cause oligohydramnios and fetal harm when administered to a pregnant woman. Pregnancy registry available. (5.6, 8.1)

----------ADVERSE REACTIONS----------

Adjuvant Breast Cancer

- Adverse reactions (≥2% higher incidence with Herceptin-containing treatment compared with control treatment) are fatigue, infection, neutropenia, anemia, myalgia, dyspnea, rash/desquamation, headache, diarrhea, and nausea. (6 1)

Metastatic Breast Cancer

- Adverse reactions (≥15% incidence with Herceptin monotherapy or≥5% with Herceptin/ paclitaxel) are nausea, fever, infection, rash, increased cough, vomiting, diarrhea, headache, and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: *01*/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING
CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY

Cardiomyopathy

Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF and decreased LVEF. The incidence and severity of left ventricular cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and strongly consider discontinuation of Herceptin treatment in patients with metastatic breast cancer for clinically significant decrease in left ventricular function. *[see Warnings and Precautions (5.1) and Dosage and Administration (2.2)]*

Infusion Reactions; Pulmonary Toxicity

Herceptin administration can result in serious infusion reactions and pulmonary toxicity. Fatal infusion reactions have been reported. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinue Herceptin for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. *[see Warnings and Precautions (5.2, 5.4)]*

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

Herceptin is indicated:

- As part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of HER2-overexpressing, breast cancer.
- As a single agent, for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR negative or with one high-risk feature) or node-positive breast cancer, following multi-modality anthracycline based therapy. [*see Clinical Studies (14.1)*]

1.2 Metastatic Breast Cancer

Herceptin is indicated:

- In combination with paclitaxel is indicated for treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Doses and Schedules

Do not administer as an intravenous push or bolus. Do not mix Herceptin with other drugs.

Adjuvant Treatment, Breast Cancer

Administer according to one of the following doses and schedules:

- Initiate Herceptin following completion of anthracycline and concurrently with paclitaxel for the first 12 weeks. Administer Herceptin at an initial dose of 4 mg/kg as a 90 minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30 minute intravenous infusions, as tolerated, for a total of 52 doses. *[see Dose Modifications (2.2)]*
- Initiate Herceptin following completion of all chemotherapy. Administer Herceptin at an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg every three weeks for a total of 17 doses (52 weeks of therapy). Administer all doses ≥4 mg/kg as 90 minute intravenous infusions. *[see Dose Modifications (2.2)]*

Metastatic Treatment, Breast Cancer

Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as a 90 minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30 minute intravenous infusions until disease progression.

2.2 Dose Modifications

Infusion Reactions

[*see Boxed Warning, Warnings and Precautions (5.2)*]

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue Herceptin for severe or life-threatening infusion reactions.

Cardiomyopathy

[*see Boxed Warning, Warnings and Precautions (5.1)*]

Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the following:

- ≥16% absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and ≥10% absolute decrease in LVEF from pretreatment values.
- Herceptin may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%.
- Permanently discontinue Herceptin for a persistent (>8 weeks) LVEF decline or for suspension of Herceptin dosing on more than 3 occasions for cardiomyopathy.

2.3 Preparation for Administration

Reconstitution

Reconstitute each 440 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21 mg/mL Trastuzumab. In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Herceptin. The stream of diluent should be directed into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Store reconstituted Herceptin at 2-8° C; discard unused Herceptin after 28 days. If Herceptin is reconstituted with SWFI without preservative, use immediately and discard any unused portion.

Dilution

- Determine the dose (mg) of Herceptin [*see Dosage and Administration (2.1)*]. Calculate the volume of the 21 mg/mL reconstituted Herceptin solution needed, withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.

3 DOSAGE FORMS AND STRENGTHS

440 mg lyophilized powder per multi-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [*see Boxed Warning Cardiomyopathy*]. Herceptin can also cause a symptomatic decline in left ventricular ejection fraction (LVEF).

There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline.

Withhold Herceptin for ≥16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal

and ≥10% absolute decrease in LVEF from pretreatment values. [*see Dosage and Administration (2.2)*] The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

Cardiac Monitoring

Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan, prior to the first dose of Herceptin. The following schedule was used to monitor cardiac function in clinical studies:

- Baseline LVEF measurement immediately prior to initiation of Herceptin
- LVEF measurements every 3 months during and upon completion of Herceptin
- LVEF measurements every 6 months for at least 2 years following completion of Herceptin
- Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction [*see Dosage and Administration (2.2)*]

In Study 1, 16% (136/844) of patients discontinued Herceptin due to clinical evidence of myocardial dysfunction or significant decline in LVEF. In Study 3, the number of patients who discontinued Herceptin due to cardiac toxicity was 2.6% (44/1678).

Among 32 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy and all other patients were receiving cardiac medication at last follow-up. Approximately half of the surviving patients had recovery to a normal LVEF (defined as ≥50%) on continuing medical management at the time of last follow-up. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

Table 1
Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

		Incidence	
Study	Event	Herceptin	Control
1 & 2	Congestive heart failure*	2% (32/1677)	0.4% (7/1600)
3	Congestive heart failure	2% (30/1678)	0.3% (5/1708)

*Includes 1 patient with fatal cardiomyopathy.

Table 2
Incidence of Cardiac Dysfunction* in Metastatic Breast Cancer Studies

		Incidence			
		NYHA I-IV		NYHA III-IV	
Study	Event	Herceptin	Control	Herceptin	Control
4 (AC)	Cardiac Dysfunction	28%	7%	19%	3%
4 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
5	Cardiac Dysfunction**	7%	N/A	5%	N/A

* Congestive heart failure or significant asymptomatic decrease in LVEF

** Includes 1 patient with fatal cardiomyopathy.

5.2 Infusion Reactions

Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. *[see Adverse Reactions (6.1)]*.

In postmarketing reports, serious and fatal infusion reactions have been reported. Severe reactions which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered, which may include: epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Herceptin after experiencing a severe infusion reaction. Prior to resumption of Herceptin infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated Herceptin infusions, others had recurrent severe infusion reactions despite pre-medications.

5.3 Exacerbation of Chemotherapy-Induced Neutropenia

In randomized, controlled clinical trials in women with metastatic breast cancer, the per-patient incidences of NCI CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was not significantly increased. [*see Adverse Reactions (6.1)*].

5.4 Pulmonary Toxicity

Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions *[see Warnings and Precautions (5.2)]*. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

5.5 HER2 Testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown. Assessment for HER2 overexpression and of HER2 gene amplification should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally 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.

Several FDA-approved commercial assays are available to aid in the selection of patients for Herceptin therapy. These include HercepTest™ and Pathway® HER-2/neu (IHC assays) and PathVysion® and HER2 FISH pharmDx™ (FISH assays). Users should refer to the package inserts of specific assay kits for information on the validation and performance of each assay.

Limitations in assay precision (particularly for the IHC method) and in the direct linkage between assay result and overexpression of the Herceptin target (for the FISH method) make it inadvisable to rely on a single method to rule out potential Herceptin benefit. A negative FISH result does not rule out HER2 overexpression and potential benefit from Herceptin. Treatment outcomes for metastatic breast cancer (Study 4) as a function of IHC and FISH testing are provided in Table 9. Treatment outcomes for adjuvant breast cancer (Studies 2 and 3) as a function of IHC and FISH testing are provided in Table 7.

HER2 Protein Overexpression Detection Methods

HER2 protein overexpression can be established by measuring HER2 protein using an IHC method. HercepTest®, one test approved for this use, was assessed for concordance with the Clinical Trial Assay (CTA), using tumor specimens collected and stored independently from those obtained in Herceptin clinical studies in women with metastatic breast cancer. Data are provided in the package insert for HercepTest®.

HER2 Gene Amplification Detection Method

The presence of HER2 protein overexpression and gene amplification are highly correlated, therefore the use of FISH to detect gene amplification may be employed for selection of patients appropriate for Herceptin therapy. PathVysion®, one test approved for this use, was evaluated in an exploratory, retrospective assessment of available CTA 2+ or 3+ tumor specimens collected as part of patient screening for clinical studies in metastatic breast cancer (Studies 4 and 5). Data are provided in the package insert for PathVysion®.

5.6 Embryo-Fetal Toxicity (Pregnancy Category D)

Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case reports suggest that Herceptin use during pregnancy increases the risk of oligohydramnios during the second and third trimesters. If Herceptin is used during pregnancy or if a woman becomes pregnant while taking Herceptin, she should be apprised of the potential hazard to a fetus. [*see Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiomyopathy [*see Warnings and Precautions (5.1)*]
- Infusion reactions [*see Warnings and Precautions (5.2)*]
- Exacerbation of chemotherapy-induced neutropenia [*see Warnings and Precautions (5.3)*]
- Pulmonary toxicity [*see Warnings and Precautions (5.4)*]

The most common adverse reactions in patients receiving Herceptin are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity *[see Dosage and Administration (2.2)]*.

6.1 Clinical Trials Experience

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

Adjuvant Breast Cancer Studies

The data below reflect exposure to Herceptin across three randomized, open-label studies, Studies 1, 2, and 3, with (n= 3355) or without (n= 3308) trastuzumab in the adjuvant treatment of breast cancer.

The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in Study 3, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

Table 3
Adverse Reactions for Study 3, All Grades*:

MedDRA (v. 7.1) Adverse Event Preferred Term	1 Year Herceptin (n= 1678)	Observation (n=1708)
Cardiac		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias**	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
Respiratory Thoracic Mediastinal Disorders		
Nasopharyngitis	135 (8%)	43 (3%)

Table 3 (cont'd)
Adverse Reactions for Study 3, All Grades*:

MedDRA (v. 7.1) Adverse Event Preferred Term	1 Year Herceptin (n= 1678)	Observation (n=1708)
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
Gastrointestinal Disorders		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
Musculoskeletal & Connective Tissue Disorders		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
Nervous System Disorders		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
Skin & Subcutaneous Tissue Disorders		
Rash	70 (4%)	10 (.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritis	40 (2%)	10 (0.6%)
General Disorders		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Aesthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (.06%)	0 (0%)
Infections		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
Immune System Disorders		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

* The incidence of Grade 3/4 adverse reactions was <1% in both arms for each listed term.

** Higher level grouping term.

The data from Studies 1 and 2 were obtained from 3206 patients enrolled, of which 1635 patients received Herceptin; the median treatment duration was

50 weeks. The median age was 49.0 years (range: 24-80); 84% of patients were White, and 7% were Black, 4% were Hispanic, and 4% were Asian.

In Study 1, only Grade 3-5 adverse events, treatment-related Grade 2 events, and Grade 2-5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2-5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (31% vs. 28%), fatigue (28% vs. 22%), infection (22% vs. 14%), hot flashes (17% vs. 15%), anemia (13% vs. 7%), dyspnea (12% vs. 4%), rash/desquamation (11% vs. 7%), neutropenia (7% vs. 5%), headache (6% vs. 4%), and insomnia (3.7% vs. 1.5%). The majority of these events were Grade 2 in severity.

In Study 2, data collection was limited to the following investigator-attributed treatment-related adverse reactions NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (11% vs. 8.4%), myalgia (10% vs. 8%), nail changes (9% vs. 7%), and dyspnea (2.5% vs. 0.1%). The majority of these events were Grade 2 in severity.

Metastatic Breast Cancer Studies

The data below reflect exposure to Herceptin in one randomized, open-label study, Study 4, of chemotherapy with (n=235) or without (n=234) trastuzumab in patients with metastatic breast cancer, and one single-arm study (Study 5; n=222) in patients with metastatic breast cancer. Data in Table 4 are based on Studies 4 and 5.

Among the 464 patients treated in Study 4, the median age was 52 years (range: 25–77 years). Eighty-nine percent were White, 5% Black, 1% Asian and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥6 months and ≥12 months were 58% and 9%, respectively.

Among the 352 patients treated in single agent studies (213 patients from Study 5), the median age was 50 years (range 28–86 years), 100% had breast cancer, 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥6 months and ≥12 months were 31% and 16%, respectively.

Table 4
Per-Patient Incidence of Adverse Reactions Occurring in ≥5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 4 and 5) (Percent of Patients)

	Single Agent* n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC n = 143	AC Alone n = 135
Body as a Whole					
Pain	47	61	62	57	42
Asthenia	42	62	57	54	55
Fever	36	49	23	56	34
Chills	32	41	4	35	11
Headache	26	36	28	44	31
Abdominal pain	22	34	22	23	18
Back pain	22	34	30	27	15
Infection	20	47	27	47	31
Flu syndrome	10	12	5	12	6
Accidental injury	6	13	3	9	4
Allergic reaction	3	8	2	4	2

Table 4 (cont'd)
Per-Patient Incidence of Adverse Events Occurring in ≥5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 4 and 5) (Percent of Patients)

	Single Agent* n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC n = 143	AC Alone n = 135
Cardiovascular					
Tachycardia	5	12	4	10	5
Congestive heart failure	7	11	1	28	7
Digestive					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Nausea and vomiting	8	14	11	18	9
Anorexia	14	24	16	31	26
Heme & Lymphatic					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34
Metabolic					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
Nervous					
Insomnia	14	25	13	29	15
Dizziness	13	22	24	24	18
Paresthesia	9	48	39	17	11
Depression	6	12	13	20	12
Peripheral neuritis	2	23	16	2	2
Neuropathy	1	13	5	4	4
Respiratory					
Cough increased	26	41	22	43	29
Dyspnea	22	27	26	42	25
Rhinitis	14	22	5	22	16
Pharyngitis	12	22	14	30	18
Sinusitis	9	21	7	13	6
Skin					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	< 1
Urogenital					
Urinary tract infection	5	18	14	13	7

* Data for Herceptin single agent were from 4 studies, including 213 patients from Study 5.

The following subsections provide additional detail regarding adverse reactions observed in clinical trials of adjuvant breast, metastatic breast cancer, or post-marketing experience.

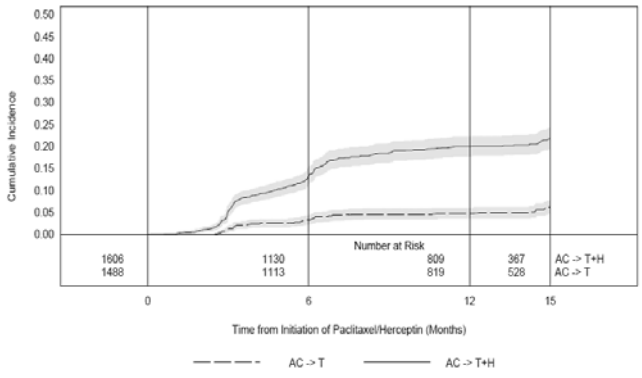
Cardiomyopathy

Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and 2, 23 months in the AC-T arm, 24 months in the AC-T arm. In Studies 1 and 2, 6% of patients were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF < 50% or ≥ 15 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2m and in patients receiving Herceptin monotherapy compared to observation in Study 3 (see Table 5, Figures 1 and 2).

Table 5
Per-patient Incidence of New Onset
Myocardial Dysfunction (by LVEF) Studies 1, 2 and 3

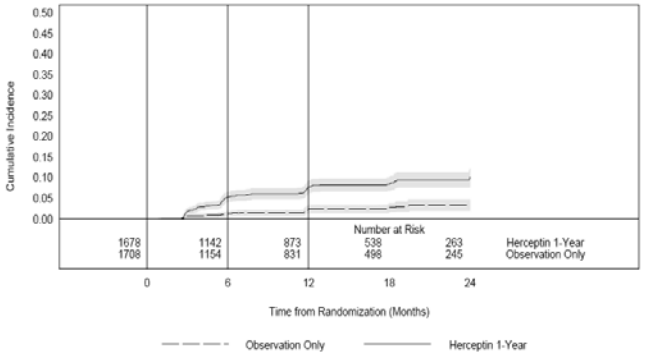
Criteria	Studies 1 and 2		Study 3	
	AC-TH (n=1606)	AC-T (n=1488)	Herceptin (n=1678)	Observation (n=1708)
Post-baseline LVEF <50%	22.8% (366)	9.1% (136)	8.6% (144)	2.7% (46)
LVEF<50% and ≥10% decrease from baseline	18.3% (294)	5.4% (81)	7.0% (118)	2.0% (35)
LVEF<50% and ≥16% decrease from baseline	11.7% (188)	2.2% (33)	3.8% (64)	1.2% (20)
LVEF absolute decrease of ≥10%, <20%	33.4% (536)	18.3% (272)	22.4% (376)	11.9% (204)
LVEF absolute decrease ≥20%	9.2% (148)	2.4% (36)	3 5% (59)	1.2% (21)

Figure 1
Studies 1 and 2: Cumulative Incidence of Time to First LVEF
Decline of ≥ 10 Percentage Points from Baseline and to
Below 50% with Death as a Competing Risk Event



Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

Figure 2
Study 3: Cumulative Incidence of Time to First LVEF
Decline of ≥ 10 Percentage Points from Baseline and to
Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

The incidence of treatment emergent congestive heart failure among patients in the metastatic breast cancer trials was classified for severity using the New York Heart Association classification system (I–IV, where IV is the most severe level of cardiac failure) (see Table 2). In the metastatic breast cancer trials the probability of cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracyclines.

Infusion Reactions

During the first infusion with Herceptin, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in < 1% of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9% of patients, on second or subsequent Herceptin infusions administered as monotherapy or in combination with chemotherapy, respectively. In the post-marketing setting, severe infusion reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

Anemia

In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 4]), of selected NCI CTC Grade 2–5 anemia (12.5% vs. 6.6% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. Following the administration of Herceptin as a single agent (Study 5), the incidence of NCI-CTC Grade 3 anemia was < 1%.

Neutropenia

In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI CTC Grade 4–5 neutropenia (2% vs. 0.7% [Study 2]) and of selected Grade 2–5 neutropenia (7.1% vs. 4.5 % [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

Infection

The overall incidences of infection (46% vs. 30% [Study 4]), of selected NCI-CTC Grade 2–5 infection/febrile neutropenia (22% vs. 14% [Study 1]) and of selected Grade 3–5 infection/febrile neutropenia (3.3% vs. 1.4%) [Study 2]), were higher in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract.

In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in

patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

Pulmonary Toxicity

Adjuvant Breast Cancer

Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2–5 pulmonary toxicity (14% vs. 5% [Study 1]) and of selected NCI-CTC Grade 3–5 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4 % vs. 1% [Study 2]) was higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 12% vs. 4% [Study 1]; NCI-CTC Grade 2–5: 2.5% vs. 0.1% [Study 2]).

Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving Herceptin compared with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients receiving Herceptin, one as a component of multi-organ system failure, as compared to 1 patient receiving chemotherapy alone.

In Study 3, there were 4 cases of pneumonitis in Herceptin-treated patients compared to none in the control arm.

Metastatic Breast Cancer

Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see *Warnings and Precautions (5.4)*.

Thrombosis/Embolism

In 3 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in two studies (3.0% vs. 1.3% [Study 1] and 2.1% vs. 0% [Study 4]).

Diarrhea

Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 2–5 diarrhea (6.2% vs. 4.8% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (1.6% vs. 0% [Study 2]), and of grade 1-4 diarrhea (7% vs. 1% [Study 3]) were higher in patients receiving Herceptin as compared to controls. Of patients receiving Herceptin as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer.

Glomerulopathy

In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of Herceptin therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Among 903 women with metastatic breast cancer, human anti-human antibody (HAHA) to Herceptin was detected in one patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer.

The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Herceptin with the incidence of antibodies to other products may be misleading.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Herceptin. 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.

- Infusion reaction [*see Warnings and Precautions (5.2)*]
- Oligohydramnios [*see Warnings and Precautions (5.6)*]
- Glomerulopathy

7 DRUG INTERACTIONS

In clinical studies, administration of paclitaxel in combination with Herceptin resulted in a 1.5-fold increase in Trastuzumab serum levels [*see Clinical Pharmacology (12.3)*].

In drug interaction studies, the pharmacokinetics of docetaxel and paclitaxel were not altered when each was administered in combination with Herceptin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Category D [*see Warnings and Precautions (5.6)*]

Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case reports suggest that Herceptin use during pregnancy increases the risk for oligohydramnios during the second and third trimester. If Herceptin is used during pregnancy or if a woman becomes pregnant while taking Herceptin, she should be apprised of the potential hazard to a fetus.

In the postmarketing setting, oligohydramnios was reported in women who received Herceptin during pregnancy, either alone or in combination with chemotherapy. In half of these women, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin was resumed after the amniotic fluid index improved, and oligohydramnios recurred.

Women using Herceptin during pregnancy should be monitored for oligohydramnios. If oligohydramnios occurs, fetal testing should be done that is appropriate for gestational age and consistent with community standards of care. Additional intravenous (IV) hydration has been helpful when oligohydramnios has occurred following administration of other chemotherapy agents, however the effects of additional IV hydration with Herceptin treatment are not known.

Reproduction studies in cynomolgus monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg trastuzumab and have revealed no evidence of harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation. Placental transfer of trastuzumab during the early (Days 20-50 of gestation) and late (Days 120-150 of gestation) fetal development period was observed in monkeys. [*See Nonclinical Toxicology (13.2)*]

Because animal reproduction studies are not always predictive of human response, Herceptin should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Registry

Pregnant women with breast cancer who are using Herceptin are encouraged to enroll in the Cancer and Childbirth Registry: phone 1-800-690-6720.

8.3 Nursing Mothers

It is not known whether Herceptin is excreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts.

Trastuzumab was present in the breast milk of lactating cynomolgus monkeys given 12.5 times the recommended weekly human dose of 2 mg/kg of Herceptin. Infant monkeys with detectable serum levels of trastuzumab did not have any adverse effects on growth or development from birth to 3 months of age; however, trastuzumab levels in animal breast milk may not accurately reflect human breast milk levels.

Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from Herceptin, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of trastuzumab and the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Herceptin in pediatric patients has not been established.

8.5 Geriatric Use

Herceptin has been administered to 377 patients who were 65 years of age or over (244 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease in Studies 4 and 5, or adjuvant therapy in Studies 1 and 2. Aside from cardiac dysfunction, limitations in data collection and differences in study design of the 3 studies of Herceptin in adjuvant treatment of breast

cancer preclude a determination of whether the toxicity profile of Herceptin in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of Herceptin treatment in older patients is different from that observed in patients <65 years of age for metastatic disease and adjuvant treatment.

10 OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 8mg/kg have not been tested.

11 DESCRIPTION

Herceptin (Trastuzumab) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous administration. Each multi-use vial of Herceptin contains 440 mg Trastuzumab, 400 mg α,α-trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution containing 21 mg/mL Trastuzumab, at a pH of approximately 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Herceptin has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Herceptin is a mediator of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, Herceptin-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

12.2 Pharmacokinetics

The pharmacokinetics of trastuzumab were studied in women with metastatic breast cancer. Short duration intravenous infusions of 10 to 500 mg Herceptin once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 2 and 12 days at the 10 and 500 mg dose levels, respectively. The volume of distribution of trastuzumab was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 mcg/mL.

In studies using an initial dose of 4 mg/kg followed by a weekly dose of 2 mg/kg, a mean half-life of 6 days (range 1-32 days) was observed. Between weeks 16 and 32, trastuzumab serum concentrations reached a steady state with mean trough and peak concentrations of approximately 79 mcg/mL and 123 mcg/mL, respectively.

In a study of women receiving adjuvant therapy for breast cancer, a mean half-life of trastuzumab of 16 days (range: 11-23 days) was observed after an initial dose of 8 mg/kg followed by a dose of 6 mg/kg every three weeks. Between weeks 6 and 37, trastuzumab serum concentrations reached a steady-state with mean trough and peak concentrations of 63 mcg/mL and 216 mcg/mL, respectively.

Sixty-four percent (286/447) of women with metastatic breast cancer had detectable circulating extracellular domain of the HER2 receptor (shed antigen), which ranged as high as 1880 ng/mL (median 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations.

Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine (≤ 2.0 mg creatinine/dL).

Mean serum trough concentrations of trastuzumab, when administered in combination with paclitaxel, were consistently elevated approximately 1.5-fold as compared with serum concentrations of trastuzumab when used in combination with anthracycline plus cyclophosphamide. In clinical studies in HER2+ metastatic breast cancer where Herceptin was administered in combination with paclitaxel, in combination with docetaxel, or in combination with paclitaxel and doxorubicin, Herceptin did not appear to alter the plasma concentrations of these chemotherapeutic agents, or the metabolites that were analyzed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Herceptin has not been tested for carcinogenic potential.

No evidence of mutagenic activity was observed when trastuzumab was tested in the standard Ames bacterial and human peripheral blood lymphocyte mutagenicity assays, at concentrations of up to 5000 mcg/mL. In an *in vivo* micronucleus assay, no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg Herceptin.

A fertility study conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels. Studies to evaluate the effects of trastuzumab on male fertility have not been conducted.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Reproductive toxicology studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg Herceptin and have revealed no evidence of impaired fertility or harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation. Placental transfer of Herceptin during the early (Days 20-50 of gestation) and late (Days 120-150 of gestation) fetal development period was observed in monkeys.

14 CLINICAL STUDIES

14.1 Adjuvant Breast Cancer

The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER-2 overexpressing breast cancer, were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 3752 women and in a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women.

In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1). Patients with a history of active cardiac disease based on symptoms, abnormal electrocardiographic, radiologic, or left ventricular ejection fraction findings or uncontrolled hypertension (diastolic > 100 mmHg or systolic > 200 mmHg) were not eligible.

Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin). In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Paclitaxel was administered either weekly (80 mg/m^2) or every 3 weeks (175 mg/m^2) for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued in patients who developed congestive heart failure, or persistent/recurrent LVEF decline *[see Dosage and Administration (2.2)]*. Radiation therapy, if administered, was initiated after the completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-free survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death, was the primary endpoint of the combined efficacy analysis.

A total of 3752 patients were included in the efficacy analyses. The data from both arms in Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. Of these patients, the median age was 49 years (range, 22–80 years; 6% >65 years), 84% were white, 7% black, 4% Hispanic, and 4% Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1, 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or PR+ tumors. At the time of randomization 53% of the population were to receive paclitaxel on a weekly regimen, and the remainder were to receive a q3 week schedule of paclitaxel.

In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory. Patients with node-negative disease were required to have ≥T1c primary tumor. Patients with a history of congestive heart failure or LVEF <55%, uncontrolled arrhythmias, angina requiring medication,

clinically significant valvular heart disease, evidence of transmural infarction on ECG, poorly controlled hypertension (systolic > 180 mm Hg or diastolic > 100 mm Hg) were not eligible.

Patients were randomized (1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy; to receive no additional treatment (n = 1693) or 1 year of Herceptin treatment (n = 1693). Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator discretion. Herceptin was administered with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks for a total of 52 weeks. The primary endpoint was disease-free survival (DFS), defined as in Studies 1 and 2.

Among the 3386 patients randomized to the two treatment arms, the median age was 49 years (range 21–80), 83% were Caucasian, and 13% were Asian. Disease characteristics: 94% infiltrating ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32% node negative, and in 11% of patients, nodal status was not assessable due to prior neo-adjuvant chemotherapy. Ninety-six percent (1055/1098 of patients with node-negative disease had high-risk features: among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and 47% (512) were ER and or PgR+ and had at least one of the following high-risk features: pathological tumor size greater than 2 cm, Grade 2–3, or age < 35 years. Prior to randomization, 94% of patients had received anthracycline-based chemotherapy regimens.

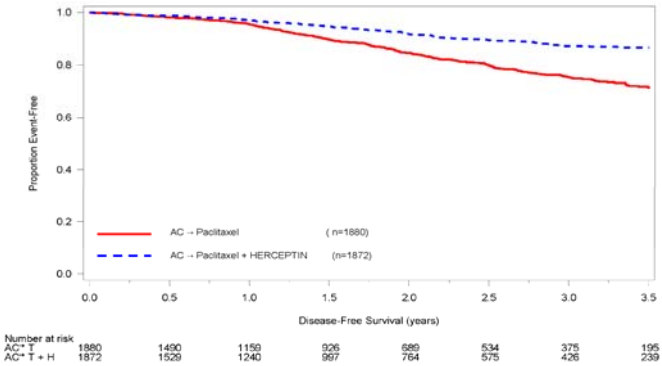
The results for DFS for the integrated analysis of Studies 1 and 2 (Figure 3) and the analysis of DFS results in Studies 1 and 2, and Study 3 are presented in Table 7. Across studies 1 and 2, there were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall patient population: patients with node negative disease, patients with low tumor grade, and patients within specific ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients). In Study 3, there were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall patient population: patients with low tumor grade, within specific ethnic/racial subgroups (Black or Hispanic patients), or > 65 years of age.

Table 6
Efficacy Results from Adjuvant Treatment of
Breast Cancer (Studies 1 + 2 and Study 3)

	Study 1 + 2		Study 3	
	AC→ Herceptin + T (n =1872)	AC→ T (n = 1880)	Chemo→ Herceptin (n =1693)	Chemo→ Observation (n = 1693)
Primary Endpoint				
DFS events	133	261	127	219
Hazard ratio (95% CI)	0.48[a] (0.39, 0.59)		0.54 (0.44, 0.67)	
p-value	< 0.0001[b]		< 0.0001[c]	
Secondary Endpoints				
Deaths	62	92	31	40
Hazard ratio 95% CI	0.67		0.75	
p-value	NS[d]		NS[d]	

CI = confidence interval.
[a] Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.
[b] stratified log-rank test.
[c] log-rank test.
[d] NS= non-significant.

Figure 3
Duration of Disease-Free Survival in
Patients with Adjuvant Treatment of Breast Cancer (Studies 1 and 2)



Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available. The results are shown in Table 7. The number of events in Study 2 was small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups.

Table 7
Treatment Outcomes in Studies 2 and 3 as a Function of
HER2 Overexpression or Amplification

	Study 2		Study 3	
HER2 Assay Result*	Number of Patients	Hazard Ratio DFS (95% CI)	Number of Patients	Hazard Ratio DFS (95% CI)
IHC 3+				
FISH (+)	1170	0.42 (0.27, 0.64)	91	0.56 (0.13, 2.50)
FISH (–)	51	0.71 (0.04, 11.79)	8	----
FISH Unknown	51	0.69 (0.09, 5.14)	2258	0.53 (0.41, 0.69)
IHC < 3+ / FISH (+)	174	1.01 (0.18, 5.65)	299 ^	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	----	------	724	0.59 (0.38, 0.93)

* IHC by HercepTest, FISH by PathVysion as performed at a central laboratory.

^ All cases in this category in study 3 were IHC 2+ .

14.2 Metastatic Breast Cancer

The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 4, n=469 patients) and an open-label single agent clinical trial (Study 5, n=222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

Previously Untreated Metastatic Breast Cancer (Study 4)

Study 4 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to receive chemotherapy alone in this study received Herceptin at the time of disease progression as part of a separate extension study.

Based upon the determination by an independent response evaluation committee the patients randomized to Herceptin and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), and a longer median duration of response, as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin and chemotherapy also had a longer median survival (see Table 8). These treatment effects were observed both in patients who received Herceptin plus paclitaxel and in those who received Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.

Table 8
Study 4: Efficacy Results in
First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemo-therapy (n = 235)	All Chemo-therapy (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC[a] (n = 143)	AC (n = 138)
Primary Endpoint						
Median TTP(mos)[b,c]	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value[d]	< 0.0001		< 0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value [e]	< 0.001		< 0.001		0.10	
Median Resp Duration (mos)[b,c]	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% quartile	6, 15	4, 8	5 ,11	4, 7	6, 15	4, 8
Med Survival (mos)[c]	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value[d]	0.05		0.17		0.16	

[a] AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate.
[d] log-rank test.
[e] χ2-test.

Data from Study 4 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 9).

Table 9
Treatment Effects in Study 4 as a
Function of HER2 Overexpression or Amplification

HER2 Assay Result	Number of Patients (N)	Relative Risk** for Time to Disease Progression (95% CI)	Relative Risk** for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+)*	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)
FISH (–)*	126	0.62 (0.42, 0.94)	1.06 (0.70, 1.63)
CTA 2+	120	0.76 (0.50, 1.15)	1.26 (0.82, 1.94)
FISH (+)	32	0.54 (0.21, 1.35)	1.31 (0.53, 3.27)
FISH (–)	83	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)
CTA 3+	349	0.42 (0.33, 0.54)	0.70 (0.51, 0.90)
FISH (+)	293	0.42 (0.32, 0.55)	0.67 (0.51, 0.89)
FISH (–)	43	0.43 (0.20, 0.94)	0.88 (0.39, 1.98)

* FISH testing results were available for 451 of the 469 patients enrolled on study.
** The relative risk represents the risk of progression or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm.

Previously Treated Metastatic Breast Cancer (Study 5)

Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 5) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at 2 mg/kg IV.

The ORR (complete response+partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to skin and lymph nodes. The overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Herceptin is supplied in a multi-use vial containing 440 mg Trastuzumab as a lyophilized sterile powder, under vacuum. Each carton contains one vial Herceptin® and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative. NDC 50242-134-68.

16.2 Stability and Storage

Vials of Herceptin are stable at 2–8 C (36–46 F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of Herceptin reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2–8 C (36–46 F). Discard any remaining multi-dose reconstituted solution after 28 days. A vial of Herceptin reconstituted with unpreserved SWFI (not supplied) should be used immediately and any unused portion discarded. **Do Not Freeze** Herceptin following reconstitution or dilution.

The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2–8 C (36–46 F) for no more than 24 hours prior to use.

17 PATIENT COUNSELING INFORMATION

- Advise patients to contact a health care profession immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more

than 5 pounds in 24 hours, dizziness or loss of consciousness [*see Boxed Warning Cardiomyopathy*].

- Advise women with reproductive potential to use effective contraceptive methods during treatment and for a minimum of six months following Herceptin [*see Pregnancy (8.1)*].
- Encourage pregnant women who are using Herceptin to enroll in the Cancer and Childbirth Registry [*see Pregnancy (8.1)*].

HERCEPTIN® [Trastuzumab]

Manufactured by:

Genentech, Inc. 4839800

1 DNA Way

South San Francisco, CA 94080-4990 ©2006 Genentech, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

SUMMARY REVIEW

Signatory Authority Decisional Review

Date	January 18, 2008
From	Patricia Keegan, M.D.; Director P. Keegan 1-18-2008 Division of Biologic Oncology Products/OODP/CDER
Subject	Division Director Summary Review
NDA/BLA # Supp #	BL STN 103792.5175
Proprietary / Established (USAN) names	Proprietary name: Herceptin USAN name: trastuzumab
Dosage forms / strength	400 mg lyophilized powder per multi-use vial
Proposed Indication(s)	"Herceptin, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel, is indicated for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer. [*See Dosage and Administration (2.1) and Clinical Studies (14.1)*]"
Action:	Approval

1. Introduction to Review

This efficacy supplement contained the results of a second randomized, multicenter, open-label trial (HERA trial, also referred to as BO 16348) evaluating the safety and efficacy of Herceptin in combination with standard adjuvant treatments in 3386 women with early stage (surgically respectable) HER2-overexpression breast cancer. This adequate and well-controlled trial was conducted by a European consortium of investigators and was not submitted to or conducted under the US IND for Herceptin (trastuzumab). It confirms the efficacy of Herceptin (a clinically important increase in disease-free survival) in women with HER2-overexpressing and surgically respectable breast cancer demonstrated in the joint analysis of NSABP B31 and NCCTG N9831; this joing analysis supported the initial labeling expansion for Herceptin, as an adjunct to surgery, chemotherapy, and if appropriate radiation and hormonal therapy, for the adjuvant treatment of HER2-overexpressing breast cancer (BL STN 103792.5150). The HERA study was well-conducted and the study design was valid and appropriate to establish treatment effects. As discussed in detail in Ms. Fedenko's review, the primary endpoint of disease-free survival (DFS), is a composite endpoints that has been generally accepted by the Agency as appropriate to determine clinical benefit in the adjuvant treatment of breast and colon cancers. Given the compelling results, in terms of magnitude of effect on DFS, robustness of results across important patient subgroups as well as consistency with findings in the joint analysis of NSABP B31 and NCCTG N9831, this single study is sufficient to support expand product labeling to a subset of women with node-negative breast cancer and to support a new dose and schedule of Herceptin. There was no disagreement among the reviewers regarding recommendations for approval of the application.

Aspects of this application that are specifically addressed in greater detail in this review:

1) Assessment of the tolerability and pharmacokinetics of a new dose and schedule of Herceptin
2) Efficacy in a new patient subgroup, patients with node-negative disease
3) Safety assessment of Herceptin given as a single agent or with hormonal therapy rather than in combination with taxane chemotherapy, with specific focus on characterizing incidence, severity and time-to-onset of myocardial dysfunction
4) Evaluation of safety signals identified in the clinical study and spontaneous post-marketing safety reports, which included oligohydramnios/ effects on fetal/infant outcomes and interstitial pnuemonitis
5) Evaluation and characterization of drug interactions and impact of circulating HER2 receptor on pharmacokinetics.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

The sole efficacy study provided to extend the currently approved indication of adjuvant treatment of HER-2 over-expressing breast cancer to patients with high-risk, ≥T1cN0 breast cancer and to support a new dose and schedule of Herceptin for adjuvant treatment of breast cancer is Study BO 16348, also known as the HERA study. This study was supported financially by Roche (the European marketer of trastuzumab) and conducted by a consortium of investigators (BIG) outside the US. The clinical study protocol was first submitted to FDA after data analysis and prior to submission of the efficacy supplement to facilitate pre-BLS discussions. Although not reviewed by FDA prior to or during initiation, FDA acknowledged that the study adequate in design and the reported study results sufficiently compelling to be likely to support labeling expansion.

The review of the efficacy supplement was complicated by issues with regard to database structure (which was rectified early in the review) and failure to submit all protocol amendments (which was identified late in the initial review). This led to requests for additional data late in the review cycle which were classified as a major amendment that extended the PDUFA goal date.

3. CMC/Microbiology/Device

CMC review was conducted to ensure that the product used in the clinical trial (Herceptin manufactured at a non-US licensed site in Europe (Roche-manufactured material at Penzberg facility) was sufficiently comparable to the US manufactured product to support extrapolation of study results to the U.S. population. The assessment was based on information submitted by amendment to the application describing differences in manufacturing process and biochemical comparability data. The CMC reviewer (Wendy Weinberg, Ph.D.) concluded that comparability was sufficient to permit such extrapolation. Because of the new dose/schedule, which results in a two-fold higher dose of Herceptin on the first infusion, Dr. Weinberg assessed and confirmed that acceptability of the endotoxin level based on current standards (5 EU/kg). Dr. Weinberg also concurred with categorical exclusion, as requested by the applicant.

In addition, Ms Colleen Hoyt of the Manufacturing Assessment and Preapproval Compliance Branch confirmed that there are no pending or ongoing compliance actions or investigations to prevent approval. The Genentech, Vacaville, CA manufacturing site inspected on 9/22-29/06 and Wyeth Biopharma, Andover, MA, was inspected on 9/18-27/07; both sites were found to be acceptable.

4. Nonclinical Pharmacology/Toxicology

No non-clinical studies were submitted, and such studies were not required, to support this efficacy supplement. Anne Pilaro, Ph.D. reviewed previously submitted non-clinical study reports to ensure that final product labeling, revised under this application to comply with 21 CFR 201.57 and recently published Guidances for Industry on product labeling, was accurate and complete.

5. Clinical Pharmacology/Biopharmaceutics

A review of Clinical Pharmacology was conducted by Angela Men, M.D., Ph.D., and was amended to consider supplemental information provided late in the review in justification of requested labeling. Dr. Men's review evaluated pharmacokinetic data from three clinical trials in support of the following new dosing regimen:

- Herceptin administered at an 8 mg/kg initial dose as a 90-minute intravenous infusion followed by 6 mg/kg administered every 3 weeks as 60 minute intravenous infusions. for a total of one year of treatment.

This application contained data from a pharmacokinetic (PK) sub-study within the HERA trial (BO 16348) and data from two additional studies in patients with metastatic breast cancer (WO 16229 and BO 15935).

Key design elements of the study design and pharmacokinetic data collection for each of these trials, as abstracted from Dr. Men's review, are reproduced below

- The HERA study is an ongoing, randomized, three-arm, open-label, multicenter study comparing 1 or 2 years of treatment with Herceptin versus observation. For the HERA PK substudy, data have been analyzed for 44 patients randomized to the 1-year treatment arm only. Blood samples for Herceptin serum concentration analysis were collected pre-dose and extensively from 1.5 hours to 21 days post-dose during Cycles 1 and 13. During Cycle 18, the final administration of Herceptin for patients in the 1-year treatment arm, samples were collected pre-dose and extensively from 1.5 hours to 42 days post-dose. In addition, a pre-dose sample was drawn on Day 1 of Cycle 3.

- Study WO 16229 is an open-label, single-arm study of efficacy and safety. Trough concentrations of Herceptin were collected. The first loading dose of Herceptin was 8 mg/kg, followed 3 weeks later by 6 mg/kg and given thereafter every 3 weeks.

- Study BO15935 is an open label PK study. A loading dose of 8mg/kg of Herceptin was given i.v. on Day 1 and thereafter a dose of 6mg/kg was administered i.v. every three weeks. For the first cycle, paclitaxel was given 24 h before Herceptin administration.

Thereafter, Herceptin was administered together with paclitaxel (175mg/m^2) every three weeks for seven cycles (Cycles 2-8). Herceptin was then continued every three weeks until progression of disease or until the patient left the study. Patients continuing Herceptin beyond Cycle 16 entered an extension protocol. The PK parameters were compared between cycles 4 and 12 for Herceptin and between cycles 1 and 4 for paclitaxel.

5.1. General clinical pharmacology/biopharmaceutics considerations, including metabolism, half-life, food effects, variability of bioavailability, and pharmacologic properties other than those related to therapeutic effect.
Dr. Men's review confirmed the applicant's characterization of the pharmacokinetic profile of single agent Herceptin in the proposed dosing regimen. Specifically, she confirmed that the mean half-life is 16.2 days (range: 11.0 - 22.8 days) and steady-state concentrations were achieved between weeks 6 and 37, with mean trough and peak concentrations of 63 mcg/mL and 216 mcg/mL, respectively.

5.2. Drug-drug interactions
Dr. Men noted that pharmacokinetic interactions were explored in one of the PK studies conducted in combination with taxane chemotherapy. The study results showed that, on average, paclitaxel C_{max} and systemic exposure was 15% lower when administered in combination with Herceptin compared to that administered alone. Dr. Men noted that "since efficacy has been demonstrated in the combination therapy, these observed PK difference is not considered clinically significant." The conclusion that efficacy is not impacted has been demonstrated in the original approval (STN 103792.0) in patients with metastatic disease and in patients receiving adjuvant chemotherapy (STN 103792.5150) in which substantial efficacy was demonstrated with the addition of Herceptin to paclitaxel.

FDA requested data to support of specific labeling statements in the Clinical Pharmacology section of the label regarding the effect on shed target antigen (extracellular domain of the HER2 receptor) on Herceptin pharmacokinetics. Given the limited sample size studied and inconsistent results, no conclusions could be drawn with respect to the relationship between circulating extracellular domain of the HER2 receptor and Herceptin serum trough concentration or clinical responses of Herceptin using data from Studies BO15935 and WO16229. While lower trough levels are observed with the highest shed antigen levels, [redacted] (b) (4)

5.3. Pathway of Elimination
No data were provided on pathway of elimination; this issue was adequately addressed in the original approval for this license application.

5.4. Demographic interactions/special populations:
No population PK data were provided in this application, but have been reviewed under previous supplements to this license application.

Based on subgroup analyses, there is no evidence of differences in drug safety or efficacy in older as compared to younger (<65 years) women. All indications for Herceptin occur primarily in adult women, so assessment by gender and in children are not relevant.

5.5. Thorough QT study or other QT assessment:
Studies to assess impact of Herceptin on QT have not been performed. The applicant has agreed to conduct such studies under a post-marketing commitment (PMC #4) to this application.

5.6. Notable issues
FDA requested additional data during the application review to support proposed

(b) (4)

[redacted]

6. Clinical/Statistical

6.1. General Discussion

The application is supported by a single, randomized, multicenter clinical trial for an expansion of a previously approved indication (adjuvant treatment of HER2-overexpressing breast cancer). The design of the study, including primary endpoint, posed no concerns. The results were robust, observed across all relevant patients subgroups, and were clinically significant. Patients were randomized at the completion of adjuvant/neoadjuvant chemotherapy, surgical resection and radiotherapy. As noted, novel features of the HERA trial were inclusion of women with node negative disease and those receiving neoadjuvant chemotherapy. All patients with node-negative disease were required to have primary tumors ≥T1c and meet the following definition of high-risk disease (ER and PR negative or ER-positive/ PgR-positive with at least one of the following: pT > 2 cm, histologic grade 2-3, or age <35 years).

The one-year Herceptin and the observation arms were well balanced for all important prognostic characteristics. The ITT population consisted primarily of younger women (median age 49 years) with good performance status (90% ECOG PS 0), and three-quarters

were from Europe, the Nordic countries or Canada. Across tumor characteristics there was a fairly equal distribution of across nodal risk groups with approximately 10% of women who received neo-adjuvant therapy and approximately one-third each with high-risk node negative disease, 1-3 positive nodes, and ≥4 positive lymph nodes and median pathologic tumor size was 22 mm. Among 1098 women with node-negative disease, 49% (543) had estrogen and progresterone receptor negative tumors and 47% (512) had ER and/or PgR+ tumors with at least one high-risk feature.

Prior to randomization, 94% of patients had received anthracycline-based chemotherapy regimens. Approximately two-thirds received anthracycline, but non-taxane-containing adjuvant chemotherapy and approximately 25% received anthracycline- and taxane-based adjuvant chemotherapy (the current standard of care in the United States). Definitive surgical treatment consisted of modified radical mastectomy in approximately half the patients and lumpectomy in approximately one quarter and 96% underwent axillary node dissection; three-quarters of the patients also received radiotherapy.

The median duration of follow-up was similar in the 1-year Herceptin (12.65 months) and observation (12.42 months) arms, however the proportion of patients with DFS events was lower (7.5% vs. 12.9%) in the Herceptin arm compared to the observation arm. At the time of the interim analysis, there was a 46% reduction in the risk of disease progression or death (DFS) among patients receiving Herceptin for up to one year. The Kaplan-Meier curves for DFS begin to separate at approximately 4-6 months and remain separated with up to two years of follow-up, beyond which there is insufficient data to provide reasonable estimates.

Primary Efficacy Analysis on Disease Free Survival

	Observation N=1693	1-yr Herceptin N=1693
Number of Patients with DFS events	219 (12.9%)	127 (7.5%)
Hazard ratio[a]	0.54	
95% CI	(0.44, 0.67)	
p-value (log-rank)	< 0.0001	

CI=confidence interval;[a] Efficacy relative to control arm; unstratified Cox regression model

This beneficial treatment effect on DFS is consistent across various subgroups, including those defined by age (<65 vs. ≥65 yrs), race (Caucasion vs. non-Caucasian [predominantly Asians]), and nodal status (none, 1-3, ≥4).

Recurrence-Free Survival (RFS) was a pre-specified secondary efficacy endpoint stated in the protocol which is calculated from date of randomization to the date of the first local, regional, or distant tumor recurrence or death. The results of RFS comparison show nominally statistically significant advantage in favor of Herceptin arm ($p<0.0001$; HR=0.51, [95% CI: 0.40, 0.64]).

Distant Disease-Free Survival (DDFS) was an additional, secondary efficacy endpoint pre-specified in the protocol. (DDFS) was calculated from the date of randomization to the first distant tumor recurrence, second primary cancer, or contralateral breast cancer, or death, whichever occurred first. Local and regional recurrences are not considered events in the calculation of DDFS. The results of the DDFS comparison also show nominally statistically significant advantage in favor of 1-year Herceptin arm ($p<0.001$ stratified log-rank test; HR=0.50, [95% CI: 0.39, 0.64])

6.2. Efficacy

6.2.1. Dose identification/selection and limitations

The dose and schedule selected is based on pharmacologic modeling. (b) (4) [redacted]. The basis for this trough level is derived from non-clinical studies, however, the relevance of this non-clinical data to clinical safety and efficacy is not known and has not been established.

6.2.2. Phase 3/essential clinical studies, including design and analytic features

The primary efficacy study is an open-label, randomized, dose-ranging and observational controlled trial, in which Herceptin is given as an adjunct to the current standard of care (surgery, radiotherapy, chemotherapy, and in ER/PgR-positive patients, hormonal therapy). The comparator arm represents the standard of care.

The primary and several key secondary composite efficacy endpoints provide mutually supportive evidence that Herceptin delays the time to disease recurrence, second primary breast cancer, or death (disease-free survival [DFS]), an endpoint that is an accepted measure of clinical benefit in supporting claims of efficacy for adjuvant treatment of solid tumors. Although the study arms were not blinded to treatment assignment, the diagnosis of recurrence is often pathologically confirmed and care in the confirmation of such events is generally more stringent because of the clinical importance of such a finding in terms of patient outcomes and management. Typically, the Agency has not required an independent radiologic/clinical confirmation of disease recurrence as it does for disease progression in metastatic solid tumors in open-label efficacy trials. There were too few deaths at the time of the interim analysis for DFS to conduct a meaningful analysis of overall survival (OS) for efficacy. Data regarding survival provided in the application are reviewed for safety signals whereas an analysis of OS for efficacy will be provided under an agreed upon PMC, when the specified number of deaths triggers a protocol-specified analysis for treatment effect.

6.2.3. Other efficacy studies

No additional efficacy studies were provided, however the findings in the HERA trial are consistent with the findings in the NCCTG N9831 and NSABP B31 joint analysis which supported the efficacy supplement (STN

103792.5150) for adjuvant treatment of HER2 overexpressing breast cancer using a weekly Herceptin dosing regimen.

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions
The primary and secondary clinical and statistical reviewers recommended approval, under the final labeling and associated post-marketing commitments.

6.2.5. Pediatric use/PREA waivers/deferrals
A wavier from the requirement to conduct pediatric studies under PREA has been granted because the indicated disease does not occur in children.

6.2.6. Notable issues
No data were provided in the clinical study report for one of the two treatment arms in the HERA trial.; this was the study arm that utilized a longer duration of Herceptin therapy (2 years of treatment). This information was requested by FDA prior to and during the review of this application, however the study steering committee refused to release the data to Roche, the supporting corporate entity. The applicant (Genentech) has obtained agreement from the study steering commitment to provide the results from this study arm in the future. The applicant will submit a final clinical study report containing data from the 2-year treatment arm under an agreed-upon post-marketing commitment.

6.3. Safety

6.3.1. General safety considerations
The safety dataset includes information from 1672 women, of whom at least half received all planned treatment. The study required routine collection of biochemical and hematology laboratory values and regularly scheduled clinic visits in both treatment arms. The frequency of assessment (clinic visits) was higher in the Herceptin arm, thus any bias in safety data collection tends to favor the control rather than the treatment arm. In addition, serial assessment of serial left ventricular ejection fractions (LVEF) were obtained in both treatment arms to assess for impact on myocardial function. The frequency of cardiac assessments was sufficient to detect subclinical disease and the frequency of clinic visits was sufficient to assess for overt/symptomatic cardiomyopathy. Non-laboratory adverse event data was coded in MedDRA version 7.1 for all 5 levels of the hierarchy, which permitted analysis using standard medical queries and laboratory data were provided in uniform units of measure.

In the 120-day safety update, there was inclusion of safety data obtained beyond the data cut-off point. This issue was problematic in that a protocol amendment activated after the date of database cut-off, permitted cross-over of patients in the control arm to treatment and re-randomization of patients in the one-year arm to one or to two years of treatment. Resolution of these issues prolonged the time to completion of the review of this supplement.

6.3.2. Safety findings from submitted clinical trials

Safety information was provided only from the HERA trial (BO 16348). The safety database included 1678 patients in the Herceptin group, consisting of all patients who received one or more doses of Herceptin regardless of randomization assignment, and 1708 patients in the observation group, consisting of all patients who did not receive Herceptin prior to disease-progression or analysis data cut-off date of March 2005, regardless of randomization assignment. In this population, the most common (≥ 5%) adverse reations in the Herceptin-treated patients were headache, arthralgia, nasopharyngitis, fatigue, diarrhea, nausea, pyrexia, back pain, and chills.

The most serious adverse reaction is cardiomyopathy, which was also the most common reason for study treatment discontinuation and for dose modification. As observed in previous studies, the incidence of clinically symptomatic cardiomyopathy was increased by approximately 6-fold (2% [30/1678] vs. 0.3% [5/1708]) in Herceptin-treated patients compared with controls and the incidence of objective evidence of myocardial dysfunction (LVEF <50% with ≥16% decline compared to baseline LVEF) was increased by three-fold (3.8% [64/1678] vs. 1.2% [20/1708]). The incidence of NCI CTC grades 1 and 2 cardiomyopathy were approximately 2-fold higher among Herceptin-treated patients compared with controls.

An additional serious adverse reaction of Herceptin that was identified in the HERA study and further confirmed by review of spontaneous post-marketing adverse reaction reports, was pulmonary signs and symptoms falling under the general term of interstitial lung disease (4 cases in Herceptin-treated patients compared with none in the observation group). This finding has also been observed in other studies, however routine evaluation with radiologic studies and pathologic evaluation is uncommon, thus the specific pathology is uncertain.

In addition, a review was conducted of post-marketing reports of pregnancy occurring in women receiving Herceptin, based on the likelihood of pregnancy in women receiving adjuvant chemotherapy and to follow-up on inconclusive reports of oligohydramnios in women receiving Herceptin in combination with multiple other drugs, including anti-neoplastic therapy. In this review, new cases of oligohydramnios, including compelling reports of positive rechallenge and dechallenge, were identified in women receiving single agent Herceptin. The mechanism by which Herceptin may cause these findings is not established, however effects on fetal development and nephrotoxic effects have been postulated. Based on these reports, product labeling has been strengthened and updated with this information and directions for patient monitoring and management. The applicant has also agreed to establish a registry for collection of data on maternal, fetal, and infant outcomes in women who use Herceptin during pregnancy.

6.3.3. Safety update

At FDA's request during a pre-submission meeting, the safety update which was submitted on April 20, 2007, was to be limited to case report forms and narrative summaries for previously unreported serious and unexpected adverse events. It was upon review of this submission that FDA first became aware of post-analysis amendments permitting cross-over and re-randomization, as discussed in 6.3.1 of this summary review memo, since some reports contained adverse events in patients originally randomized to observation who subsequently received Herceptin or among patients in the one-year arm who were re-randomized to two years of Herceptin. No substantive new information was provided in the 120-day safety update, however the information raised concerns about loss of control and one-year treatment arms for future comparisons of incidence rates and determination of long-term or delayed toxicities through this loss of randomized comparator groups.

6.3.4. Immunogenicity, where pertinent

The protocol did not require the collection of baseline and serial post-treatment samples to assess for anti-product antibodies. Given the efficacy results and lack of safety signals regarding immunogenic responses, the lack of such data was not considered important enough to impact a decision regarding approval of this supplemental indication.

6.3.5. Special safety concerns

Safety concerns of special interest include the myocardial dysfunction, interstitial lung disease/interstitial pneumonitis, and adverse outcomes in pregnant women using Herceptin, including oligohydramnios and impaired maternal, fetal, and infant outcomes.

6.3.6. Discussion of primary and secondary reviewers' comments and conclusions

The primary and secondary reviewers concurred that the risks of treatment are manageable or monitorable in the short-term. Further, the clinical reviewers agree that these risks are acceptable in light of the benefits, however continued assessment is necessary to evaluate for delayed effects, particularly myocardial dysfunction. These data will be collected and provided under agreed-upon post-marketing commitments associated with this application and BL STN 103792.5150.

6.3.7. Notable issues

There were no additional issues regarding safety beyond those discussed in earlier sections of this summary review memo.

6.4. Clinical Microbiology

Clinical microbiology data were not provided or requested for inclusion because such data are not relevant to this product or proposed indication.

7. Advisory Committee Meeting

An advisory committee meeting was not convened because of the magnitude and statistically robust effects on disease-free survival which were compelling as well asl consistent with results in the adjuvant patient population reviewed under BL STN 103792.5150 and supported by clinical efficacy data in patients with metastatic disease (original approval) and no safety findings were identified in the application which were considered to potentially outweigh the benefits of treatment.

8. Risk Minimization Action Plan

8.1. General considerations on the need for, and goals of, any RiskMAP

No formal RiskMAP was developed; Safety concerns (cardiac toxicity and pregnancy/fetal outcomes) will be further assessed under agreed-upon post-marketing commitments for long-term study data and data collection within a pregnancy registry.

8.2. Important issues

No additional issues.

9. Other Regulatory Issues

9.1. Application Integrity Policy (AIP) - _None identified.

9.2. Exclusivity/patent issues – Not applicable for products regulated under the PHS Act.

10. Financial Disclosure

There was no evidence of substantive financial conflicts of interest as self-reported by study investigators. Reporting information was generally complete. In addition, given the size of the study and the small percentage of study subjects enrolled at any individual site, the study results could not have been impacted by individual investigators/clinical study sites.

11. Labeling

11.1. Proprietary name

The proprietary name was approved in 1998 and no new safety concerns(e.g., medication errors) have arisen with the current name..

11.2. Physician labeling

All major issues were resolved. A summary of changes and rationale are listed below:

Indications and Usage

- Added indication for use following adjuvant chemotherapy, modified applicant's proposed wording (b) (4) for consistency with other approved indications, (b) (4) , and added clarifying description of the node-negative patient population "≥T1c, high risk" to specify subpopulation in which benefit is demonstrated.
- Revised this section for brevity and critical elements

Dosage and Administration

- Deleted initial capitalized statement for brevity (b) (4)
- Revised section 2.1 for brevity, critical content, and active voice. (b) (4)

- Revised Section 2.2 for brevity, critical content, and active voice; deleted [redacted] (b) (4)
- Revised section 2.3 for brevity, critical content and active voice. Moved statement on inspection of particulates; added storage information following reconstitution: [redacted] (b) (4)

Dosage Forms and Strengths

- Revised for brevity and critical content

Warnings and Precautions

- Section 5.1 revised to include new information from Study 3; Study 3 information integrated with Study 1 & 2 data; revised for brevity, critical content, and active voice. Re-ordered to provide described steps to be taken to reduce toxicity to early in section. Data regarding incidence of significant/symptomatic cardiomyopathy for all studies changed from text to tabular format for prominence and more rapid communication. Information on [redacted] (b) (4)
- Section 5.2 revised for brevity and critical information; second sentence in last paragraph deleted because of redundancy with last sentence in last paragraph.
- Section 5.3 revised for brevity and critical information
- Section 5.4 added "interstitial" before pneumonitis as reports in study 3 and AERS mapped to the MedDRA higher level term "interstitial lung disease". Because ILD should be pathologically confirmed (which did not happen in the clinical studies), such events are classified as interstitial pneumonitis throughout the PI.
- Section 5.5 revised to include information [redacted] (b) (4) regarding the importance of assay methodology in interpreting results; revised for brevity and critical information (removed sentences 2 and 3 from first paragraph)
- Section 5.6 (Embryofetal toxicity) added to Warnings and Precautions section with change in pregnancy category from C to D.

Adverse Reactions

- Revised for consistency with Guidance documents, to first summarize most serious and most common adverse reactions.
- Data from clinical studies summarized under section 6.1 with adjuvant and metastatic disease treatment studies combined under this section. Tables presenting adverse reactions moved to front of this section and more detailed discussion of specific adverse reactions follow [redacted] (b) (4)

- [redacted] (b) (4) table from Study 3, as Study 3 had longer and more complete patient follow-up and more complete assessment of all adverse reactions.
- Supplementary information from Studies 1 & 2 described in text. In description of cardiomyopathy, [redacted] (b) (4) replaced with data on objective LVEF findings and integrated with results of Study 3. Interpretation of LVEF data more readily understandable, can be displayed consistently across studies, and not filtered by interpretations of symptoms. Included figures with time-to-first LVEF event to provide information cardiac risks over time from Study 3 and Studies 1 & 2, as easier to read/interpret than previous tables with similar information.
- Subsection on pulmonary toxicity revised to more clearly identify events in the adjuvant and metastatic disease settings.
- Remaining subsections revised to include any new information from Study 3 and for brevity and critical information.
- Added Section 6.3 on Post-Marketing [redacted] (b) (4)

Drug Interactions

- Revised to include information from pharmacokinetic studies in this application, evaluating effects of Herceptin on docetaxel and on paclitaxel pharmacokinetics.

Use in Specific Population

- Section 8.1 changed to pregnancy category D based on additional reports with single agent Herceptin of oligohydramnios. Updated to reflect additional reports, to describe patient management and monitoring, and to recommend that pregnancy women enroll in Cancer and Childbirth Registry.
- Section 8.3 revised to provide more detail on NHP studies and to clarify likelihood of exposure to infants based on published information.

Description

- Revised for brevity and critical content.

Clinical Pharmacology

- Section 12.1 revised for brevity; non-essential information on [redacted] (b) (4) deleted. Title of section changed for consistency with Guidance documents and labeling regulations.
- Section 12.2 revised to include pharmacokinetic information from Study 3, to include results of studies assessing effects of highest levels of HER2-receptor shed antigen on trastuzumab pharmacokinetics, and to include information on effects of trastuzumab on taxane pharmacokinetic profile.

Nonclinical Toxicology

- [redacted] (b) (4) Studies to assess mutagenesis revised for brevity and critical information. Information on fertility studies revised to include information regarding aspect of fertility evaluated and lack of information in males.
- Added subsection 13.2 on reproductive toxicology and moved information previously described in Pregnancy section (8.1).

Clinical Studies

- Retitled sections for easier identification of section of interest.
- Integrated information on Studies 1, 2, and 3 in the same section (14.1). [redacted] for brevity [redacted] Added details regarding study design/node negative patient population, for Study 3. [redacted]
- Re-ordered tables in section 14.2 so that Herceptin column comes first (before control arm)
- [redacted]

How Supplied

- Minor revisions for clarity

Patient Counseling

- Revised for brevity and active voice

11.3. Carton and immediate container labels

No concerns were noted regarding carton or container labels

11.4. Patient labeling/Medication guide

Neither patient labeling nor a medication guide was considered for this agent, which must be administered in a hospital or clinic infusion center.

12. DSI Audits

Biomonitoring inspections were not requested because of the large number of study sites with relatively few patients enrolled per site, such that no one site could have substantially altered study findings. In addition, the results of these trial are consistent with safety and efficacy findings in previous controlled trials in the adjuvant and metastatic disease setting, which are mutually supportive of each other.

13. Conclusions and Recommendations

13.1. Regulatory action

All members of the review team (primary and secondary reviewers) recommended approval. My recommendation is also for approval with revised labeling and post-marketing commitments as agreed-upon with the applicant.

13.2. Safety concerns to be followed postmarketing

The primary safety concern in this population would be those which result in death or long-term disability. The major toxicity which falls into this category is myocardial dysfunction, a previously well-known adverse reaction of Herceptin. The mechanism by which Herceptin causes this effect is unknown. The incidence and severity of myocardial dysfunction during or shortly

following completion of Herceptin has been roughly determined in several settings, however late effects and long-term outcomes are less well known and will be evaluated under post-marketing commitments with continued patient monitoring in this and in other clinical trials.

Two additional safety concerns will also be further evaluated: 1) the risks and maternal/fetal/infant outcomes of oligohydramnios in pregnant women using Herceptin, under PMC #3 and 2) the risks of interstitial lung disease, which is best evaluated in future controlled clinical trials, supplemented by regular re-assessment of spontaneous post-marketing reports.

13.3. Risk Minimization Action Plan, if any

In consultation with the Maternal Health Team (Dr. Karen Feibus) and as agreed to by Genentech, Inc., product labeling was updated in include new information regarding reports of oligohydramnios, with specific recommendations for patient management and monitoring in pregnant women who elect to continue Herceptin. In addition, Genentech has committed to the following commitment (PMC #3, below) in order to gather more detailed information and track outcomes in pregnant women using Herceptin in a patient registry:

- To submit a protocol for review for a prospectively and actively enrolled pregnancy registry that will collect information assessing pregnancy complications and birth outcomes in women with breast cancer exposed to a Herceptin-containing regimen prior to conception or during pregnancy. Notice of a pregnancy registry and the telephone contact number will be included in the package insert. A proposal, including a prospective protocol for FDA review will be submitted to FDA by June 30, 2008. The registry will become active by December 31, 2008, and interim reports of all data collected will be submitted on an annual basis to FDA through December 31, 2019.

13.4. Postmarketing studies

13.4.1. Required studies:

There are no required studies under PREA because the indication approved is expected to occur very rarely if at all in children. The approval for this supplement was granted under regular approval and they required studies under 21 CFR 601 Subpart E do not apply.

13.4.2. Commitments (PMCs)

PMC #1 (below) was requested by FDA because of concerns that the optimal duration of Herceptin therapy has not been established and the findings of the 2-yr arm should address whether a longer duration is more or less effective and whether such prolonged use substantially increases toxicity.

- To provide a final clinical study report (CSR) of the safety and efficacy of 2-years of trastuzumab treatment in Study BO16348 (HERA)in order to provide a final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility. The final study report will include the primary datasets and programs for generation of analyses; analyses will include, but not be limited to the analyses described in the statistical analysis plan. The final CSR will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the final CSR will be submitted by December 31, 2009.

PMC #2 (below) was requested by FDA to allow further characterization of the delayed toxicity, specifically with relationship new or worsening cardiac toxicity over time, in women receiving up to one year of Herceptin.

- To provide updated safety information of the observation and 1-year trastuzumab arms in Study BO16348 (HERA). Interim cardiac safety updates (narratives of new primary or secondary cardiac events) will be provided on an annual basis beginning in December 2008 and continuing until the time of the final CSR, which will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the CSR will be submitted by December 31, 2009.

PMC #4 (below) was requested by FDA to assess for potential effects on cardiac conduction, in accordance with ICH E14 guidance.

- To conduct a QT protocol according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in a minimum of 50 subjects receiving trastuzumab. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by March 31, 2009, and will be completed by 31 March, 2013. A final study report will be submitted by September 30, 2013. A supplement with revised labeling, if applicable, will be submitted by March 31, 2014.

13.4.3. Other agreements: None

13.5. Summary of reviewers' comments: None

13.6. Comments to be conveyed to the applicant: None

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

MEDICAL REVIEW(S)

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

CLINICAL REVIEW

Application Type: BLA
Submission Number: 103972
Submission Code: 5175

Letter Date: 2006 December 21
Stamp Date: 2006 December 22
PDUFA Goal Date: 2008 January 21
Reviewer Name: Katherine Fedenko, MS, CRNP, Senior Clinical Analyst KF 1/18/2008
Through: Joseph Gootenberg, M.D., Acting Team Leader, DBOP, OODP
Review Completion Date: 18 January 2008 Kfenko for J. Gootenberg 1-18-2008

Established Name: Trastuzumab
(Proposed) Trade Name: Herceptin
Therapeutic Class: HER2/neu receptor antagonist
Applicant: Genentech
Priority Designation: S

Formulation: 440mg/vial 21 mg/ml Intravenous
Dosing Regimen: Initial dose 8 mg/kg intravenous three weeks later 6 mg/kg intravenous given every three weeks for one year

Indication: Adjuvant Breast Cancer
Intended Population: Overexpressing HER-2 positive primary invasive breast cancer, node positive or high-risk node negative

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is the recommendation of this reviewer to approve the BLA efficacy supplement STN 103792/5175, for the use of HERCEPTIN™ (Trastuzumab), at the recommended dose for early stage HER2-overexpressing breast cancer for both node positive and node negative disease greater than one centimeter, following multi-modality, anthracycline based chemotherapy.

The recommendation for approval is based on the interim results comparing two of the three, protocol-specified treatment arms in Study BO16348 (HERA); the comparison is between patients randomized to 1-year of Herceptin post-chemotherapy or to no Herceptin therapy (referred to as "observation only"). HERA is single, randomized, open label, multicenter study conducted outside the United States. With a total of 3386 women randomized between the two arms, the study demonstrated a clinically important and statistically significant prolongation in disease free survival (DFS), ($p<0.0001$ based on log-rank test; hazard ratio=0.54, 95%CI=[0.44, 0.67]). This manifested as an absolute difference in K-M estimated 2-year DFS of 7.6% , favoring the 1-year Herceptin arm. An unplanned analysis of overall survival, conducted at the time of the interim analysis of DFS at FDA's request, did not suggest worse survival in the Herceptin treatment arm. This is a supplemental application for an agent previously approved for treatment of metastatic breast cancer and adjuvant therapy in node positive breast cancer. Safety signals contained in this submission are similar to those previously identified; the most important toxicity of HERCEPTIN™ is cardiomyopathy, which can be fatal and serious. In addition the following safety signals were identified or better characterized:

- The risk of a clinically important reduction in left ventricular ejection fraction (LVEF) of below 50% and ten percentage points below baseline LVEF, which is three times higher than the risk of cardiomyopathy in patients receiving not Herceptin.
- Pregnancy category was elevated to a D from a B based on compelling post marketing data for oligohydramnios in dechallenge and rechallenge of Herceptin and a pregnancy registry commitment from the applicant.
- Hypertension and arrhythmias was added to warnings and precautions of the label.
- Interstitial pneumonitis was added to the black box warning.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The planned risk management activities include an agreed-upon PMC for collection of additional information on risks of Herceptin to pregnant women and fetuses.

To submit a protocol for review for a prospectively and actively enrolled pregnancy registry that will collect information assessing pregnancy complications and birth outcomes in women with breast cancer exposed to a Herceptin-containing regimen

prior to conception or during pregnancy. Notice of a pregnancy registry and the telephone contact number will be included in the package insert. A proposal, including a prospective protocol for FDA review will be submitted to FDA by June 30, 2008. The registry will become active by December 31, 2008, and interim reports of all data collected will be submitted on an annual basis to FDA through December 31, 2019.

This PMC was generated in conjunction with consultants from the Maternal-Fetal Health Team. For details, see consult reviews by Dr. Karen Feibus.

1.2.2 Required Phase 4 Commitments

There are no post-marketing commitments required because regular approval is granted under 21 CFR 601 and a waiver is granted for required PMCs under PREA because the indication (HER-2 overexpressing, surgically resected breast cancer) does not occur in the pediatric population.

1.2.3 Other Phase 4 Requests

1. **Safety and Efficacy of the 2-year Trastuzumab Arm in HERA**
   To provide a final clinical study report (CSR) of the safety and efficacy of 2-years of trastuzumab treatment in Study BO16348 (HERA)in order to provide a final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility. The final study report will include the primary datasets and programs for generation of analyses; analyses will include, but not be limited to the analyses described in the statistical analysis plan. The final CSR will be submitted by December 31,2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the final CSR will be submitted by December 31, 2009.

2. **Updated Safety of the Observation and 1-year Trastuzumab Arms in HERA**
   To provide updated safety information of the observation and 1-year trastuzumab arms in Study BO16348 (HERA). Interim cardiac safety updates (narratives of new primary or secondary cardiac events) will be provided on an annual basis beginning in December 2008 and continuing until the time of the final CSR, which will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the CSR will be submitted by December 31, 2009.

3. **To perform a QT Study**
   To conduct a QT protocol according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in a minimum of 50 subjects receiving trastuzumab. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by March 31, 2009, and will be completed by March 31, 2013. A final study report will be submitted by September 30, 2013. A supplement with revised labeling, if applicable, will be submitted by March 31,

2014.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG_1 kappa that contains human framework regions with the complimentarity-determining regions of a murine antibody (4D5) that binds to HER2. rastuzumab is produced by a mammalian cell (Chinese Hamster Ovary [CHO]) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The only route of administration is intravenous. The requested indication is for adjuvant treatment of primary invasive breast cancer in tumors that overexpress HER2, and have either node positive or high-risk, node-negative disease. Herceptin is administered every three weeks for 52 weeks, initiated after surgical resection and completion of (neo) adjuvant chemotherapy and radiation,.

The clinical program leading to this submission consisted of a single trial conducted outside the United States. The applicant submitted interim results of study BO16348, the Herceptin Adjuvant (HERA) trial was an international, multi-center, open-labeled randomized three-arm trial comparing 1 year and 2 years of Herceptin to observation alone. This study was conducted in multiple centers outside the United States and was supported by F. Hoffman-La Roche, the European marketer of trastuzumab. The applicant for this efficacy supplement is Genentech Oncology, the U.S. license holder.

The clinical protocol for the HERA study was not submitted to the US IND until 2006, after the conduct of the interim analysis and dissemination of the study results and thus no Special Protocol Assessment (SPA) was requested or performed for study BO16348 (HERA).

The BO16348 trial was a randomized, open-label, three arm study comparing the addition of either 1 year or 2 years of Herceptin following completion of chemotherapy to no additional treatment (observation) after completion of the standard of care (surgery, adjuvant chemotherapy) for the adjuvant treatment of women with surgically resectable, HER2-overexpressing breast cancer. Women in all three arms were also to receive, as appropriate, hormonal therapy and radiation in accordance with the standard of care, based on surgical treatment/results and estrogen or progesterone receptor expression in the tumor. There were a total of 5079 women enrolled and randomized to one of the three study arms. The total number of subjects registered and randomized to the one-year Herceptin and to the "no Herceptin" (observation) arms was 3386; this constitute the intent-to-treat population evaluated in analyses of efficacy. The intent to treat population contained 1693 subjects each in the observation and one-year Herceptin arms. The safety analysis population consisted of treatment administered rather than assigned, with 1708 women who received no Herceptin evaluated for safety in the observation group and 1678 women who received one or more doses of Herceptin evaluated in the Herceptin treatment

group.

This is the second trial demonstrating a clinically meaningful and highly significant improvement in disease-free survival with the addition of Herceptin to adjuvant chemotherapy for the treatment of HER2 overexpressing breast cancer. The safety and efficacy results of BO16348 (HERA) trial are consistent with the findings of the joint analysis of NSABP-B31 and NCCTG N9831, which supported the first labeling expansion of Herceptin for adjuvant treatment of HER-2 positive breast cancer.

This application supports further expansion of the label to include adjuvant treatment of women with early-stage, node- negative HER2-overexpressing breast cancer whose tumors are greater than one centimeter ($T1_CN0$) as well as confirmation of treatment effect in node-positive disease. Adjuvant chemotherapy consisted of anthracycline-based, combination chemotherapy in 94% of the population. The application also supports an new dosing regimen as follows:

- Initiation of Herceptin following completion of all chemotherapy. Administer Herceptin at an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg every three weeks for a total of 17 doses (52 weeks of therapy). Administer as a 90 minute intravenous infusion.

The clinical safety data obtained in this study was collected at protocol-specified serial timepoints, and coded in MedDRA, version 7.1 and supplemented toxicity severity grading using the NCI CTCAE version 2.0, for non-cardiac adverse events and coded for severity according to the New York Heart Association (NYHA) classification system for symptomatic congestive heart failure. Post-marketing surveillance using the adverse events reporting system (AERS) was utilized for confirmation of new safety signals.

1.3.2 Efficacy

The clinical data submitted in support of the proposed indication was derived from interim analysis of a single, randomized, open label, multicenter study, Study BO16348 (HERA). Data were submitted by the applicant only from two of the three study arms: the one-year Herceptin and observation arms. Across these two arms, a total of 3386 women were randomized to either one year of Herceptin (n=1693) or observation (n=1693) following completion of chemotherapy and the trial was designed to assess the impact of Herceptin therapy on disease-free survival (DFS) as the primary objective.

Randomization was 1:1:1, one-year Herceptin versus two-year Herceptin versus observation. Prior to randomization, patients were stratified for a number of factors; age, geographical region, nodal status, hormone receptor status and associated endocrine therapy, type of previous adjuvant chemotherapy regimen, and ECOG Performance status ECOG (0 vs. 1). A minimization procedure according to Pocock and Simon was used for allocation of subjects to the treatment arms in order to secure a balance between the treatments for stratification factors. For subjects randomized to the one-year Herceptin arm, therapy began after surgery and completion of (neo) adjuvant chemotherapy and/or radiation. The initial dose of Herceptin was 8 mg/kg IV followed by doses of 6 mg/kg IV

three weeks later and every subsequent three weeks for one year (52 weeks). The schedule of assessments for disease status and toxicity was identical across treatment arms.

The primary efficacy endpoint was disease free survival (DFS), as defined in the next paragraph. Secondary efficacy endpoints overall survival (OS), recurrence-free survival (RFS), and distant disease-free survival (DDFS).

The primary efficacy endpoint of DFS was measured from the date of randomization to the date of the first DFS-defining event. A DFS event included any of the following: any loco-regional or distant recurrence of breast cancer, the development of a secondary primary cancer other than basal or squamous carcinoma of the skin and carcinoma *in situ* of the cervix, and death from any cause. Lobular carcinoma in situ (LCIS) was not considered a DFS-defining event. Diagnosis of a second cancer had to be confirmed histologically whenever possible. The diagnosis of first breast cancer recurrence could be made only when both clinical and laboratory findings met the criteria for loco-regional or distant recurrence.

The study opened for enrollment on November 30, 2001, the data cut-off date for the interim analysis was March 29, 2005, and the interim analysis was performed on April 25, 2005. Data clean-up continued over the 6 months following data cut-off with the database closure October 7, 2005. The date interim analysis was performed on April 25, 2005. At the time of the interim analysis, the median duration of follow-up was similar across both arms: 1-year Herceptin (12.65 months) and observation (12.42 months).

The interim analysis was planned for each pair-wise comparison (one-year Herceptin vs. observation and two-year Herceptin vs. observation) after 50% of the planned 951 events for the final analysis of that pair-wise comparison had occurred (e.g., 475 events). A step-down adjustment procedure of the Bonferroni method was to be used for the pair-wise comparisons. Based on this procedure, the significance levels for the second pair-wise comparison were 0.001 for the interim analyses and 0.0247 for the final analysis. If the significance was reached, the significance levels for the second pair-wise comparison were to be 0.002 for the interim analysis and 0.0494 for the final analysis. This procedure was to assure that the overall study-wise significance level was controlled at 0.050 level.

The required number of events to conduct the interim analysis for DFS appear to have occurred by March 2005 for both of the planned pair-wise comparisons, however only the one-year Herceptin versus observation arm comparison were provided, along with supporting data, in this supplemental application. The results of the interim analysis showed significant results in favor of one-year Herceptin arm and the IDMC recommended to the HERA Steering committee the disclosure of data from 1-year Herceptin arm and the observation arm.

The interim analysis results demonstrated a beneficial treatment effect on disease-free survival for the 1-year Herceptin arm in women receiving adjuvant treatment for HER2-overexpressing breast cancer ($p<0.0001$ based on log-rank test; hazard ratio of 0.54 [95% CI: 0.44, 0.67]). This beneficial treatment effect on DFS appears to be consistent across

various subgroups, such as age, race, nodal status, and HER2 assay results. There were fewer total DFS events in the one-year Herceptin arm, with 7.5% of patients experiencing a DFS event compared to 12.9% in the observation arm. There was also a statistically significant advantage in two-year DFS rates with an absolute increase of 7.6% higher K-M estimated two-year DFS rates among patients in the 1-year Herceptin arm compared to the observation arm.

Since the 2-year Herceptin arm data was not submitted and based on the original statistical plan, the protocol pre-specified comparisons can not be completed. The original statistical plan was inclusive of the 2-year Herceptin arm data that was not submitted; as a result the protocol pre-specified comparisons can not be completed. The comparison of 2-year Herceptin arm to observation arm must be performed in order to determine whether there is any remaining alpha to test the secondary endpoints. As a consequence, in the current submission, any further evaluation of secondary efficacy endpoints will not be meaningful. Overall, the applicant's primary and secondary endpoints are based on composite measures which are not well documented, the interpretation of the results is not clear.

1.3.3 Safety

The safety database consists of the following groups: Herceptin group (n =1678) which included all patients who received one or more doses of Herceptin regardless of randomization assignment and observation group (n= 1708) which included all patients who did not receive Herceptin prior to disease-progression or analysis data cut-off date of March 2005, regardless of randomization assignment.

Exposure information is provided for 1672 patients who received one or more doses of trastuzumab. The median duration of exposure was 51 weeks. The 25^{th} % and 75^{th} % of duration of Herceptin administration are 33 and 51 weeks respectively.
While the applicant reported the extent of exposure to Herceptin in 1678 subjects, an analysis performed by the reviewer reveals exposure data in datasets for only 1672 subjects, a six subject discrepancy. The applicant was made aware of this discrepancy early in the review and provided an explanation amendment 1 to the application. A limitation of the exposure data it is unclear how many subjects actually completed a full course of drug. The datasets entitled "EXIT" contains information on the subjects who completed the study or discontinued prematurely from study. One of the variables in this data set codes as "yes" or "no" whether the subject completed the study. One hundred ninety-one subjects were coded under both the "yes" and "no" flags.

Table 1. Duration of Herceptin in the Randomized Treatment for Efficacy

N	Mean	Median	Lower Quartile	Upper Quartile	Minimum	Maximum
1672	42.0669856	51.1428571	33.0714286	51.1428571	0.1428571	59.5714286

The Means Procedure
[Calculated using MEDT dataset (last MTENDDT-MTBEGDT +1)/7]

The clinical safety data were captured in datasets using MedDRA coding version 7.1 and toxicity grading assigned according to NCI CTCAE version 2.0 non-cardiac toxicity and according to the New York Heart Association (NYHA) classification system for symptomatic congestive heart failure. Safety data in this application was supplemented by analyses of the FDA post-marketing surveillance database, AERS (adverse events reporting system), for confirmation of new safety signals.

Key safety findings concerning Herceptin therapy emerging from study BO16348 (HERA):

- Treatment emergent signs and symptoms were cardiac failure congestive, cardiac failure and ejection fraction decreased.

- In the 1 year Herceptin arm there were more grade 3-4 toxicities under Cardiac Disorders compared to the observation arm: cardiac failure congestive 0.4 % (7/1678) vs. 0%; cardiac failure .02% (4/1678) vs. 0.1% (1/1708); tachyarrhythmia 0.1 % (2/1678) vs. 0%; sudden death 0.1% (1/1678) vs. 0%.

- New information regarding overall incidence of hypertension and arrhythmia not previously reported in legacy studies revels a higher incidence of both in Herceptin-treated subjects. The incidence of hypertension is 4% (64/1678) with Herceptin compared to 2% (35/1708) without Herceptin and the incidence of arrhythmia is 3 % (43/1678) compared to 1% (17/1708).

- Common ($\geq$ 5%) adverse events of any grade with higher incidence ($\geq$ 2%) in the Herceptin-treated patients were reported as the following: Headache, arthralgia, nasopharyngitis, fatigue, diarrhea, nausea, pyrexia, back pain, and chills.

- Rare and serious adverse reactions associated with Herceptin are known cardiomyopathy with an incidence of <1% (2/1678).

- Better characterized risk of clinical significant cardiomyopathy (left ventricular ejection fraction (LVEF) dropping to less than 50 % and ≥ 10 % point drop from baseline) is three times higher for subjects receiving Herceptin.

- New finding of interstitial lung disease (4/1678).

- Pregnancy category was elevated to a D from a B based on compelling post marketing data for oligohydramnios.

- A limitation of this application in the safety findings was that safety for the 2 year Herceptin arm data was not disclosed.

New safety signal of interstitial lung disease (ILD) was flagged with standardized medical query (SMQ). Cases of ILD were n=4 (0.2%) p-Value = 0.0435. The office of surveillance and epidemiology (OSE) was consulted. An AERS (adverse event reporting system) data mining report was generated revealing a disproportionate risk ratio of two times the expected incidence of ILD in reporting with trastuzumab use.

The incidence of heart failure (composite term combining preferred terms "cardiac failure congestive" and "cardiac failure") was 2% among Herceptin-treated patients compared to 0.5% in patients not receiving Herceptin. Further characterization of decline in cardiac function was captured under preferred term "ejection fraction decreased"; all events were reported as grade 1-2 in severity and thus were apparently asymptomatic. The incidence of "ejection fraction decreased" was 3.5 % in Herceptin-treated subjects compared to 0.6% in patients who received no Herceptin.

1.3.4 Dosing Regimen and Administration

The currently approved, recommended schedule of Herceptin for treatment of both metastatic and adjuvant treatment of HER2 overexpressing breast cancer is as an intravenous infusion once every seven days. The approved initial dose is 4 mg/kg administered over 90 minutes. The recommended subsequent weekly doses is 2 mg/kg administered over 30 minutes. The recommended duration of therapy in metastatic breast cancer is until tumor progression. For adjuvant treatment of breast cancer, recommended duration of therapy is 52 weeks.

The proposed application requests inclusion of the following new dose and schedule in the adjuvant treatment of HER2-overexpressing breast cancer in women with node-positive and pre-defined high risk node-negative disease in the product labeling.

- An initial dose of 8 mg/kg as an intravenous infusion administered over 90 minutes
- Subsequent doses of 6 mg/kg as an intravenous infusion administered over 90 minutes every three weeks
- Total duration of treatment of 52 weeks.

Reviewer comments: The HERA protocol was not conducted under United States IND. The standard anthracycline used in the HERA clinical trial most frequently was epirubicin in both arms followed by doxorubicin. In the United States, clinical trials leading to approval of anthracycline-based chemotherapy regimens use doxorubicin. Overall, anthracycline therapy with epirubicin was given in 66% of HERA study subjects compared to 34% treated with doxorubicin-containing adjuvant chemotherapy regimens. The HERA protocol has data only to support adjuvant single agent use of trastuzumab post-completion of anthracycline-based chemotherapy, but not use of this dose/schedule in combination with taxanes..

1.3.5 Drug-Drug Interactions

No formal drug interaction-drug interactions studies were conducted. in support of this application and none were required because Herceptin is administered as a single agent (monotherapy) in the proposed indication. However, pharmacokinetic data were provided for three studies, a subset of 44 patients in the HERA trial and two studies employing the proposed dose/schedule of Herceptin in combination with taxane-based chemotherapy in women with HER-2 overexpressing, metastatic breast cancer. These data were used to investigate the interactions between Herceptin and circulating levels of shed target antigen (extracellular domain of the HER2/*neu* receptor which can be detected and measured in the blood) and interactions between taxane chemotherapy and Herceptin.

1.3.6 Special Populations

Pharmacokinetic data were provided from Studies BO15935 and WO16229, in women with metastatic breast cancer and in 44 patients in the 1-year treatment arm of the HERA PK substudy. In the HERA PK substudy, Herceptin serum concentration data were available from 37 patients at Cycle 1, from 12 patients at Cycle 13, and from 8 patients at Cycle 18 who provided extensive samples.

Across the pharmacokinetic dataset, there were insufficient numbers of elderly women (age 65 years or greater) or with renal or hepatic dysfunction to permit an assessment of the impact of these patient factors on Herceptin pharmacokinetics. There are no studies of the pharmacokinetics of Herceptin in males or in pediatric subjects; in both these groups, the incidence of HER2-overexpressing breast cancer is expected to be extremely rare.

Given the limited sample size studied and inconsistent results, no conclusions could be drawn with respect to the relationship between circulating extracellular domain of the HER2 receptor and Herceptin serum trough concentration or clinical responses of Herceptin using data from Studies BO15935 and WO16229.

Subgroup analyses of safety and efficacy in the elderly population were conducted. The proportion of subjects age $\geq$ 65 years, combining the observation and one year Herceptin arms, comprised of 7% of the total ITT population (120 women in the one-year Herceptin arm and 114 in the observation arm). There were insufficient numbers of events in this subgroup to reliably assess for differential treatment effects in older versus younger patients. There did not appear to be substantially increased toxicity, particularly cardiac

toxicity, in older versus younger women.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

- Established Name: Trastuzumab
- Trade Name: Herceptin
- Pharmacologic Class: Humanized monoclonal antibody
- Target: Selectively binds to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2.
- Proposed Indication: (b) (4)
- The applicant proposes administration of trastuzumab (b) (4)
- Route of administration: Intravenous

Trastuzumab is produced by a mammalian cell (Chinese Hamster Ovary [CHO]) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Herceptin is supplied as a sterile, white to pale yellow preservative-free lypholized powder. The nominal content of each Herceptin vial is 440 mg trastuzumab, 400 mg α, α-trehalose dehydrate, 9.9 mg L-histidine HCL, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 ml of the supplied Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/ml trastuzumab, at a Ph of approximately 6.

2.2 Currently Available Treatment for Indications

In the *adjuvant* setting for breast cancer there is currently no other product approved for marketing the target of the human epidermal growth factor receptor 2 protein, HER2.

For node-positive, HER-2 overexpressing, breast cancer the results from studies NSABP B-31 and NCCTG 9831 resulted in FDA approval in November 2006 for the expanded indication of the addition of trastuzumab to chemotherapy treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel. This approval was based on a highly robust and clinically important increase in disease-free survival in Herceptin-treated patients.

2.3 Availability of Proposed Active Ingredient in the United States

Herceptin® is commercially available. It was approved by the FDA in 1998 for use as a single agent for the treatment of patients with HER2 -over-expressing metastatic HER-

overexpressing breast cancer who have received one or more chemotherapy regimens for their metastatic disease and also in combination with paclitaxel for the adjuvant treatment of patients with HER2 -over-expressing metastatic node-positive HER-2 overexpressing breast cancer who have not received chemotherapy for their metastatic disease. In November 2006 the FDA approved the addition of Herceptin to treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel.

2.4 Important Issues with Pharmacologically Related Products

There are no commercially available pharmacologically related products.

Herceptin is the only US-FDA approved antibody product directed against the HER2 receptor. The key safety issues continue to be those reflected in the known black box warning; cardiac and pulmonary toxicity. Based on safety information derived from the HERA study and supplemented by voluntary post-marketing reports, the FDA has revised the product label to provide additional characterization of treatment-induced myocardial dysfunction and new information regarding interstitial lung disease.

There is one approved drug, lapatinib (Tykerb), a tyrosine kinase inhibitor that is approved for treatment of HER2-overexpressing metastatic breast cancer that has progressed following Herceptin therapy, based on evidence of improvement in progression-free survival and evidence of no decremental effect on overall survival. The toxicity profile of of lapatinib includes decrease in left ventricular ejection fraction, interstitial lung disease, and pneumonitis.

2.5 Presubmission Regulatory Activity

2.5.1 Regulatory History of Trastuzumab Biologics License Application

U.S. FDA Marketing Authorization for trastuzumab was granted on September 25, 1988, for the indication of treatment of metastatic breast cancer whose tumors overexpressed the HER2 protein, as a single agent in women who received one or more chemotherapy regimens for metastatic disease and in combination with paclitaxel for patients who have not received chemotherapy for metastatic disease.

Two studies supported initial approval in HER2- overexpressing metastatic breast cancer. The first study, a randomized open label trial in previously untreated metastatic disease (n=469) with the endpoint of time to tumor progression (TTP) and the second, a single arm study in previously untreated metastatic disease (n=222) with the endpoint of overall response rate (ORR). The results of the trials demonstrated patients randomized to Herceptin and chemotherapy experienced a significantly longer median time to disease progression, a higher ORR, and a longer median duration of response, as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin and chemotherapy also had a longer median survival.

An efficacy supplement was approved on November 16, 2006 (BL STN 103792.5150) to expand labeling claims to include adjuvant treatment of HER2 overxpressing breast cancer. The data supporting this supplemental application were derived from a combined, interim analysis of two studies (NCCTG N9831 and NSABP B31), two NCI-funded cooperative group studies. In both studies, patients were randomized to chemotherapy alone (doxorubicin and cyclophosphamide every three weeks for four cycles followed by 12 weeks of Taxol (AC→T) or to weekly trastuzumab given weekly following completion of for cycles of doxorubicin and cyclophosphamide, for one year (AC→TH). The first 12 weeks of trastuzumab therapy was administered concurrently with paclitaxel with the remainder administered as a single agent. The approval was based on demonstration of a significant improvement in disease-free survival [The time to recurrence or death among patients who received trastuzumab and chemotherapy was reduced by 52% compared with those receiving chemotherapy alone (hazard ration of 0.48; 95% CI: 0.39, 0.59; $p \leq 0.0001$ stratified log rank, 2-sided test). An interim analysis of survival was conducted which did not cross the pre-specified boundary for statistical significance, however there was no evidence of a shorter survival in the treatment arm.

2.5.2 Regulatory History of this Application

The key milestones in the regulatory history of the current application are summarized in the following table. The clinical protocol for Study BO16348 (HERA) was first submitted to the US IND in preparation for the first pre-sBLA submission. The FDA requested that the original three arms of the study be submitted for review at pre-sBLA meeting on May 31, 2006. At a second pre-sBLA meeting held on November 17, 2006, the FDA requested IDMC minutes regarding the 2-year Herceptin arm be disclosed. The Breast International Group (BIG) issued a letter to Genentech responding to FDA request that was submitted as part of an addendum to the HERA submission (refer to Appendix A) stating :

> "...complying with the FDA request would require us to go against the charter and recommendations of our own IDMC".

Table 2. Summary of sBLA Milestones

(communications in italics)

Pre-Submission History	
May 31, 2006	First Pre-sBLA meeting. - FDA requested arm 3 data from HERA (2- year Herceptin) . Genentech could not commit to provide this data but did commit to request the data from DMC.
November 20, 2006	Teleconference with Genentech at the request of the FDA. - FDA requests data the from 2- year Herceptin arm including survival data be included in the proposed supplement. Requeste not granted (see Appendix A).
Submission History	
December 22, 2006	Supplement receipt date
January 30, 2007	*Amendment 1: explanation of randomization procedures and neo-adjuvant chemotherapy regimen dataset*
January 31, 2007	Teleconference regarding inadequacy of submitted data structure, requested new data sets with data shell examples given
February 13, 2207	Amendment 2: revised datasets submitted
February 15, 2007	Amendment 3: response to manufacturing status of the Herceptin used in HERA trial
February 27, 2007	*Filing letter*
February 28, 2007	Amendment 4: List of independent Ethics Committees (membership lists)
March 6, 2007	*74-day deficiency letter*
March 29, 2007	Amendment 5: Response to 74-day Deficiency Letter 815 pages
April 20, 2007	Amendment 6: 120-Day Safety Update
April 24, 2007	*Teleconference discussing coding of cardiac endpoints. Agency requested GNE to review data coding of NYHA vs. CTC v2.0*
May 8, 2007	Amendment 7: Responses to March 6, 2007, deficiency letter
June 12, 2007	*Teleconference Agency requested status of cardiac endpoints coding*
June 21, 2007	Amendment 8, Responses to April 24, May1 and May 18 2007, teleconference questions.
	{Deleted informal submissions/communications}
July 17, 2007	*Teleconference discussing responses to cardiac endpoints coding and proposed new 5 dataset submission. Formal letter from the Agency by week's end.*
July 20, 2007	*Information request letter*
August 20, 2006	Amendment 9: response to 7-20-07 FDA letter containing revised datasets for cardiac endpoints
January 21, 208	New PDUFA date

The HERA trial results were published in:

- October 2005, in the New England Journal of Medicine, which contained limited 2 year Herceptin arm data published;
- January 2007, Lancet; and
- June 2007, Clinical Breast Cancer.

2.6 Other Relevant Background Information

There are 65 countries other than the United States registered for use in adjuvant treatment of HER-2 overexpressing breast cancer based on the interim analysis of two of the three arms of study BO16348 (HERA).

Foreign market approvals include 440 mg and 150 mg strengths. Not all countries are approved for use in both strengths. In Mexico 150 mg was de-registered and in the Philippines 440 mg was deregistered and replaced by 150 mg.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

For details, see CMC review by Wendy C. Weinberg, Ph.D.

Trastuzumab is an IgG_1 kappa recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2.

Chemistry, manufacturing, and controls information was submitted to this application to support the comparability of the product used in the clinical efficacy study to the U.S. licensed product, Herceptin. Specifically, the CMC review of the process and biochemical characteristics of EU approved trastuzumab Drug Substance manufactured by Roche in their Penzberg facility using the v1.0 process compared to trastuzumab manufactured by Genentech under their FDA license using the v1.0 and v1.1 processes. The HERA study in this application utilized EU approved Herceptin manufactured at Penzberg by Roche. Dr. Weinberg concluded that the product used in the clinical study is sufficiently comparable to the US licensed product to permit extrapolation of the results to the marketed product, Herceptin.

In addition, the CMC review considered the acceptability of endotoxin levels of FDA approved Herceptin at the intended dose for this application and Genentech's claim of categorical exclusion. Dr. Weinberg concluded that the dose of 8 mg/kg would yield a maximum endotoxin exposure of (b)(4) EU/kg, well within the USP limit of 5 EU/kg and that the categorical exclusion claim is appropriate.

3.2 Animal Pharmacology/Toxicology

For details, see Toxicology review memo by Anne Pilaro, Ph.D.

No new nonclinical data were submitted in this supplement and none were required to support the proposed extended labeling claims. However, a review of nonclinical data was required to assess the accuracy and appropriateness of revised product labeling, specifically to the *WARNINGS and PRECAUTIONS* (Section 5.6, *Pregnancy Category D*), *USE IN SPECIFIC POPULATIONS* (Section 8.1, *Teratogenic Effects* and Section 8.3, *Nursing Mothers*), and *NONCLINICAL TOXICOLOGY* (Section 13.1; *Impairment of Fertility* and 13.2, *Animal Toxicology and/or Pharmacology*) which were modified for compliance to the Physician Labeling Rule (PLR) format. In order to evaluate the modifications to these sections of the labeling, Genentech submitted pdf copies of three nonclinical, reproductive and/or developmental toxicology studies with trastuzumab, conducted in cynomolgus monkeys, for ease of reviewer reference. These studies were previously

reviewed within the original BLA (BL STN 103792.0000).

Dr. Pilaro concluded that these studies were of appropriate design (e.g., included appropriate dose range of trastuzumab with resulting exposure margins comparable to human dosing; contained information on the fetal outcomes and data regarding evaluation of male fertility parameters) to support the proposed labeling modifications and conversion to PLR format. Based on her review of these study reports, Dr. Pilaro verified that accuracy of the claims as described in the relevant sections of the proposed package insert reviewed under this efficacy supplement.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of data used in this review was derived from a single study, BO 16348, HERA. The electronic version of the study report and protocol for study BO 16384 were reviewed. Electronic raw and derived datasets were analyzed using statistical program JMP 6.0. Case report forms and narratives submitted by the applicant were reviewed and cross-referenced against the datasets provided by the Applicant. In addition, voluntary post-marketing surveillance reports from the FDA's Adverse Event Reporting System (AERS) were analyzed by review staff in FDA's Office of Surveillance and Epidemiology and by this reviewer to verify new safety signals identified in the analysis of the safety datasets for Study BO 16348.

Raw and Derived Datasets Reviewed	
Safety Review	Efficacy Review
AE (adverse event)	EFEX (Efficacy and special safety assessments)
CAB (Cardiac Advisory Board Review)	EFEXLVEF (LVEF)
CHEMOTX (Prior chemotherapy)	EFEXRE (radiological exam)
DEMO (demographic data)	EFFEXSURV (disease recurrence and survival)
DIAG (previous and current diseases)	* CARDIAC (cardiac\LVEF data)
DIED (Death information)	* CARDIC 2 (secondary cardiac LVEF, CAB)
EFEXCE (Cardiac Event)	*PAT (efficacy analysis data)
EFEXCQ (cardiac questionnaire)	
EXCL (Exclusions)	
EXIT (study completion/discontinuation	
HORMTX (hormone therapy)	
LABP (Laboratory results)	
MEDO (previous and concomitant treatment)	
MEDT (Study drug administration)	

4.2 Tables of Clinical Studies

Results of the following studies were submitted as clinical study reports, in summary form, and supported by datasets containing raw and derived data in support of this submission (Table 3).

Table 3. List of Clinical and Pharmacokinetic Studies

Study	Title	No. of Patients
Efficacy and Safety Data		
HERA :BO16348	A randomized phase III multi-center trial for comparison of 1 year of Herceptin treatment versus observation only in women with HER-2 positive primary breast cancer who have completed adjuvant therapy.	3386
Pharmacokinetic Data		
BO 15935	A phase I/II study to determine the safety, tolerability and pharmacokinetics of Herceptin (trastuzumab) and paclitaxel in three weekly combination in women with metastatic breast cancer.	31
WO 16229	A phase II study of Herceptin monotherapy administered 3 weekly in women with HER2 overexpression/amplification in metastatic breast cancer,	105

4.3 Review Strategy

Study BO 16348 was reviewed for evidence of safety and efficacy. The electronic submission, with the Clinical Study Reports, Summary of Clinical Safety, Summary of Clinical Efficacy, and other relevant portions were reviewed. Throughout the review process, consistency between the SAS dataset entries and case report forms (CRFs)was examined. Major efficacy and safety analyses were reproduced using raw datasets in JMP. In addition statistical, pharmacology/toxicology, and product reviewers were part of the multi-disciplinary approach.

4.4 Data Quality and Integrity

Early in the review process issues of data quality were identified regarding the organization of the data within the dataset, which did not permit ease of analysis. The applicant addressed FDA's concerns through submission of datasets in a revised structure in amendment 2. The applicant could not comment on the quality assurance monitoring program during data collection as conducted by the European cooperative group or as supplemented by monitoring or auditing by F. Hoffman-La Roche.

Because this is the second study in the treatment of adjuvant breast cancer and the HERA data were consistent with the results of the previous trial, as well as the fact that the trial was conducted by an experienced cooperative group and the clinical trial results were consistent across study sites, FDA did not request source data verification and auditing of study sites through FDA's Division of Scientific Integrity.

4.5 Compliance with Good Clinical Practices

Included in the BLS was a statement of compliance with the principles outlined in the "Guideline for Good Clinical Practice: ICH Tripartite Guideline (January 1997) based on the principles of the Declaration of Helsinki (1996) or with the laws and regulations of the country in which the research was conducted, which ever afforded a greater protection to the subject.

The study was supervised by an Independent Data Monitoring Committee (IDMC). The IDMC was to be composed of medical oncologists, a statistician, cardiologists, and a patient representative. The members of the IDMC would be independent of the trial. The purpose of the IDMC was to ensure the protection of subjects participating in the HERA trial. Both safety and ethical conduct of the study was monitored. The IDMC was responsible for the review of safety data, with primary focus on cardiac safety and efficacy at estimated six month intervals. The IDMC was to provided the Steering Committee (SC) of HERA with written recommendations to either modify/stop the trial, make the interim study results public, or to continue the trial unchanged. However, the final decision to amend the protocol or discontinue the trial would be taken by the Steering Committee. The responsibility of the Steering Committee in the protocol was not defined. There was also an Executive committee (EC) with the responsibility of management of day-to-day issues during the conduct of the trial.

On May 31, 2006, in a teleconference with Genentech, the FDA requested minutes to be included in the supplemental BLA submission, including the IDMC meeting noting that the interim results of the 2 year Herceptin arm should not be disclosed at this time. The sBLA submission did not contain the requested information.

4.6 Financial Disclosures

The major randomized, controlled trial is the only study submitted with this application with a design adequate for registration. Per the Applicant's report, financial disclosure information was available for 2853 of 2945 (97%) investigators and subinvestigators that participated and enrolled patients in the 1 year Herceptin and observation only arms of HERA. Of the 2853 respondents, there were 2 investigators (one principal investigator and one subinvestigator) who recorded a financial interest. Each of the qualifying disclosures is summarized in the following table.

Site No.	# of Patients Enrolled	Name	Disclosure
		(b) (6)	Speaking honorarium and consulting for Roche (together <$25,000)
			Indeterminate financial disclosure information available at the time of filing

Reviewers comment: There is minimal potential for bias of clinical study results as a result of these financial interests. The primary endpoint of HERA was disease free survival with a secondary endpoint of overall survival. It is not expected that the financial interest disclosed here and of those who did not file financial disclosure would affect the study results.

5. CLINICAL PHARMACOLOGY

For details, see Clinical Pharmacology reviews by Dr. Angela Men.

5.1 Pharmacokinetics

The application contained two studies with pharmacokinetic data intended, together with the results of study BO16348(HERA), to support a new every 3-week dosing regimen. In this submission, Genentech (b) (4) (b) (4) (b) (4) Meanwhile, Genentech provided additional information on the pharmacokinetic (PK) simulation (b) (4)

(b) (4) This model was based on PK parameters that better match HERA PK than the population PK parameter estimates.

The simulation results show that after a 7-day or 14-day dose delay, restart of 6 mg/kg of Herceptin undershoots trough concentrations and it takes 2-4 cycles of standard treatment to catch the trough concentrations. An 8 mg/kg reload matches trough concentrations by taking up to 2-cycle treatment. However, this reload of 8 mg/kg Herceptin results in approximately 30% higher in peak concentration compared to the observed peak concentration in HERA study, which raises a safety concern.

(b) (4) If Herceptin dosing is delayed by more than one week (> 28 days from the last actual dose), Herceptin will be still administered at doses of 6 mg/kg once every three weeks without loading dose of 8 mg/kg.

5.2 Pharmacodynamics

There were no studies provided in the application which justified the dose and schedule based on pharmacodynamic findings. The mechanism(s) of action of trastuzumab are not well-understood. In previous submissions, a rough correlation between pharmacodynamic effects, specifically the blockade of HER-2 receptor signaling and anti-tumor activity has been identified in preclinical but not in clinical models. No additional data were provided in the application that investigated the pharmacodynamic effects of trastuzumab at the new dose and schedule.

5.3 Exposure-Response Relationships

The application did not contain data which addressed exposure-response relationships. The primary efficacy study was conducted at a fixed dose and dose-ranging studies were not provided which could have provided insight into the relationship between dose and efficacy or safety outcomes.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication sought is: HERCEPTIN™ is indicated for the treatment (b) (4)

The approved indication is: HERCEPTIN™ is indicated as a single agent, for the adjuvant treatment of HER2-overexpressing breast cancer following multi-modality anthracycline based therapy for node positive and high-risk node negative disease.

Unique aspects of this application are every three week dosing of Herceptin, administration after completion of all adjuvant chemotherapy, and expansion of the indication to patients with high-risk, node-negative disease.

6.1.1 Methods

The clinical efficacy data are derived from a single, international, multi-center, open-label, three-arm, controlled and duration-ranging study, BO16348; these data support the analyses provided in this section of the clinical review. Data for efficacy are limited support this application consisted of two of the three arms of the study: one-year of Herceptin and no Herceptin.

Efficacy analyses that were prespecified in the protocol and provided in the application by the applicant included the primary endpoint of disease free survival (DFS); and the secondary efficacy endpoints of overall survival (OS), recurrence-free survival (RFS), and distant disease-free survival (DDFS). The submitted efficacy analyses, as provided by the applicant and summarized in section 6.1.4, were verified by this reviewer (using JMP 6.0) and the biostatistical reviewer, Dr, Yuan Li Shen (using SAS). Dr. Shen also provide a series of analyses for the primary efficacy endpoint (DFS) in relevant subgroups. These results are summarized in Dr. Shen's review. In addition, Dr. Shen performed analyses characterizing the patient population in support of the characterization of the efficacy database and in support of labeling negotiations to define the indicated population as well as to ensure that the arms were well-balanced for prognostic factors for which randomization was not stratified. Dr. Shen also confirmed the applicant's analyses of the primary safety endpoints: which was determination and comparison of the incidence of symptomatic cardiac dysfunction and death (primary cardiac endpoint events) and of the incidence of asymptomatic cardiac dysfunction (secondary cardiac endpoint events) in patients in the safety analysis population. These results will be discussed in detail in section 7 of this review.

6.1.2 General Discussion of Endpoints

The recommendation for approval of Herceptin (b) (4) is based on the demonstration of clinically important and statistically

significant prolongation of disease-free survival following one year of Herceptin therapy compared to observation only.

Primary Endpoint

The primary objective of this study was efficacy defined by a comparison of disease free survival (DFS) of subjects treated in two arms. According to the Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics published in May 2007, the most frequent use of DFS endpoint is in the adjuvant setting. DFS has been the primary basis for approval for hormonal therapy, for trastuzumab (103792.5150), and for cytotoxic therapy for the adjuvant treatment of breast cancer. In this setting, DFS is considered to provide direct evidence of clinical benefit.

DFS was calculated in the HERA study as the time between randomization and the date of first event. A DFS event was defined as any loco-regional or distant recurrence of breast cancer, the development of secondary primary cancer other than basal or squamous carcinoma of the skin and carcinoma *in situ* of the cervix, death from any cause without documentation of one these events. Lobular carcinoma in situ (LCIS) was not considered a DFS event. Diagnosis of a second cancer, per-protocol was to be confirmed histologically whenever possible.

Secondary Endpoints

- Overall Survival (OS), defined in the protocol as the time from date of randomization to date of death due to any cause.
- Recurrence Free Survival (RFS), defined as the time from date of randomization to the date of the first instance of local, regional or distant tumor recurrence.
- Distant Disease Free Survival (DDFS), defined as the time from date of randomization to the date of the first distant tumor recurrence, second primary cancer, or contralateral breast cancer, whichever occurred first.

The secondary endpoints of RFS and DDFS are composite endpoints with incorporate some but not all of the events which are also part of the composite endpoint of DFS. All three include distant disease recurrence as events, which is one of the most common events anticipated in this setting. The endpoints of RFS and DFS both include local-regional and distant disease recurrence which are the events which drive both analyses and are very similar measures of treatment effect. Therefore, RFS and DDFS are not independent measures of treatment effect which verify the primary endpoint. In contrast, overall survival measures a very different but related measure of treatment effect. This endpoint, when mature, will provide information regarding a different and very important measure of clinical benefit of Herceptin treatment. It will also provide information regarding potential risks which could outweigh other benefits and is considered both a safety and efficacy endpoint.

6.1.3 Study Design

Protocol Title

HERA (BO16348): A Randomized Multi-Center Comparison of 1 year of Herceptin Treatment versus Observation in Woman with HER2-positive Primary Breast Cancer Who

Have Completed Adjuvant Therapy.

Study Sites
The study was conducted in 462 centers in 39 non-US countries.

Study Period
Enrollment opened: November 30, 2001
First patient randomized: December 7, 2001
Last patient randomized: March 11, 2005
Date of data cut-off: March 29, 2005
IDMC recommended the disclosure of data from the 1 year arm: April 25, 2005
Data base closure: October 7, 2005
Date of survival data cut-off: March 29, 2005

Objectives
Primary
- To compare disease-free survival (DFS) in patients with HER2-overexpressing breast cancer who have completed acceptable adjuvant chemotherapy and radiotherapy, if applicable, and who have been randomized to Herceptin for *one year* versus no Herceptin.
- To compare disease-free survival (DFS) in patients with HER2-overexpressing breast cancer who have completed acceptable adjuvant chemotherapy and radiotherapy, if applicable, and who have been randomized to Herceptin for *two years* versus no Herceptin.

Secondary
- To compare overall survival (OS) in patients randomized to no Herceptin versus one year or two years of Herceptin
- To compare recurrence-free survival (RFS) in patients randomized to no Herceptin versus one year or two years of Herceptin
- To compare distant disease-free survival (DDFS) in patients randomized to no Herceptin versus one or two years of Herceptin
- To evaluate the safety and tolerability of Herceptin
- To compare the incidence of cardiac dysfunction in patients treated and not treated with Herceptin

Cardiac Objectives
- Estimate the incidence of symptomatic cardiac dysfunction and asymptomatic cardiac dysfunction in the adjuvant setting in patients who received adequate systemic adjuvant therapy followed or not by Herceptin treatment for one year
- Identify patients at risk for cardiotoxicity with chemotherapy and/or Herceptin

Pharmacokinetic Objectives
- To estimate the terminal elimination half-life of trastuzumab after three-weekly administration of Herceptin for one year's duration

- To evaluate the extent of accumulation of trastuzumab after three weekly administration of Herceptin after one year of treatment
- To compare the steady state pharmacokinetic parameters of trastuzumab administered as adjuvant treatment with data obtained previously in woman with metastatic breast cancer.

Study Design

This was a randomized, three arm, open-label study designed to enroll 5079 patients with early stage breast cancer whose tumors overexpress HER2, after completion of (neo) adjuvant chemotherapy. Randomization was 1:1:1, one or two year Herceptin versus observation only.

Prior to randomization patients were stratified for a number of factors; age, geographical region, nodal status, hormone receptor status and associated endocrine therapy, and previous adjuvant chemotherapy regimen.

Table 4. Stratification Factors Employed in the HERA Trial

- Nodal status [A]:
  1. Any nodal status, neo-adjuvant chemotherapy (nodal status unknown prior to chemotherapy)
  2. No positive nodes, no neoadjuvant chemotherapy
  3. 1-3 nodes positive, no neoadjuvant chemotherapy
  4. ≥4 nodes positive, no neoadjuvant chemotherapy
- Adjuvant chemotherapy regimen:
  1. no anthracyclines or taxanes
  2. anthracyclines but no taxanes
  3. anthracyclines + taxanes
- Receptor status and endocrine therapy[A,B,C]:
  1. negative
  2. positive and no endocrine therapy
  3. positive and endocrine therapy
- Age: [D]
  1. < 35 years
  2. 35 - 49 years
  3. 50 - 59 years
  4. ≥ 60 years
- Region [E]

[A] Patients with synchronous bilateral breast primaries: Stratification was based on the highest stage tumor and was considered hormone receptor status positive if at least one tumor had positive receptors as defined below.

[B] Hormone receptor status had to be known for each patient in the study. For this study, hormone receptor status ("negative" or "positive") followed the definition of the local lab for both estrogen and progesterone receptors, or estrogen receptors alone for centers that did not routinely measure progesterone receptors. Actual values obtained from assays were used to define cohorts for exploratory analyses

[C] Endocrine therapy included tamoxifen, anastrozole (Arimidex) and ovarian ablation. Chemotherapy induced amenorrhea was not considered endocrine therapy.

[D] Based on age at time of randomization

[E] Geographic region

Table 5. Definition of Risk Categories For Patients with Node Negative Breast Cancer

Risk Category	Endocrine Responsive[1]	Endocrine Non-Responsive[1]
"Minimal/Low Risk"[2]	ER and/or PgR positive, and all of the following features: pT* ≤ 2 cm, and Grade 1**, and Age*** ≥ 35 years	Not Applicable
"Average/High Risk"	ER and/or PgR positive, and at least one of the following features: pT* >2 cm, or Grade 2-3**, or Age*** <35 years	ER and PgR negative

(St. Gallen Consensus Conference 2001, [31])
[a] Definition at time of study start

[1] Responsiveness to endocrine therapies is related to expression of ER and PgR in the tumor cells. The exact threshold of ER and/or PgR staining (with currently available immunohistochemical methods), which should be used to distinguish between endocrine responsive and endocrine non-responsive tumor is unknown. Even a low number of cells stained positive (as low as 1% of tumor cells) identify a cohort of tumors having some responsiveness to endocrine therapies [32]. Probably, as typical for biological systems, a precise threshold does not exist. However empirically chosen, about 10% positive staining of cells for either receptor might be considered as a reasonable threshold, accepted by most. Furthermore, it is clear that the lack of staining for both receptors confers endocrine non-responsiveness status.

[2] Some Panel members recognize lymphatic and/or vascular invasion as a factor indicating greater risk than minimal or low. On the other hand, mucinous histological type is associated with low risk of relapse.

* pT = pathological tumor size (i.e., size of the invasive component).

** Histologic and/or nuclear grade.

*** Patients with breast cancer at young age have been shown to be at high risk of relapse [33].

Node-positive breast cancers are all considered at average/high risk of relapse. Offering adjuvant treatments is based upon endocrine responsiveness or non-responsiveness of the tumor and the patient's menopausal status and age.

Inclusion Criteria

- Female gender
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status ≥ 1
- Non-metastatic operable primary invasive adenocarcinoma of the breast that was: histologically confirmed, adequately excised[A,F], axillary node positive[B] or negative[C], and tumor size ≥T1c according to TNM [H]
- Known hormone receptor status (ER/PgR or ER alone)
- Must have received at least four cycles of an approved (neo-) adjuvant chemotherapy regimen
- Baseline LVEF ≥ 55% measured by echocardiography or MUGA scan after completion of all (neo-) adjuvant chemotherapy and radiotherapy.
- Completion of radiotherapy for any patients undergoing radiotherapy
- Overexpression of HER2 in the invasive component of the primary tumour[G], according

to one of the following definitions[D]:

- 3+ overexpression by IHC or 2+ overexpression by IHC and FISH test (PathVysion or INFORM® HER-2/neu test) demonstrating c-erbB2 gene amplification (ratio of c-erbB2 gene signals to centromere 17 signals ≥ 2 or > 4 copies Her2/neu gene observed, where there was no centromere control)
- c-erbB2 gene amplification by FISH (PathVysion or INFORM.HER-2/neu test: ratio of c-erbB2 gene signals to centromere 17 signals = 2 or > 4 copies Her2/neu gene observed, where there was no centromere control)
- Completion of all necessary baseline laboratory and radiologic investigations
- Signed written informed consent[E] (approved by the Independent Ethics Committee [IEC] and obtained prior to any study specific screening procedures).

(See Appendix B for footnote descriptions)

Exclusion Criteria

- History of any prior (ipsi- and/or contralateral) invasive breast carcinoma[A].
- Past or current history of malignant neoplasms, except for curatively treated: Basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix
- Any "clinical" T4 tumor, including inflammatory breast cancer.
- Maximum cumulative dose of doxorubicin > 360 mg/m2 or maximum cumulative dose of epirubicin > 720 mg/m2 or any prior anthracyclines unrelated to the present breast cancer.
- (Neo-) or adjuvant chemotherapy using peripheral stem cell or bone marrow stem cell support.
- Any prior mediastinal irradiation except internal mammary node irradiation for the present breast cancer[B].
- Patients with positive or suspicious internal mammary nodes identified by sentinel node technique which had not been irradiated[B] or patients with supraclavicular lymph node involvement[C].

- Prior use of anti-HER2 therapy for any reason or other prior biologic or immunotherapy for breast cancer.
- Concurrent anti-cancer treatment in another investigational trial, including hormone therapy, immunotherapy, and bisphosphonate therapy[D]
- Serious cardiac illness or medical conditions[E] including but not confined to:
    - History of documented congestive heart failure (CHF)
    - High-risk uncontrolled arrhythmias
    - Angina pectoris requiring antianginal medication
    - Clinically significant valvular heart disease
    - Evidence of transmural infarction on ECG
    - Poorly controlled hypertension[F] (e.g. systolic > 180 mm Hg or diastolic greater than 100 mm Hg).
- Other concurrent serious diseases that could interfere with planned treatment including severe pulmonary conditions/illness.
- Any of the following abnormal laboratory tests immediately prior to randomization:

- serum total bilirubin > 2.0 × upper limit of normal (ULN)
- alanine amino transferase (ALAT) or aspartate amino transferase (ASAT) > 2.5 × ULN
- alkaline phosphatase (ALP) > 2.5 × ULN
- serum creatinine > 2.0 × ULN
- total white blood cell count (WBC) < 2,500 / mm3
- absolute neutrophil count < 1,500 / mm3
- platelets < 100,000 / mm3.

- Pregnant or lactating women[G].
- Women of childbearing potential or less than one year after menopause (unless surgically sterile) who were unable or unwilling to use adequate contraceptive measures during study treatment[H].

(See Appendix C for footnote descriptions)

Randomization
Eligible patients were randomized in a ratio of 1:1:1 to either one or two years of post-chemotherapy/post-surgical Herceptin or to no Herceptin (referred to as the "observation" arm). Randomization was stratified for age, geographical region, nodal status, hormone receptor status and associated endocrine therapy, and previous adjuvant chemotherapy regimen. (Table 4). A minimization procedure according to Pocock and Simon was used for the allocation of subjects to the treatment arms in order to secure a balance between the treatments for stratification factors. Randomization was performed by an automated Interactive Voice Response System (IVRS).

The protocol specified that patients should be randomized to treatment assignment within seven weeks from day one of the last chemotherapy cycle or within six weeks from the end of radiotherapy, or definitive surgery, whichever was last. Herceptin treatment was to be initiated within two weeks of randomization assignment.

Blinding
Study BO16348 (HERA) was open-label. In the setting of adjuvant cancer treatment, confirmation of disease recurrence frequently requires biopsy or unequivocal confirmation of disease recurrence. This is because a diagnosis of disease recurrence alters all future patient prognostic considerations and results in initiation of toxic chemotherapies in patients who would otherwise not receive such interventions. This differs from diagnosis of disease progression in patients with metastatic disease where disease progression and subsequent therapy is inevitable. Given the higher level of certainty typically employed in making a determination of disease recurrence and frequent use of pathological confirmation, blinding is generally not required in registrational trials for adjuvant therapy indications.

Treatment Plan

Overview

HER2 screening	Randomization	Herceptin Therapy	(Safety)[A, B] follow-up[C] after completion of treatment period	Follow-up
Time	Time	Week	Week	Month
Any time before randomization but after signed screening consent form	Within 7 weeks from day 1 of the last chemotherapy cycle or 6 weeks from the end of radiotherapy, or definitive surgery, whichever was last and within 2 weeks of start of Herceptin therapy	1 to 52[A] 1 to 103[B]	56 107	14 to 120[A] 27 to 120[B] 1 to 120[C]

[A] Patients randomized to one year of Herceptin
[B] Patients randomized to two years of Heceptin
[C] Patients randomized to observation

Schedule of Assessments

	Prior to randomization (Baseline)	Treatment Period: Beginning of Week number (corresponding to/within 5 days prior to Herceptin infusion number)									Safety follow-up (week) ±8 days
Mandatory items		1 (1)[A]	13 (5)	25 (9)	37 (13)	52 (18)	64 (22)[D]	79 (27)[D]	91 (31)[D]	103 (35)[D]	56[B]; 107[B]
Informed Consent	×										
HER2 determination	×										
Demographics, Medical History	×										
Radiologic Exam:											
- Chest X-ray	×[1]					×				×	
- Bone scan [5]	(×)					(×)				(×)	
- bilateral Mammogram	×[2,4]					×[4]				×[4]	
- Liver imaging	(×)					(×)				(×)	
Pregnancy Test	×[3]										
Physical Exam.	×[3]		×	×	×	×	×	×	×	×	×
Card. Monitoring:											
- ECG	×[3]		×	×		×		×		×	
- LVEF 6	×[3]		×	×		×		×		×	
- Signs/symptoms	×[3]		×	×		×		×		×	
- Cardiac questionnaire	×[3]		×	×		×		×		×	
Hematology and Biochemistry	×[3]			×		×		×		×	×
Soluble ECD (only in subset of patients) [7]	×[3]			×		×		×		×	
Adverse Events [F]		→	→	→	→	→	→	→	→	→	→
SAE [G]		→	→	→	→	→	→	→	→	→	→
Herceptin IV (q3 weekly)		1 + 2 year Herceptin group [C,D] →						2 year Herceptin group [D] →			

Schedule of Assessments Continued

	Follow-up Every three months (± 28 days)[H]				Follow-up Every six months (± 28 days)[B]					
Mandatory items	**Month 15**	**Month 18**	**Month 21**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**
Radiologic Exam:										
- Chest X-ray				×		×		×		×
- Bone scan [5]				(×)		(×)		(×)		(×)
- Bilateral Mammogram				×[4]		×[4]		×[4]		×[4]
- Liver imaging				(×)		(×)		(×)		(×)
Physical Exam.	×	×	×	×	×	×	×	×	×	×
Card. Monitoring:										
- ECG		×		×	×	×				×
- LVEF		×		×	×	×				×
- Signs/symptoms		×		×	×	×				×
- Cardiac questionnaire		×		×	×	×				×
Haematology and Biochemistry		×		×	×	×	(×)	×	(×)	×
Soluble ECD (only in subset of patients) [7]		×		×		×		×		×
Adverse Events (only specific AEs as defined in the protocol)										
SAE (only specific SAEs as defined in protocol)										

[A] Day 1 of week 1 corresponds to the date of first Herceptin infusion. Patients randomized into the observation arm did not return until their "week 13" visit
[B] All patients randomized. Timing starts from date of Herceptin treatment, or date of randomization for observation patients. Safety follow-up visits were to be performed within 4 weeks from period.
[C] Patients randomized to the 1-year Herceptin arm.
[D] Patients randomized to the 2-year Herceptin arm.
[E] Cardiac questionnaire: to be filled out once at 10 years after randomization. The questionnaire is not required for years 6, 7, 8, or 9 post randomization
[F] All adverse events occurring up to 28 days after the last infusion of study medication were to be reported and are included in the adverse event and safety assessments.
[G] Any event related to study drug that met the definition of an SAE was reported as such at any time during the course of the study regardless of the time elapsed since last dose of study drug.
[H] Patients randomized to the 1-year Herceptin or observation group. Visits correspond to weeks 64, 79, 91 and 103 of the 2-year Herceptin group.
[1] Within six months prior to randomization.
[2] Within one year prior to randomization.
[3] Within seven days prior to randomization.
[4] Unilateral for patients with mastectomy.
[5] Plain films (CAT scan in the case of vertebral column abnormalities) were required to exclude metastatic disease if a bone scan was positive
[6] LVEF assessment results had to be available prior to administration of the next scheduled Herceptin dose. A decision to give or withhold that dose was to be based on the algorithm in Figure
[7] Investigated in the first 900 patients only.

Herceptin Dosing

Subjects randomized to Herceptin were required to begin study drug within 2 weeks of randomization. Herceptin was administered at an initial dose of 8 mg/kg intravenously over ninety minutes. Three weeks later Herceptin was administered at a dose of 6 mg/kg intravenously over ninety minutes; this dose was repeated every three weeks for a total of one year of treatment.

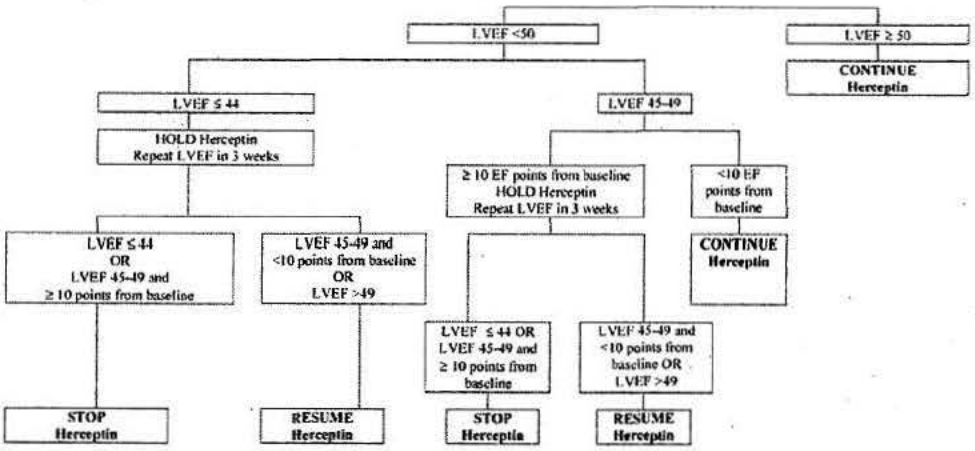
Dose Modifications and Delays

Hematologic and Non-Hematologic Toxicity
Actions for Herceptin Related Toxicity

Toxicity Related to Herceptin	Action
Non-hematological, grade 1 or 2 (NCI-CTC; excluding cardiac*)	Continue Herceptin therapy.
Non-hematological, grade 3 or 4 (NCI-CTC; excluding cardiac*), and toxicity resolved within a maximum of 5 weeks calculated from last planned administration	Hold Herceptin therapy until recovery to grade ≤ 2.
Non-hematological, grade 3 or 4 (NCI-CTC; excluding cardiac*), and toxicity not resolved to grade ≤ 2 or disappeared within a maximum of 5 weeks calculated from last planned administration	Action (discontinue or resume Herceptin therapy) in individual cases to be decided by HERA Executive Committee
Non-hematological, grade 3 or 4 (NCI-CTC; excluding cardiac*), upon re-challenge with Herceptin	Discontinue Herceptin therapy permanently
Cardiac (asymptomatic drop in LVEF or symptomatic congestive heart failure)	Herceptin therapy to be held, continued or resumed according to the algorithm depicted in Figure 2. Herceptin therapy to be discontinued permanently in case of symptomatic CHF
Cardiac (NCI-CTC; other cardiac toxicities not covered by treatment algorithm in Figure 2)	Actions must follow rules 1. to 4. for non-hematological toxicities
Hematological	Herceptin dose should not be held

* Severity corresponding to NYHA criteria

Algorithm for Continuation and Discontinuation of Herceptin Bases on Interval LVEF Assessments



Cardiac Function

All patients were required to undergo a baseline LVEF evaluation; only patients with an LVEF of greater than or equal to 55% were eligible for study registration and randomization. LVEF was to be monitored serially over the course study as specified in the schedule of assessments. If an investigator was concerned that an adverse event was related to cardiac dysfunction or if cardiac dysfunction was documented, additional LVEF measurements were to be performed.

Patients with a significant drop in LVEF were managed according to the monitoring and treatment algorithm outlined in the Figure 2. A significant LVEF drop was defined as an absolute decrease of at least 10 points below the baseline measurement and LVEF values f less than 50%.

Herceptin was to be discontinued in patients who developed NYHA class III/IV cardiac dysfunction. In such patients Herceptin was not resumed, even after resolution of symptoms or normalization of LVEF. However, patients remained on study and were to complete all protocol-specified assessments as originally planned.

Infusion Associated Symptoms

Patients who experienced severe cardiorespiratory components of an infusion reaction on the first dose (e.g. tachypnea, bronchospasm, hypotension, and hypoxia) were withdrawn from study medication.

Patients who experienced severe or moderate infusion symptoms were managed by:
- Slowing or stopping the Herceptin infusion
- Supportive care with, for example, oxygen, beta agonists, antihistamines, corticosteroids.

Patients who experienced mild or moderate infusion symptoms were treated with

antipyretics and antihistamines.

Patients who experienced mild, moderate or severe infusion reactions on the first dose could be retreated with Herceptin. Premedication with corticosteroids, antihistamines, and antipyretics could be used before subsequent Herceptin infusions.

Herceptin Dosing in the Event of Delayed Scheduled Doses

Delay of Herceptin Administration	Action
Dose delayed by up to and including 7 days (≤ 28 days from last actual dose)	It was recommended to give a dose of 6 mg/kg as soon as possible and continue the maintenance doses (6 mg/kg every 3 weeks) according to the original schedule.
Dose delayed more than 7 days (> 28 days from last actual dose)	It was recommended to re-start the treatment as if the patient were a new patient. The treatment was to be re-started as soon as possible with a loading dose of 8 mg/kg followed by the usual maintenance dose of 6 mg/kg every 3 weeks thereafter.

Concomitant Treatment

- Any hormonal therapy, including TAM and/or surgical and radiation-induced ovarian ablation and drug induced ovarian suppression (type, drug name, dose and schedule, anticipated duration of therapy).
- Any additional medication that was necessary for the management of the patient could be used at the discretion of the investigator.
- Acetaminophen (paracetamol) and antihistamines (e.g. diphenhydramine) could be used to relieve Herceptin infusion-associated symptoms.
- Administration of any adjuvant chemotherapy was not allowed during this study (all previous adjuvant chemo- and radiotherapy had to be completed before randomization).
- Patients may have started bisphosphonate therapy before entering the study. Bisphosphonate therapy could also be initiated during the HERA trial for treatment of documented osteoporosis. The use of bisphosphonates for prevention of bone metastases was not allowed before being licensed for this indication and approved by the HERA Steering Committee.
- Concomitant use of TAM (tamoxifen), anastrozole (Arimidex) or ovarian ablation was permitted.

Statistical Analysis Plan (Refer to statistical analysis and review by Yuan Li Shen, Ph.D., Mathematical Statistician for detailed review)

Efficacy Endpoints

The primary efficacy endpoint is disease free survival (DFS). DFS is calculated from the time between randomization and the date of first event. An event was defined as any loco-regional or distant recurrence of breast cancer, the development of secondary primary cancer other than basal or squamous carcinoma of the skin and carcinoma *in situ* of the cervix, death from any cause without documentation of one these events. Lobular carcinoma in situ (LCIS) was not considered an event. Diagnosis of a second cancer had to be confirmed histologically whenever possible.

The diagnosis of first breast cancer recurrence could be made only when both clinical and laboratory findings met the criteria for loco-regional or distant recurrence.

All subjects were followed according to the schedule of assessment irrespective of the arm to which they were randomized.

Secondary Endpoints

- Overall survival was the key secondary efficacy endpoint. The study objective was to compare overall survival (OS) in patients randomized to no Herceptin versus one year of Herceptin. OS was defined as the time to randomization to death due to any cause. For subjects alive at the time of analysis, the censoring date was the date of ;last radiological exam, last LVEF assessment, date of randomization, last contact, last survival follow-up, or last post-study treatment.
- To compare recurrence-free survival (RFS) in patients randomized to no Herceptin versus one year. This was defined as the time form randomization to the first local, regional and/or distant tumor recurrence. For subjects without an event the censoring date was the first date of the second primary cancer, contralateral breast cancer, death without evidence of disease recurrence, or the last date of last radiological exam, last LVEF assessment, date of randomization, last contact, or last survival follow-up.
- To compare distant disease-free survival (DDFS) in patients randomized to no Herceptin versus one year of Herceptin. DDFS was defined as the time between randomization and the date of the first distant tumor recurrence, second primary cancer, or contralateral breast cancer, whichever occurred first. Local and regional recurrences were ignored for calculating DDFS. Subjects who died without evidence of disease, the censoring time is the date of death. For subjects without events, the censoring time is the date of last radiological exam, last LVEF measurement, date of randomization, last contact, last survival follow-up.
- To evaluate the safety and tolerability of Herceptin
- To compare the incidence of cardiac dysfunction in patients treated and not treated with Herceptin.

The primary analysis of each of the efficacy endpoints was carried out on the intent-to-treat (ITT) population known as the full analysis set. The full analysis set consists of randomized patients as they were randomized irrespective of Herceptin treatment received and eligibility.

Amendments to Protocol

The original version of the protocol was dated May/June 2001 and initiated on November 30, 2001. Overview of the major changes made to the protocol are listed below:

Amendment A (Date: June 5, 2001)

1. Original protocol per applicant

Amendment B (Date: December 3, 2001)

1. Specifying Follow up Time

2. The requirement for a consistent chest X-ray for diagnosis of symptomatic heart failure was removed.
3. Monitoring Visit Schedule in Observation Arm
4. First Herceptin Dosing
   - The first Herceptin dose was recommended to be given two weeks after randomization rather than 4 weeks after randomization.
5. Schedule of Assessments and Procedures – Inclusion of Time Windows

Amendment C (Date: November 25, 2002)
1. Introduction of Cardiac Marker Sub-Protocol .
2. Positive Margins and Primary Tumor
3. Change in HER2 Testing Strategy - Central Reconfirmation of Local HER2 Status
4. Recommendation for Herceptin Dosing in Case of Delayed Scheduled Doses

Protocol Amendment D (Date: November 13, 2003):
1. Increase in Sample Size
   - Original estimates of event rates and disease-free survival were based on retrospective sub-group analysis of HER2 positive patients in the NSABP B15 adjuvant trial. In calculating a sample size for HERA, the major prognostic factors, lymph node status and prior adjuvant chemotherapy, as well as the expected proportion of patients in different prognostic sub-groups, were taken into consideration. However, it was clear at the time, that there were relatively few data on which to base the estimates and that there was considerable uncertainty around them. The 5-year disease-free survival for the control arm (observation, no Herceptin) was estimated to be 60%. It is now known that the distribution of patients entering the HERA trial regarding the stratification factors was not exactly as predicted. More patients with lymph node (LN) -negative disease were entered and fewer patients with 1-3 positive LNs. This necessitated reassessment of the sample size.
2. Weekly Taxanes in the Adjuvant Setting
3. Concomitant Hormonal Therapy with Anastrozole (Arimidex)
4. Cardiac Endpoints, Definitions and Reporting Requirements
5. Clarification of Target Population

Revision of Acceptable Chemotherapy Regimens for the HERA Trial

6.1.4 Efficacy Findings

There were 3386 women enrolled and randomized to the 1-yr Herceptin and observation arms between November 30, 2001 and March 29, 2005 at 462 sites in 39 non-U.S countries (Table 6). There were 1693 women randomized to each of the two treatment arms (one - year Herceptin and observation). The following series of tables characterizes the countries/geographic regions and regional distribution of the clinical study sites. The highest-accruing individual clinical study sites were located in the Russian Federation, Hungary, Germany, and Japan (Table 7).

Table 6. Countries with Investigation Sites for the HERA Trial

Argentina	Croatia	Italy	Russian Federation
Austria	Denmark	Japan	Singapore
Australia	France	Korea	Slovakia
Belgium	Germany	Mexico	South Africa
Brazil	Great Britain	Netherlands	Spain
Canada	Greece	New Zealand	Sweden
Chile	Guatemala	Norway	Switzerland
China	Hungary	Panama	Taiwan
Colombia	Ireland	Poland	Thailand
Costa Rica	Israel	Portugal	

Table 7. Geographic Region for Single Highest-Accruing Clinical Sites

Site	Country	Patients	% (of 3386)
31181	Russian Federation	76	2.2
31230	Hungary	54	1.6
31295	Germany	39	1.2
31654	Japan	37	1.1
31303	Germany	34	1.0
31247	Germany	31	0.9

The next series of tables provide descriptive statistics showing the distribution between the two treatment arms of baseline entry characteristics for the ITT population. The two treatment arms were well balanced for all important prognostic characterics. The ITT population consisted primarily of younger women (median age 49 years) with good performance status (90% ECOG PS 0), and three-quarters were from Europe, the Nordic countries or Canada. Across tumor characteristics there was a fairly equal distribution of across nodal risk groups with approximately 10% of women who received neo-adjuvant therapy and approximately one-third each with high-risk node negative disease, 1-3 positive nodes, and ≥4 positive lymph nodes and median pathologic tumor size was 22 mm. Approximately two-thirds received anthracycline, but non-taxane containing adjuvant chemotherapy and approximately 25% received anthracycline-taxane-based adjuvant chemotherapy (the current standard of care in the United States). Definitive surgical treatment consisted of modified radical mastectomy in approximately half the patients and lumpectomy in approximately one quarter and 96% underwent axillary node dissection;

three-quarters of the patients also received radiotherapy.

Table 8. ITT Population Characteristics by Stratification Variables

	Observation (n=1693)	Herceptin (n=1693)
Nodal Status		
neo-adjuvant chemotherapy	176 (10.4%)	190 (11.2%)
Node-negative, no neoadjuvant therapy	555 (32.8%)	543 (32.1%)
1-3 LN, no neo-adj chemotherapy	490 (28.9%)	483 (28.5%)
≥4 LN, no neo-adj chemotherapy	471 (27.8%)	477 (28.2%)
missing values	1 (0.1%)	0 (0.0%)
Adjuvant Chemotherapy Regimen[1]		
No Anthracyclines or Taxanes	99 (5.8%)	97 (5.7%)
Anthracyclines but no Taxanes	1154 (68.2%)	1150 (67.9%)
Anthracyclines + Taxanes	438 (25.9%)	443 (26.2%)
Receptor Status and Endocrine Therapy		
Negative	841 (49.7%)	838 (49.5%)
Positive and no Endocrine Therapy	34 (2.0%)	53 (3.1%)
Positive and Endocrine Therapy	818 (48.3%)	802 (47.4%)
Age group		
< 35 years	126 (7.4%)	126 (7.4%)
35 - 49 years	749 (44.2%)	751 (44.4%)
50 -59 years	546 (32.3%)	546 (32.3%)
≥ 60 years	272 (16.1%)	270 (15.9%)
Region		
Europe, Nordic Countries, Canada,	1222 (72.2%)	1208 (71.4%)
South Africa, Australia, New Zealand		
Asia Pacific and Japan	202 (11.9%)	202 (11.9%)
Eastern Europe	175 (10.3%)	189 (11.2%)
Central and South America	94 (5.6%)	94 (5.6%)
ECOG Performance Status		
0	1542 (91%)	1550 (92%)
1	149 (8.8%)	143 (8%)
Missing	2 (0.1%)	0 (0%)

Table 9. Additional Baseline Characteristics (ITT Population)

	Herceptin (n=1693)	**Observation (n=1693)**
Median age in yrs (range)	49.0 (21-80)	49.0 (23-77)
pts < 40 yrs	18%	18%
pts 40-64 yrs	75%	76%
pts ≥ 65 yrs (%)	7%	7%
Race		
Caucasian	84%	83%
Black	0.5%	0.3%
Oriental	12%	12%
Other	3%	4%
Menopausal Status		
Postmenopausal	45%	46%
Premenopausal	15%	14%
Uncertain	40%	41%
Radiotherapy		
YES	77%	76%
NO	23%	24%
Cardiac Disease		
YES	22%	23%
NO	78%	77%
Weight in kg	(n=1686)	(n-1675)
Mean	68	67
SD	13.1	13.0
Median (Min-Max)	66 (36-149)	65 (40-138)
Height in cm	(n=1688)	(n=1689)
Mean	162	162
SD	7	7
Median (Min-Max)	162(129-185)	162(136-96)

Table 10. Primary Tumor Pathology (ITT Population)

	Herceptin (n=1693)	Observation (n=1693)
Pathology		
Comedo	8%	7%
Ductal	95%	94%
Infiltrating	0.2%	0.1%
Lobular	6%	5%
Medullary	1%	1%
Mucinous	1%	1%
Tubular	0.8%	0.7%
Other	5%	6%
Tumor Grade		
G1	2%	2%
G2	32%	33%
G3	60%	60%
Gx	4%	5%
NA	0.1%	0.1%
ND	0.6%	0.3%
Receptor Status		
ER + / PR+-	31%	27%
ER + / PR -	12%	15%
ER - / PR +	5%	5%
ER - / PR -	48%	48%
ER + /PR UNK	2%	4%
ER UNK /PR +	0.06%	0%
ER-/PR UNK	2%	2%

NA=Not Available
ND= Not Done

Table 11. Definitive Surgical Approach (ITT Population)

	1-yr Herceptin (n=1693)	Observation (n=1693)
Lumpectomy	22%	25%
Radical Mastectomy	4%	5%
Modified Radical Mastectomy	48%	48%
Simple Mastectomy	4%	6%
Segment *	31%	30%
Resection of Axillary Lymph Nodes	95%	96%

*=Quadrantectomy-segmentectomy

Table 12. Tumor Size and Margins

	1 Yr Herceptin (n=1693)	Observation (n=1693)
Clinical Size		
Mean	44.4 mm	47.3 mm
Median	40 mm	40 mm
Range	0-200 mm	0-170 mm
Pathological Size		
Median	22 mm	22 mm
Range	0-260 mm	0-220 mm
Free Margins		
Left		
YES	49%	52%
NO	1%	1%
Right		
YES	49%	46%
NO	1%	1%

Table 13. HER2 Tumor Status by Central and Local Testing in ITT Population

	Observation (n=1693)	1 Yr Herceptin (n=1693)
Central Results		
IHC 3+ only	1160 (68.5%)	1098 (64.9%)
FISH (+) only	342 (20.2%)	382 (22.6%)
IHC 3+ and FISH (+)	38 (2.2%)	53 (3.1%)
IHC 2+ and FISH (+)	148 (8.7%)	151 (8.9%)
Local Results		
IHC 2+ only	136 (8.0%)	146 (8.6%)
IHC 3+ only	1340 (79.1%)	1312 (77.5%)
FISH (+) only	18 (1.1%)	21 (1.2%)
IHC 3+ and FISH (+)	123 (7.3%)	132 (7.8%)
Other	76 (4.5%)	82 (4.8%)

Table 14. Summary of Adjuvant Endocrine Therapy

	Herceptin 1-year (n=1693)	Observation (n=1693)
Patients with Adjuvant Endocrine Therapy	828 (48.9%)	844 (49.9%)
Tamoxifen alone	521 (30.8%)	516 (30.5%)
AI alone	71 (4.2%)	75 (4.4%)
LHRH alone	13 (0.8%)	18 (1.1%)
Ovarian Ablation alone	7 (0.4%)	11 (0.6%)
Tamoxifen -> AI	63 (3.7%)	83 (4.9%)
Tamoxifen + LHRH	103 (6.1%)	93 (5.5%)
Tamoxifen + Ovarian Ablation	17 (1.0%)	16 (0.9%)
Tamoxifen + LHRH -> AI	10 (0.6%)	15 (0.9%)
Tamoxifen + LHRH + Ovarian Ablation	3 (0.2%)	2 (0.1%)
Tamoxifen + Ovarian Ablation -> AI	4 (0.2%)	3 (0.2%)
Tamoxifen + Ovarian ablation + LHRH ->AI	0 (0.0%)	1 (0.1%)
LHRH -> AI	12 (0.7%)	9 (0.5%)
LHRH + Ovarian Ablation	0 (0.0%)	0 (0.0%)
LHRH + Ovarian Ablation -> AI	2 (0.1%)	1 (0.1%)
AI + Ovarian Ablation	2 (0.1%)	1 (0.1%)

AI: Aromatase Inhibitor; ->: followed by

Efficacy results

Primary endpoint

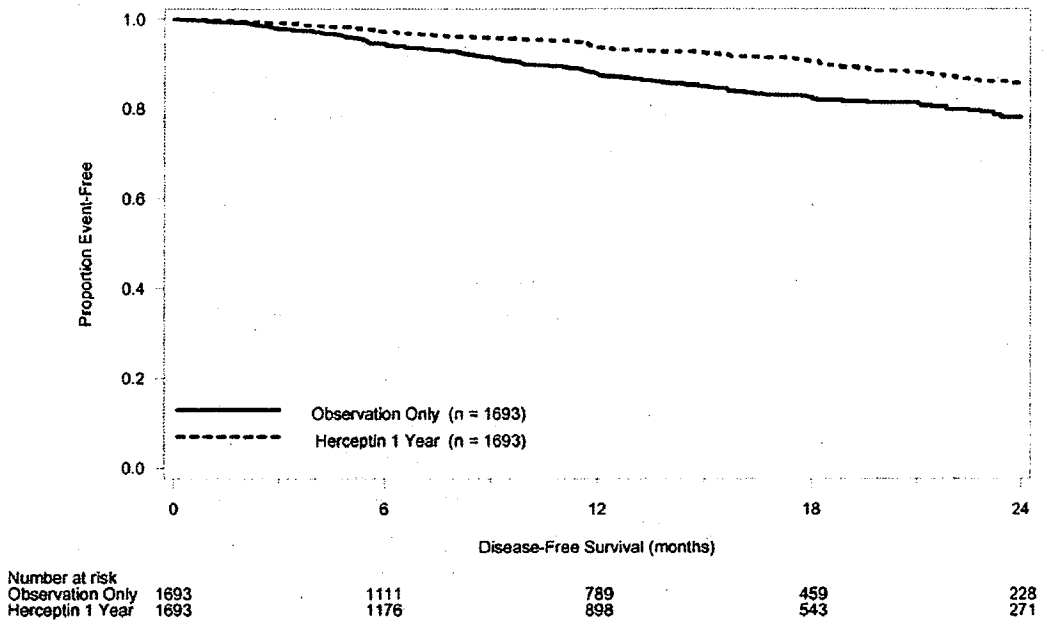
The following series of tables summarized the primary and key secondary efficacy analysis results. These FDA has confirmed the results, provided by the Applicant, and summarized in following tables and figures. The median duration of follow-up was similar in the 1-year Herceptin (12.65 months) and observation (12.42 months) arms, however the proportion of patients with DFS events was lower (7.5% vs. 12.9%) in the Herceptin arm compared to the observation arm, Table 15. Summary of Disease Free Survival At the time of the interim analysis, there was a 46% reduction in the risk of disease progression or death (DFS) among patients receiving Herceptin for up to one year. The Kaplan-Meier curves for DFS begin to separate at approximately 4-6 months and remain separated with up to two years of follow-up, beyond which there is insufficient data to provide reasonable estimates, Figure 1.

Table 15. Summary of Disease Free Survival

	Observation N=1693	1-yr Herceptin N=1693
Number of Patients with DFS events	219 (12.9%)	127 (7.5%)
Hazard ratio[a]	0.54	
95% CI	(0.44, 0.67)	
p-value (log-rank)	< 0.0001	

CI=confidence interval;[a] Efficacy relative to control arm; unstratified Cox regression model

Figure 1. Kaplan – Meier Disease Free Survival in Intent to Treat Population



The results demonstrated a beneficial treatment effect of the 1-year Herceptin arm on disease-free survival for non-metastatic breast cancer ($p<0.0001$ log-rank test; hazard ratio 0.54, [95% CI:0.44, 0.67]). . This beneficial treatment effect on DFS is consistent across various subgroups, including those defined by age, race (Caucasian vs. non-Caucasian), and nodal status. There was an absolute increase of 7.6% in two-year K-M estimated DFS rates for the 1-year Herceptin arm.

Since the 2-year Herceptin arm data was not submitted and based on the original statistical plan, the protocol pre-specified comparisons can not be completed. The original statistical plan was inclusive of the 2-year Herceptin arm data that was not submitted; as a result the protocol pre-specified comparisons can not be completed. The comparison of 2-year Herceptin arm to observation arm must be performed in order to determine whether there is any remaining alpha to test the secondary endpoints. As a consequence, in the current submission, any further evaluation of secondary efficacy endpoints will not be meaningful. Overall, the applicant's primary and secondary endpoints are based on composite measures which are not well documented, the interpretation of the results is not clear.

Secondary Endpoints
The protocol-specified secondary efficacy endpoints were as follows:

- Overall Survival (OS), defined in the study as the time from randomization to death due to any cause.
- Recurrence Free Survival (RFS), defined as the time from randomization to the first local, regional and/or distant tumor recurrence.
- Distant Disease Free Survival (DDFS), defined as the time between randomization and

the date of the first distant tumor recurrence, second primary cancer, or contralateral breast cancer, whichever occurred first.

At FDA's request, Genentech submitted the results of an unplanned interim analysis of overall survival between the 1-year Herceptin arm and observation; this was requested to evaluate safety and was not intended to support efficacy claims. With a total of 71 events, as expected, the analysis did not demonstrate a statistically significant difference in overall survival. FDA confirmed the results provided by the Applicant and summarized in Table 16 .

Table 16. Summary of Overall Survival

	Observation N=1693	1-Yr Herceptin N=1693
Number of patients with event	40 (2.4%)	31 (1.8%)
Number of patients without event[1]	1693 (97.6%)	1662 (98.2%)
Range of OS time (months)[3]	0.00, 36.21	0.00, 36.24
Log-rank statistic (vs. observation)	1.393	
p-value vs observation (log-rank test)	0.2379	
Hazard Ratio vs observation	0.75	
95% CI for hazard ratio	(0.47, 1.21)	

1 Censored
2 Kaplan-Meier estimates
3 Including censored observations

Recurrence-Free Survival (RFS) was a pre-specified secondary efficacy endpoint stated in the protocol which is calculated from date of randomization to the date of the first local, regional, or distant tumor recurrence or death. Since the majority of DFS events also include and are primarily driven by local and distant tumor recurrence, the RFS results are similar to the comparison of DFS. Unlike DFS, the analysis of RFS does not include second primary tumors as an event and thus is a better measure of adjuvant treatment effects on the index cancer. The results of RFS comparison show nominally statistically significant advantage in favor of Herceptin arm ($p<0.0001$; HR=0.51, [95% CI: 0.40, 0.64]) Table 17.

Table 17. Applicants Summary of Recurrence-Free Survival

	Observation (n-1693)	Herceptin (n-1693)
Number of subjects with event	208 (12.3%)	113 (6.7%)
P-Value vs, observation ((log-rank test)	<0.0001	
Hazard Ratio vs observation	0.51	
95% CI for hazard ratio	(0.40, 0.64)	

Distant Disease-Free Survival (DDFS) was an additional, secondary efficacy endpoint pre-specified in the protocol. (DDFS) was calculated from the date of randomization to the first distant tumor recurrence, second primary cancer, or contralateral breast cancer, or death, whichever occurred first. Local and regional recurrences are not considered events in the calculation of DDFS. Similarly to RFS, since the majority of DFS events were distant tumor recurrence, the comparison of the DDFS results was similar to the comparison of DFS between study arms. The results of the DDFS comparison also show nominally statistically significant advantage in favor of 1-year Herceptin arm ($p<0.001$ stratified log-rank test; HR=0.50, [95% CI: 0.39, 0.64]) Table 18.

Table 18. Applicants Summary of Distant Disease-Free Survival

	Observation (n=1693)	1 Yr Herceptin (n=1693)
Number of patients with event	184 (10.9%)	99 (5.8%)
P-Value vs observation (log-rank test)	<.0001	
Hazard Ratio vs observation	0.50	
95% CI for hazard ratio	(0.39, 0.64)	

6.1.5 Clinical Microbiology

No clinical microbiology data were provided in the application. Clinical microbiology was not required or relevant for this product and proposed indication.

6.1.6 Efficacy Conclusions

The results of study BO16348 (HERA) demonstrated beneficial treatment effect of the 1-year Herceptin arm on disease free survival (DFS) for adjuvant breast cancer. This beneficial treatment effect on DFS appears to be consistent across various subgroups, such as age, race, and nodal status.

Since the 2-year Herceptin arm data was not submitted and based on the original statistical plan, the protocol pre-specified comparisons can not be completed. The original statistical plan was inclusive of the 2-year Herceptin arm data that was not submitted; as a result the protocol pre-specified comparisons can not be completed. The comparison of 2-year Herceptin arm to observation arm must be performed in order to determine whether there is any remaining alpha to test the secondary endpoints. As a consequence, in the current

submission, any further evaluation of secondary efficacy endpoints will not be meaningful. Overall, the applicant's primary and secondary endpoints are based on composite measures which are not well documented, the interpretation of the results is not clear.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In this application, data from 3386 subjects who received either Herceptin (n=1678) or were observation (n=1708) after completion of multimodality anthracycline-based therapy, were reviewed and analyzed to assess safety. The safety database was analyzed at all levels of the MedDRA hierarchy in order to identify new safety signals using a series of standardized medical queries (SMQs) designed for use with MedDRA coded databases. The relevant data sources in the application are the clinical study report, pertinent case report forms (CRF's), case narratives, post-marketing reports from the adverse events reporting system (AERS), and data listings were reviewed in order to assess specific safety issues. Table 19, displays the raw and derived datasets reviewed for study BO16348 (HERA).

Table 19. Raw and Derived Datasets Reviewed for study BO16348 (HERA)

Safety Review	Efficacy Review
AE (adverse event)	EFEX (Efficacy and special safety assessments)
CAB (Cardiac Advisory Board Review)	EFEXLVEF (LVEF)
CHEMOTX (Prior chemotherapy)	EFEXRE (radiological exam)
DEMO (demographic data)	EFFEXSURV (disease recurrence and survival)
DIAG (previous and current diseases)	* CARDIAC (cardiac\LVEF data)
DIED (Death information)	* CARDIC 2 (secondary cardiac LVEF, CAB)
EFEXCE (Cardiac Event)	*PAT (efficacy analysis data)
EFEXCQ (cardiac questionnaire)	
EXCL (Exclusions)	
EXIT (study completion/discontinuation	
HORMTX (hormone therapy)	
LABP (Laboratory results)	
MEDO (previous and concomitant treatment)	
MEDT (Study drug administration)	

* Derived data

Subjects were evaluated for safety the same whether they received study drug Herceptin or not. The schedule of assessments included physical examination and cardiac monitoring (ECG, LVEF, signs/symptoms, and cardiac questionnaire) every 12 weeks up to month 24, then every six months from month 30-60. In addition yearly radiological exams (chest x-ray, bone scan, bilateral mammogram, and liver imaging) starting with week 52 through month 60. From years five through ten yearly follow-up consisted of bilateral mammogram, physical exam, cardiac questionnaire, chemistry and hematology labs. Adverse event collection was ongoing throughout the study. All adverse events reported during the clinical study from randomization for non-Herceptin and from the date of first

Herceptin treatment were included in the analyses of adverse events The trial was not blinded, but was controlled and adverse events were all attributed to drug in the 1-year Herceptin arm if the adverse event occurred at a higher incidence (≥ 2%) in comparison to the control arm.
Adverse events per-event incidence were reproducible from the reviewer using the raw datasets and was comparable to the applicant's table (see Table 20).

Table 20. Summary of per-Event Incidence of Adverse Events

Reviewer	**Observation Events=2246**	**Herceptin Events=5271**
AE Grade		
1	1405 (62.5%)	3526 (66.9%)
2	726 (32.3%)	1547 (29.3%)
3	103 (4.59%)	184 (3.49%)
4	12 (0.53%)	14 (0.27%)

Per-Patient Incidence of Serious Adverse Events

	Observation n=1708	**Herceptin n=1678**
Any SAE	93 (5.4%)	135 (8.0%)
AEs Resulting in Death	2 (0.1%)	4 (0.2%)
AE Resulting in Discontinuation of Herceptin	N/A	103 (6.1%)
Premature Withdrawal due to AE	N/A	97 (5.8%)

The most common adverse events reported with ≥ 5% of any grade with higher incidence ≥ 2% in the 1-year Herceptin arm were: headache, arthralgia, nasopharyngitis, fatigue diarrhea, nausea, pyrexia, back pain, and chills.

The most serious adverse events reported in the 1-year Herceptin arm was: congestive heart failure, cardiac failure, cerebral vascular accident, and sudden death.

7.1.1 Deaths

Table 21. Overall Causes of Death

	Observation	Herceptin
	40/1693 (2%)	31/1693 (2%)
Progressive Disease	38 (2%)	26 (2%)
Adverse Event	2 (0.1%)	4 (0.2%)
Missing	0	1

Case report forms, narratives, and subject profiles were reviewed for the six subjects whose deaths were reported as an adverse event, Table 22 . The AE.xpt dataset was the primary source of analysis for serious adverse events (SAE's) in addition the DIED.xpt dataset was

analyzed for further death information. Serious adverse events occurring at anytime during the conduct of the study were identified. Multiple occurrences of the same SAE were eliminated by reducing each adverse event to one row per subject at maximum grade of toxicity reported

There were seventy-one deaths were reported total between the one year Herceptin arm versus observation. The one year Herceptin arm reported 31 deaths with 4 reported as adverse events (cerebral vascular accident, acute appendicitis, sudden death, and cerebral hemorrhage), all reported as not related to the study drug. The Herceptin 1-year arm reported 26 deaths due to progression of disease with one missing data point reported for death. The one year observation arm reported 40 deaths with two related to adverse events (heart failure and suicide) and 38 reported progression of disease.

Table 22. Deaths During Active Treatment Phase of Study Reported as Adverse Event

Pt #	Age	Treatment Received	Death Date	Death Study Day	Site ID	Adverse Event
(b) (6)	65	HERCEPTIN 1 YR	(b) (6)	289	(b) (6)	Cerebral Vascular Accident
	41	HERCEPTIN 1 YR		366		Acute Appendicitis
	39	HERCEPTIN 1 YR		290		Sudden Death
	58	HERCEPTIN 1 YR		115		Cerebral Hemorrhage
	75	OBSERVATION		205		Cardiac Death/Heart Failure
	29	OBSERVATION		146		Suicide

Death study day was defined by the applicant as follows:

- 1-year Herceptin Arm, based on the date of first Herceptin administration to date of death.
- Observation Arm, based on date of randomization to date of death.

Applicant and Reviewer's Attribution for Cause of Death Related to Study Drug

Pt #	Cause of Death	Herceptin 1-Year		Observation	
		Applicant	Reviewer	Applicant	Reviewer
(b) (6)	Cerebral Vascular Accident	N	Y	-	-
	Acute Appendicitis	N	N	-	-
	Sudden Death	N	Y	-	-
	Cerebral Hemorrhage	N	N	-	-
	Cardiac Death/Heart Failure	-	-	N	N
	Suicide	-	-	N	N

N= Not attributable

Y= High Index of suspicion to be attributable

Subject (b) (6).
Event: Cerebral Vascular Accident
Sixty-five year old, postmenopausal, Hispanic female was diagnosed with ductal carcinoma

of the right breast s/p right simple mastectomy on (b) (6), and pathological diagnosis was made (b) (6). The tumor was ER and PR negative. The subject completed 4 cycles of cyclophosphamide, methotrexate, and fluorouracil from (b) (6), through (b) (6).

The subject was a non-smoker with a past medical history positive for type II diabetes mellitus since 1994, treated with isophane insuline (200 units/day subcutaneous) and hypertension since 1997 treated with atenelol (100 mg/day) and chlorthalidone (50 mg/day). Family history was negative for coronary artery disease.
Baseline ECG performed on (b) (6) reported QT prolongation "Light" and repolarization abnormality "Light". The subject was randomized to Herceptin on (b) (6). For the first seven doses the subject received premedication of dexamethasone and dipenhydramine for prevention of infusional side effects from Herceptin. Completed 12 cycles of Herceptin on (b) (6). On (b) (6), the subject experienced a neurological event on rising consisting of rapid onset of right hemiplegia, irregular respiration, dilated fixed pupil, spasticity, stupor and coma. The subject died an hour later. The investigator and family physician considered the picture compatible with the diagnosis of cerebral vascular accident of a hemorrhagic type, with intracranial hypertension and cerebral edema. No autopsy or brain imaging were performed . According to the investigator the event was not related to Herceptin.

Subject (b) (6)
Event: Sudden Death
Thirty-nine year old, oriental female, diagnosed with lymph node negative, ER positive/PR negative and HER2 positive (IHC 3+) ductal carcinoma of the left breast on (b) (6). Underwent lumpectomy on (b) (6), followed by modified radical mastectomy and resection of Axillary lymph nodes on (b) (6). Subsequently receives six cycles of adjuvant chemotherapy with cyclophosphamide, fluorouracil and Methotrexate from (b) (6). The subject was categorized as premenopausal and started Tamoxifen 20 mg/day on (b) (6). Randomized to receive 1 –year Herceptin on (b) (6).

The subject was a non-smoker with no family history of heart disease. The subject did not report any previous or current disease. The only concomitant medication was Tamoxifen and a reported allergy to penicillin. Baseline visit (b) (6), reported that the ECG and echocardiogram revealed no signs or symptoms of cardiac disease. Blood pressure 110/80 mm Hg, LVEF 68%, and ECOG performance status 0.

The first dose of Herceptin was given (b) (6). Echocardiogram on scheduled assessment week 13 ((b) (6)) and week 25 ((b) (6)) reported normal findings with LVEF values of 64% and 60%. Blood pressure week13, 120/80 and week 25, 110/70. The ECG of week 13 and 25 showed myocardial repolarization disorder in lead V_1-V_4 (T-wave and ST segment was abnormal, but not clinically significant to the investigator). Laboratory tests performed at week 25 were reported all in normal range. On (b) (6) s/p 13 cycles of Herceptin the patient fell suddenly from her chair and went into a coma. She presented polypnea and cyanosis of the lips, no neurological

symptoms. She was brought to a local hospital/emergency facility where she received an injection of adrenalin. Subsequently she was transferred to another hospital. According to the medical record the patient was dead on arrival. ECG showed cardiac arrest. The diagnosis of death was "sudden death:, the cause of death is unknown, an autopsy was refused. The investigator considered sudden death of the subject not to be related to Herceptin. Upon request for further information the investigator declared the following; the subject had no cardiovascular diseases, thromboembolic disease or other, The blood pressure 140-150/80 mm Hg sometime, no sign of brain metastases during the course of the study, and a follow-up ECG after week 25 visit on (b) (6) no longer showed any abnormalities.

Table 23, are additional deaths related to study drug that the applicant submitted within the 120 day safety update.

Table 23. 120 Day Safety Update: Attribution for Cause of Death Related to Study Drug

Pt#	Age	Cause of Death	Herceptin 1-Year		Observation	
			Applicant	Reviewer	Applicant	Reviewer
(b) (6)	60	Cardiac Failure	Y	Y	-	-
	71	Anaplastic Menigioma	N	N	-	-
	57	Metastatic Renal Cell Carcinoma	N	N	-	-
	69	Pulmonary Sepsis	-	-	N	N
	55	Pulmonary Embolism	-	-	N	N
	58	Myocardial Infarction			N	N

N= Not attributable

Y= High Index of suspicion to be attributable

Reviewer Note: The reviewer attributes death of subjects (b) (6) and (b) (6) as related to study drug. In subject (b) (6) the symptoms of stroke are correlative with known incidence of thrombotic events with Herceptin. In three randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in subjects receiving Herceptin and chemotherapy compared to chemotherapy alone. This is in the current labeling of Herceptin.

7.1.2 Other Serious Adverse Events

Accuracy of coding from verbatim term to MedDRA 7.1 Preferred Term (PT) was verified by a review of AE line listings. Events were then grouped and analyzed at individual levels of the MedDRA hierarchy, by treatment group and other relevant subgroups. Data listings, CRF's and narratives were also reviewed for cases of particular interest. Finally, these data were compared to the legacy study data.

In HERA a serious adverse event was defined as any experience that suggests a significant

hazard, contraindication, side effect or precaution. It is any adverse event that at any dose fulfills at least on of the following criteria: fatal (results in death); life threatening; required inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; congenital anomaly/birth defect; medically significant or requires intervention to prevent one or other of the outcomes previously listed. In addition subjects entered into the primary cardiac endpoint and also pregnancy was instructed to the investigators to be recorded as an SAE. The definition of SAE used in the HERA study is consistent with 21 CFR 312 (a). Serious adverse events were presented and graded according to NCI CTC version 2.0., except for symptomatic cardiac failure (NYHA class II/III/IV), in which case the New York Heart Association (NYHA) Classification system be used.

Table 24, represents the incidence of reported SAEs grouped by treatment arm and MedDRA System Organ Class (SOC). The clinical reviewer's analysis revealed a total of 228 subjects who experienced an SAE, 5.4% (93/1708) subjects in the Observation arm and 8.0% (135/1678) subjects in the Herceptin arm.

Table 24. Reviewers' Table of SAE Incidence by Treatment Arm

MedDRA SOC	Observation (n=1708)	Herceptin 1-year (n=1678)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	1
CARDIAC DISORDERS	4	23
EAR AND LABYRINTH DISORDERS	0	1
ENDOCRINE DISORDERS	1	1
EYE DISORDERS	2	0
GASTROINTESTINAL DISORDERS	8	8
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2	16
HEPATOBILIARY DISORDERS	2	2
IMMUNE SYSTEM DISORDERS	1	0
INFECTIONS AND INFESTATIONS	17	40
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	7	9
METABOLISM AND NUTRITION DISORDERS	1	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5	3
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	13	10
NERVOUS SYSTEM DISORDERS	6	8
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	5	2
PSYCHIATRIC DISORDERS	1	1
RENAL AND URINARY DISORDERS	1	2
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	13	19
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9	5
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	4
SURGICAL AND MEDICAL PROCEDURES	7	1
VASCULAR DISORDERS	5	10

The most common serious adverse event reported related to drug was cardiac failure, congestive, cardiac failure, and cardiomyopathy in the 1-year Herceptin arm (Table 25).

Table 25. Reviewer's Cardiac Disorders Incidence of SAE by Treatment Arm

Preferred Term	Observation (n=1708)	Herceptin (n=1678)
ANGINA PECTORIS	1	2 (0.1%)
ATRIAL FIBRILLATION	1	1
CARDIAC FAILURE	1 (.06%)	4 (0.2%)
CARDIAC FAILURE CONGESTIVE	0 (0%)	7 (0.4%)
CARDIOMYOPATHY	0 (0%)	2 (0.1%)
CORONARY ARTERY STENOSIS	0	1
EXTRASYSTOLES	0	1
PERICARDITIS LUPUS	0	1
SUPRAVENTRICULAR TACHYCARDIA	0	1
TACHYARRHYTHMIA	0	2 (0.1%)
TACHYCARDIA	0	1

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Premature withdrawal was defined as withdrawal of the patient from the study prior to completion of the protocol defined treatment/observation period for any of the following reasons: adverse event, death, insufficient therapeutic response, loss to follow-up, violation of eligibility criteria or other protocol violations.

A total of 485 patients (14%) were reported withdrawn prematurely during the observed period of the study: 267/1708 (16%) observation subjects and 218/1678 (13%) from the Herceptin treated subjects. Three patients were "withdrawn" from the observation group due to death and 1 patient was "withdrawn" from this group due to an adverse event. Among Herceptin treated subjects arm, 3 were "withdrawn" from the study due to death and 97 patients were withdrawn as a result of an adverse event.

The most common pre-defined non-safety reason for premature withdrawal from the study indicated on the CRF was 'insufficient therapeutic response' (recurrence of disease, second non-breast malignancy or contralateral breast cancer). One hundred and forty eight patients withdrew from the observation and 69 patients withdrew from the Herceptin arm for this reason.

One hundred observation arm patients and 40 Herceptin patients were withdrawn from the study for refusal of treatment including 'did not co-operate' and 'withdrew consent'. Eleven patients (6 in the observation arm, 5 receiving Herceptin) were withdrawn due to a violation of selection criteria at entry and 1 observation arm patient was withdrawn due to a protocol violation. Seven patients (6 in the observation arm, 1 in the Herceptin arm) failed to return and 5 patients (2 observation, 3 Herceptin) withdrew for administrative or other reasons. At the time of database closure, study completion information was not available for all patients and was still being collected.

Summary of Premature Withdrawals by Reason

Reason for Withdrawal	Observation Only N = 1708 No. (%)	Herceptin 1 Year N = 1678 No. (%)
Safety	4 (<1)	100 (6)
Adverse Event(a)	1	97
Death	3	3
Non-Safety	263 (15)	118 (7)
Insufficient Therapeutic Response	148	69
Violation of Selection Criteria at Entry	6	5
Other Protocol Violation	1	0
Refused Treatment(b)	100	40
Failure to Return	6	1
Other	2	3
Total	267 (16)	218 (13)

7.1.3.2 Adverse events associated with dropouts

The applicant provided in this submission a table titled "Summary of Patients Discontinuing Study Treatment as a Result of an Adverse Event (safety Population)" referenced as table 36 in the clinical study report. In cross referencing the adverse event dataset against the narrative summaries, the adverse events were separated into two sets: "Narratives for Patients who Discontinued Herceptin because of an Adverse Event"; and "Narratives for Premature Withdrawal Due to Adverse Events". Further subjects who were followed in the primary and secondary cardiac endpoints had a separate list of narrative summaries. Within these summaries were subjects followed in cardiac endpoints who discontinued Herceptin due to adverse event.

Table 26, was compiled by the Reviewer from the following data sources : Adverse Event dataset; Narratives for Patients who Discontinued Herceptin because of an Adverse Event; Narratives for Premature Withdrawal Due to Adverse Events; and Narratives of subjects in the cardiac endpoints who discontinued drug due to adverse event. The table includes the subject number to ensure no double counting of events.

Clinical Reviewer Summary of Drop Outs and Discontinuations in Patients receiving Herceptin

Event	# of Patients (n=1678)	Incidence
Discontinuation for any cause	**93/1678**	**5.5%**
Discontinued On-study*	30/1678	1.8%
Withdrawal Due to Non-Cardiac Adverse Event	26/1678	1.5%

*Patients who discontinue observation or Herceptin treatment within less than one year from randomization (observation patients) or first Herceptin infusion for any reason (except withdrawal of study consent and disease recurrence) should complete the first safety follow-up visit (week 56) within 4 weeks from discontinuation (observation

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patients) or the last Herceptin administration.

Table 26. Herceptin Premature Withdrawal/Discontiuations

Herceptin Discontinued Onstudy*
Herceptin Premature Withdrawal Due to Adverse Events
Primary Cardiac Endpoints Discontinued Herceptin
Secondary Cardiac Endpoints Discontinued Herceptin

Pt # (b) (6)	Adverse Event	AE Intensity	Cardiac Endpoint	Outcome
	CHEST DISCOMFORT	1	Secondary CE	Resolved
	EJECTION FRACTION DECREASED	1	Secondary CE	Unresolved
	EJECTION FRACTION DECREASED (Narrative dx CHF NYHA class I)	1	Secondary CE	Resolved with sequelae
	CARDIAC FAILURE CONGESTIVE	2	Secondary CE	Unresolved
	EJECTION FRACTION DECREASED	1	Secondary CE	Unresolved
	EJECTION FRACTION DECREASED	1	Secondary CE	Unresolved
	MULTIPLE GATED ACQUISITION SCAN ABNORMAL	1	Secondary CE	Unresolved
	EJECTION FRACTION DECREASED (Narrative states CHF NYHA Class I)	2	Secondary CE	Resolved
	CARDIAC FAILURE CONGESTIVE	3	Secondary CE	Unresolved
	ARTHRALGIA	3		
	EJECTION FRACTION DECREASED	1		Resolved
	CARDIAC FAILURE CONGESTIVE (Positive re-challenge)	3	Secondary CE	Unresolved
	DYSPNEA	1		Resolved
	CARDIAC FAILURE (Narrative reports CHF NYHA class II)	1	Secondary CE	Resolved
	INFLUENZA	3		Resolved
	FATIGUE	3		Unresolved
	MYALGIA	2		Resolved
	TRANSIENT ISCHAEMIC ATTACK	2		Resolved
	CARDIAC FAILURE CONGESTIVE	1	Secondary CE	Resolved
	CARDIAC FAILURE CONGESTIVE	2	Secondary CE	Resolved
	CARDIAC FAILURE CONGESTIVE	4	Primary CE	Resolved
	CARDIAC FAILURE CONGESTIVE	1	Secondary CE	Resolved
	CARDIAC FAILURE CONGESTIVE	3	Secondary CE	Unresolved - Completed 1 year Herceptin - Protocol violation
	ELECTROCARDIOGRAM T WAVE INVERSION	2		Unresolved
	ABDOMINAL DISCOMFORT	2		Resolved
	CHILLS	2		Resolved
	NAUSEA	2		Resolved
	TREMOR	1		Resolved
	VERTIGO	2		Resolved
	EXANTHEM /Rash Pruritic	2		Unresolved
	CARDIAC FAILURE (Narrative dx CHF NYHA class II)	2	Secondary CE	Resolved
	CARDIAC FAILURE	3	Primary CE	Resolved
	MASTITIS	3		Resolved

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Pt #	Adverse Event	AE Intensity	Cardiac Endpoint	Outcome
(b) (6)	CARDIAC FAILURE (Decompensatio cordis) Narrative states CHF (NYHA II/III)	3	Primary CE	Resolved with sequale
	EJECTION FRACTION DECREASED (Narrative CHF NYHA class I)	2	Secondary CE	Unknown
	EJECTION FRACTION DECREASED	1		Unresolved
	EJECTION FRACTION DECREASED (Narrative dx CHF NYHA Class II)	2	Secondary CE	Resolved
	JOINT SPRAIN	2		
	VENTRICULAR HYPOKINESIA	1		
	EJECTION FRACTION DECREASED	2	Secondary CE	Resolved
	CARDIAC DISORDER	1	Secondary CE	Unresolved
	CARDIAC FAILURE CONGESTIVE	2	Secondary	Unresolved
	CARDIAC DISORDER	2		
	ELECTROCARDIOGRAM T WAVE INVERSION	1		
	ECHOCARDIOGRAM ABNORMAL	1	Secondary CE	Unresolved
	ASTHENIA	3		
	EJECTION FRACTION DECREASED (Narrative reports CHF NYHA Class II)	2	Secondary CE	Resolved
	CARDIAC FAILURE CONGESTIVE	1	Secondary CE	Resolved
	EJECTION FRACTION DECREASED	2	Secondary CE	Resolved
	EJECTION FRACTION DECREASED	2		
	VENTRICULAR DYSFUNCTION	1		
	EJECTION FRACTION DECREASED	1	Secondary CE	Unresolved
	CARDIOTOXICITY	1	Secondary CE	Unresolved
	EJECTION FRACTION DECREASED	2	Secondary CE	Resolved
	CARDIAC FAILURE CONGESTIVE	2	Secondary CE	Resolved
	ARTHRALGIA	3		
	EJECTION FRACTION DECREASED	1		
	CARDIAC FAILURE CONGESTIVE	1	Secondary CE	Resolved with sequale
	EJECTION FRACTION DECREASED	2	Secondary CE	Resolved
	VENTRICULAR HYPOKINESIA	1		
	CARDIAC FAILURE CONGESTIVE	2	Secondary CE	Unresolved
	DYSPNEA	2		
	RASH	2		
	EJECTION FRACTION DECREASED		Secondary CE	Unresolved
	CARDIAC DISORDER	1		
	ECHOCARDIOGRAM ABNORMAL	2		
	PALPITATIONS	2		
	CARDIAC FAILURE Narrative CHF NYHA IV vs I	4	Primary CE	Unresolved
	CARDIAC FAILURE CONGESTIVE		Secondary CE	Unknown
	CARDIAC FAILURE CONGESTIVE	3	Primary CE	Unresolved
	EJECTION FRACTION DECREASED	1	Secondary CE	Resolved
	ANGINA PECTORIS	3	Secondary CE	Resolved
	CARDIAC FAILURE CONGESTIVE	2	Secondary CE	Unresolved
	CARDIAC FAILURE CONGESTIVE	2	Secondary CE	Resolved
	EJECTION FRACTION DECREASED		Secondary CE	Resolved
	CARDIAC FAILURE CONGESTIVE	3	Check CRF	
	EJECTION FRACTION DECREASED (Narrative CHF NYHA class I)	1	Secondary CE	Unresolved

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Pt #	Adverse Event	AE Intensity	Cardiac Endpoint	Outcome
(b) (6)	PERICARDIAL EFFUSION	2		
	HEPATITIS TOXIC	2		
	EJECTION FRACTION DECREASED	1		
	CARDIAC FAILURE CONGESTIVE	2		
	CARDIOMYOPATHY	2		
	CARDIAC FAILURE	3	Primary CE	Unresolved
	FATIGUE	3		
	JAUNDICE	2		
	CARDIAC FAILURE CONGESTIVE	2	Secondary CE	Resolved
	CARDIAC FAILURE (Narrative CHF NYHA Class 1)	1	Secondary CE	Unresolved
	DYSPNEA	2		
	ERYTHEMA	2		
	CARDIAC FAILURE CONGESTIVE	3	Primary CE	Unresolved
	SUDDEN DEATH	4		
	DRUG HYPERSENSITIVITY	3		
	CARDIAC FAILURE CONGESTIVE	3	Primary CE	Unresolved
	VENTRICULAR DYSFUNCTION	1		
	EJECTION FRACTION DECREASED	1	Secondary CE	Completed Herceptin
	HYPOTENSION	2		
	EJECTION FRACTION DECREASED (Narrative CHF NYHA Class 1)	1	Secondary CE	Unresolved
	TACHYARRHYTHMIA	3		
	CARDIAC FAILURE CONGESTIVE	3	Primary CE	Unresolved
	CARDIAC FAILURE CONGESTIVE	1	Secondary CE	Resolved with sequale

Adverse events leading to treatment discontinuation:
In total 6.1% (103/1678) subjects in the Herceptin arm discontinued treatment because of one or more adverse events. Ejection fraction decreased and congestive cardiac failure were the most common adverse events each being reported as reason for discontinuation in 1% (23/1678) of Herceptin subjects. Seven discontinued due to cardiac failure 0.4%. Of the103 subjects who had adverse events that lead to discontinuation of treatment 5.2 % (87/1678) were considered related to Herceptin.

Adverse events leading to premature withdrawal from study:
97 subjects were prematurely withdrawn from a study as a result of at least one adverse event. Eighty eight of the 97 subjects who prematurely withdrew from study due to an adverse event considered related to Herceptin. The most common adverse event leading to premature withdrawal from the study was congestive heart failure (23 subjects) and ejection fraction decreased (21 subjects).

The following Table 27, is a sub table derived from table characterizing discontinuation of Herceptin in the cardiac endpoints subpopulation.

Table 27. Cardiac Endpoints with Adverse Events Leading to Discontinuation of Herceptin

Adverse Event by Preferred Term	n (%) 37	AE Intensity CTC v2.0
Primary Cardiac Endpoint		
Cardiac Failure Congestive	5 (14)	3-4
Cardiac Failure	4 (11)	3-4
Secondary Cardiac Endpoint		
Cardiac Failure Congestive	12 (32)	1-2
Ejection fraction Decreased	12 (32)	1-2
Angina Pectoris	1 (3)	3
Cardiotoxicity	1 (3)	1
Cardiac Disorder	1 (3)	1
Cardiac Failure	1 (3)	1
Echocardiogram abnormal	1 (3)	1
MUGA Abnormal	1 (3)	1

7.1.3.3 Other significant adverse events

Table 28, summarizes the combined routine schedule of LVEF assessment and "back of the book" variable which categorized subjects requiring monitoring of LVEF outside routine parameters. The "back of the book week" was collapsed into the week closest to the routine schedule of assessment week. For multiple back of the book dates, the worst LVEF was used. The mean and median at baseline for both arms was identical. By week 25 the Herceptin group mean decreased to 61 % and remained their through week 52 (completion of 1-year of Herceptin). At the month 18 follow-up visit the mean LVEF began to recover close to the original baseline number 63% vs. 64% for the Herceptin group. Notable there were no changes in LVEF from baseline through week 52 in the Observation arm. After month 24 of follow-up the number of subject assessed was less than five percent of the safety population in the respective arms. As s result, this reviewer cannot draw clinically meaningful or statistical significance of the long-term follow-up data

Table 28. Overall Summary of LVEF Changes Based on Worst LVEF *

	n (%)	Mean	Median	
Herceptin	1677 (100)	64	64	**Baseline**
Observation	1707 (100)	64	64	
Herceptin	1592 (95)	62	62	**Week 13**
Observation	1509 (88)	64	64	
Herceptin	1465 (87)	61	62	**Week 25**
Observation	1392 (81)	64	64	
Herceptin	1049 (63)	61	62	**Week 52**
Observation	947 (55)	64	64	
Herceptin	606 (36)	63	63	**Week 79/**
Observation	540 (32)	64	65	**Month 18**
Herceptin	270 (16)	64	64	**Week 103/**
Observation	253 (15)	64	64	**Month 24**
Herceptin	68 (4)	66	66	**Month 30**
Observation	66 (4)	64	65	
Herceptin	4 (0.2)	70	71	**Month 36**
Observation	2 (0.1)	66	66	

*Based on Raw data
Herceptin total # subjects= 1678
Observation total # subjects=1708

Table 29. Applicant's Summary of LVEF Over Time Applicant's Summary of LVEF Over Time

stslvef_3001 - Summary of LVEF Over Time (incl. additional examinations)

Study BO16348 (HERA): Herceptin in Adjuvant Breast Cancer
Safety population

	Observation Only N=1708	Herceptin 1 Year N=1678
Overall (worst value)		
n	1545	1600
Increase or no change	516 (33.4 %)	323 (20.2 %)
Decrease < 10%	816 (52.8 %)	883 (55.2 %)
Decrease >= 10%	213 (13.8 %)	394 (24.6 %)
LVEF < 50%	49 (3.2 %)	144 (9.0 %)
LVEF < 50% and decrease >= 10	35 (2.3 %)	118 (7.4 %)

Reviewer comment: The above applicant's Table 29 was *not included in the clinical study report (CSR),instead was a line listed table with submission.*

To assess overall cardiac function using an objective measurable parameter, LVEF function for both arms was compared across study. Table Table 30 reflects changes in LVEF based on the following parameters: NCI CTC version 2 , definition for cardiac left ventricular

function; HERA protocol algorithm for continuation and discontinuation of Herceptin based on the following interval assessment, drop of ≥ 10 Ejection Fraction (EF) points from baseline and LVEF < 50%; and criteria of change in LVEF ≥ 16% and LVEF < 50% based on previous labeling of product in dose modifications section.

Table 30. Summary of Changes from Baseline to Worst LVEF *

LVEF	Observation only	Herceptin
Change from baseline ≥ 10%	213/1708(12.47%)	394/1678(23.48%)
Post LVEF <50%	49/1708(2.87%)	144/1678(8.58%)
Significant drop :LEVF<50% and change ≥ 10%	35/1708(2.05%)	118/1678(7.03%)
CTC grade 1 : LVEF <20%, ≥ 10% drop	204/1708(11.94%)	376/1678(22.41%)
CTC grade 2 : LVEF ≥ 20% drop	21/1708(1.23%)	49/1678(2.94%)
Change in LVEF ≥ 16% and LVEF<50%	20/1708(1.17%)	64/1678(3.81%)

*Based on Applicant's Derived Variables

Table 31summarizes subjects excluded from the LVEF summary analysis as the CTC grade for these subjects required clinical judgment from the reporting investigator and this data was not properly collected, an noted as a protocol violation, by the Sponsor of the study. For detailed explanation see *section 7.1.5.1.*

Table 31. Cardiac Events Excluded from CTC Summary of LVEF

Pt #	NYHA Class
(b) (6)	IV
	III
	III
	IV
	III
	III
	III
	III
	III
	III

The majority of subjects fell into three categories for LVEF; change from baseline ≥ 10% was 23% (394/1678) for Herceptin group vs. 12% (21/1708) for Observation group, grade 1 toxicity for cardiac left ventricular function 22 % (376/1678) for the Herceptin group vs. 12% (204/1708) for the Observation group, and post baseline LVEF < 50% was 9% (144/1678) for the Herceptin group vs. 3% (49/1708) for the Observation group.

Table 32. Summary of LVEF by Advanced Age

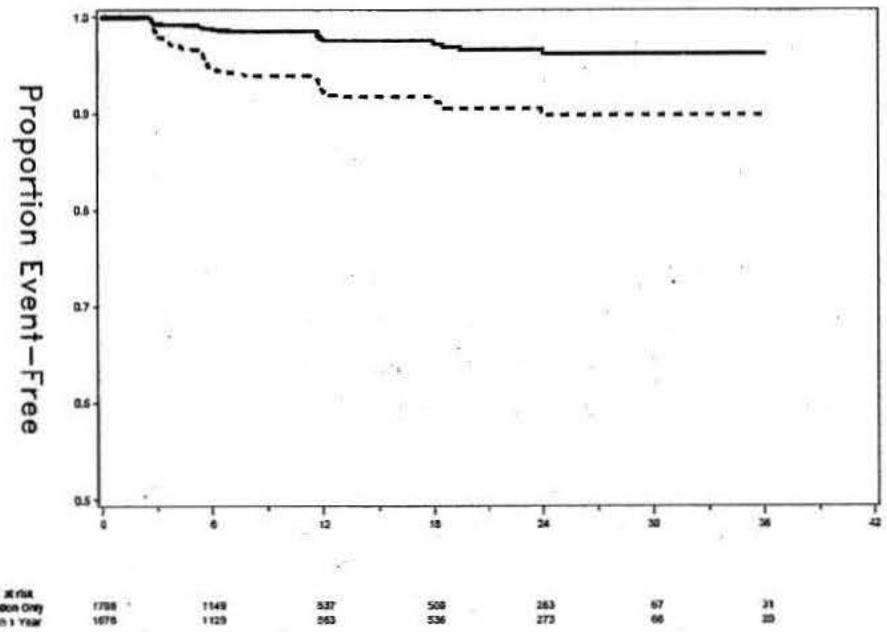
LVEF	Age	Observation	Herceptin	*p-Value
LVEF Significant Drop	< 65	32/1594 (2.01%)	112/1558 (7.19%)	<0.0001
	≥ 65	3/114 (2.63%)	6/120 (5.00%)	0.1771
LVEF Drop ≥ 10%	< 65	203/1594 (12.74%)	376/1558 (24.13%)	<0.0001
	≥ 65	10/114 (8.77%)	18/120 (15.00%)	0.0557
LVEF < 50%	< 65	45/1594 (2.82%)	133/1558 (8.54%)	<0.0001
	≥ 65	4/114 (3.51%)	11/120 (9.17%)	0.0464

* Fisher's Exact Test

Statistical significant differences in decreasing LVEF are seen between the Herceptin and Observation groups consistently in the age group less than 65 years old. Due tothe small sample size in the greater than or equal to 65 years of age category, statistically difficult to interpret. No difference in LVEF parameters can be found based on this subgroup Table 32).

After looking at LVEF changes at intervally scheduled and unscheduled time points, the next approach was too look at LVEF drops over time. Figure 2,is a Kaplan-Meier curve that represents time to event analysis using first LVEF decline using the parameter greater than or equal to ten percent of baseline and LVEF below 50%. Subjects who did not experience LVEF drop as defined above were censored at the *last date* of the following; follow-up date, radiological exam, LVEF assessment, contact, survival follow-up, or disease recurrence, whichever occurs last.

Figure 2. Time to First LVEF Decline of ≥ 10% from Baseline and to Below 50 % Subjects Based on Safety Population (Reviewer's Analysis)



Number at risk							
Observation Only	1708	1149	537	508	283	67	31
Herceptin 1 Year	1678	1129	563	536	273	66	20

_____ Observation (n=1708)
---------- Herceptin (n=1678)

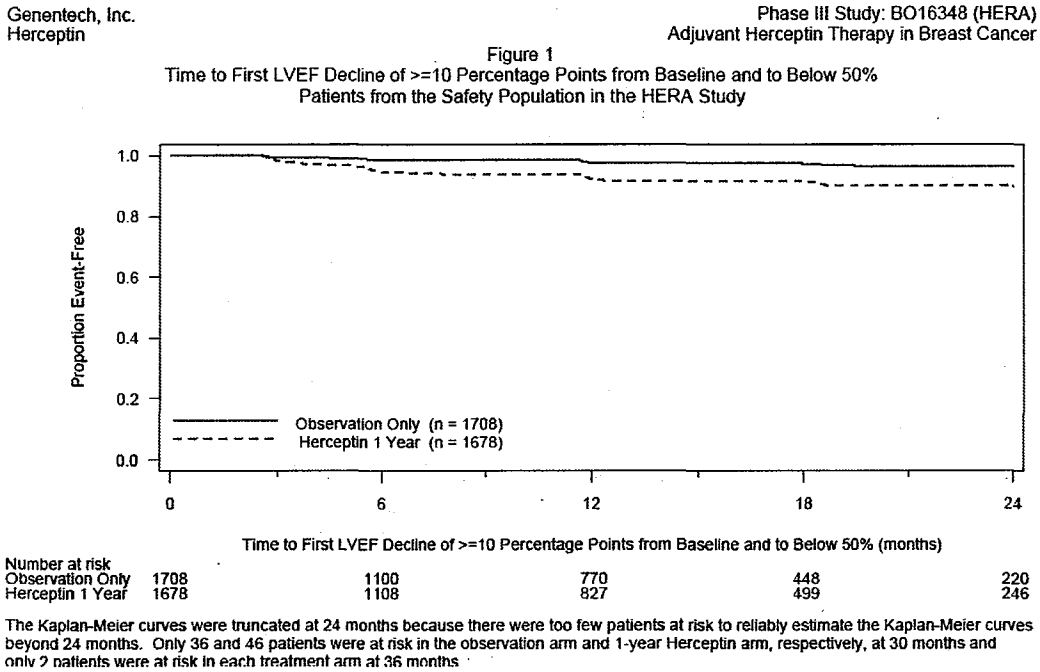
Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
TRTSAF	1	1.19573	0.19249	38.5878	<.0001	3.306	2.267	4.821	Actual treatment (for Safety)

[Hazard ratio 3.306, 95%CI (2.27, 4.82), p-value by log rank < .0001]

Figure 3, provides the Applicant's time to event analysis which includes disease recurrence as well as death as a competing risk. If subjects did not have a significant LVEF drop, then the last date of; follow-up, radiological exam, LVEF assessment, contact, or survival follow-up was used. However the results are similar.

Figure 3. Time to First LVEF Decline of ≥ 10% from Baseline and to Below 50 % Subjects Based on Safety Population (Sponsor's Analysis)



[Hazard ratio 3.23, 95%CI (2.21, 4.71), p-value by log rank <.0001]

Reviewer Comment: Based on the Kaplan-Meir Curve, Time to First LVEF Decline of ≥ 10% from Baseline and to Below 50 % and hazard ratio, subjects treated in the 1-year Herceptin arm had three times the risk of LVEF dropping below 50% and ≥ 10% decline from the baseline compared to the Observation arm. This finding is the first reported in any study with the use of Herceptin. This finding is clinically meaningful and statistically significant and will have direct implication in the label of Herceptin.

7.1.4 Other Search Strategies

Standardized Medical Query (SMQ)

Table 33 and Table 34 summarize adverse events by Standardized Medical Queries using a MedDRA based analysis tool for adverse events. The SMQ is a grouping of terms from one or more MedDRA SOC that relate to a defined medical condition or area of interest. The results of the SMQ level analysis can highlight areas of further inquiry. Terms are grouped as either broad or narrow in scope which correlates to sensitivity and specificity. Note that p-values are intended for ranking purposes only and are not intended for a determination of statistical significance.

Table 33. Standardized MedDRA Queries by p-Value (Broad Scope)

p-Value	SMQ	Observation	Herceptin
		(N=1708)	(N=1678)
	At least 1 SMQ	413 (24.2%)	729 (43.4%)
0.0000	Cardiac Failure	413 (24.2%)	729 (43.4%)
0.0000	Cardiac Arrhythmias	21 (1.8%)	98 (5.8%)
0.0064	Peripheral Neuropathy	37 (2.2%)	63 (3.8%)
0.0201	Parkinson-like Events	8 (0.5%)	20 (1.2%)

* p-Values are derived from a Mantel-Haenszel test for ranking purposes only

Table 34. Standardized MedDRA Queries by p-Value (Narrow Scope)

p-Value	SMQ	Observation	Herceptin
		(N=1708)	(N=1678)
	At least 1 SMQ	129 (7.6%)	236 (14.1%)
0.0000	Cardiac Failure	20 (1.2%)	96 (5.7%)
0.0435	Interstitial Lung Disease	0 (0.0%)	4 (0.2%)
0.0435	Hemorrhagic Cerebrovascular Condition	0 (0.0%)	4 (0.2%)
0.0450	Malignant or unspecified tumors	17 (1.0%)	7 (0.4%)
0.0805	Parkinson-like events	0 (0.0%)	3 (0.2%)

* p-Values are derived from a Mantel-Haenszel test for ranking purposes only

Table 34, using the narrow scope SMQ identified cases of interest, specifically interstitial lung disease.
Narratives of subjects with a safety signal que for interstitial lung disease:

Subject (b) (6)
Non-smoker and no documented radiation therapy. Randomized to 1-year Herceptin.

Last dose of Herceptin: (b) (6). Adverse event reported chronic pulmonary obstruction with dyspnea Grade 1. Onset (b) (6).
Treatment: Tiotropium bromide (b) (6).
Outcome: Unresolved.

Last dose of Herceptin: (b) (6). Adverse event obstructive bronchitis with Dyspnea -Grade 1. Onset (b) (6)

Treatment: Beclomathasone [redacted].
Outcome: Resolved [redacted].

Last dose of Herceptin: [redacted]. Adverse event productive bronchitis -Grade 1.
Onset [redacted].
Treatmetn: clarithromycin, [redacted]
Cefadroxyl [redacted]
Codeine, [redacted]
ambroxol [redacted]
Outcome Resolved [redacted].

Subject: [redacted]
Completed radiotherapy to right breast [redacted]. Randomized to 1-year Herceptin.
2 adverse events 1-pulmonary and 1-cardiac

Last dose of Herceptin: [redacted]. Adverse event reported pneumonitis actinica - Grade 2.
Onset: [redacted].
Treatment: Prednisone [redacted]
Ranitidine [redacted]
Salbuterol [redacted]
Brexotide [redacted]
Outcome: Resolved [redacted]

Last dose of Herceptin: [redacted]. Adverse event reported pericardial effusion-Grade 1. Onset [redacted].
Treatment: None reported
Echocardiogram: [redacted] reported as normal.
Outcome Resolved [redacted]. Unresolved [redacted].

Subject [redacted]
Completed left chest wall radiotherapy [redacted]. Non-smoker. Randomized to 1-year Herceptin.

Last dose of Herceptin: Incomplete CRF no initial dose (8mg/kg) documented or reason not given. The next dose closest to adverse event [redacted].
Adverse event chronic pneumonitis due to radiotherapy Grade 1.
Onset [redacted]
Treatment; None reported
Outcome: Unresolved
Comments on AE "the causality is probably due to radiotherapy"

Last dose of Herceptin [redacted]. Adverse event reported respiratory infection Grade 3. Onset [redacted].
Treatment; Levofloxacin [redacted]
Ceftriaxone [redacted]

"Tioprobio" (b) (6)
Chest/abdominal CT (b) (6) (results not reported).
Outcome: Resolved (b) (6)
Comments on AE "Hospitalization due to SAE"

Subject (b) (6)
Chest radiotherapy completed (b) (6). Randomized to 1-year Herceptin.

Last dose of Herceptin (b) (6). Adverse event reported Upper respiratory infection-Grade 1. Onset (b) (6).
Treatment: Fenspiride (b) (6)
Loratadine (b) (6).
Acemet (b) (6)
Outcome Resolved (b) (6).

Last dose of Herceptin: (b) (6). Adverse event reported radiation pneumonitis – Grade-1. Onset (b) (6)
Treatment: Fluticasone accuh (b) (6).
Sputant (b) (6).
Outcome Resolved (b) (6)

Reviewer Note: Subject (b) (6) *had the most compelling data revealing onset of respiratory symptoms following Herceptin in less than seven days after dosing with all three adverse events reported.*

New safety signal of interstitial lung disease (ILD) was flagged with standardized medical query (SMQ). Cases of ILD were n=4 (0.2%) p-Value = 0.0435. The office of surveillance and epidemiology (OSE) was consulted. An AERS (adverse event reporting system) data mining report was generated revealing a disproportionate risk ratio of two times the expected incidence of ILD in reporting with trastuzumab use.

Post marketing reports were reviewed from AERS that identified 110 unduplicated cases of interstitial lung disease (ILD) by narrow scope SMQ in patients receiving Herceptin.

In general the 110 cases are complex and confounding variables for interpretability : scattered missing information; confounding by concomitant treatments that have known pulmonary toxicity; and confounding by potential complications of the underlying disease. Disease stage and treatment history were incomplete and variably reported. Radiation exposure as well as chemotherapy exposure is also variably reported.

Summary of AERS Postmarketing Report on ILD

n = 110 cases

Age (n=90): Median = 56 y, Range = 32 – 79 y

Gender (n=107): Female = 95.3%, Male = 4.7%

Death outcome:	n = 31
Primary pulmonary event:	Pneumonitis/ILD = 29 Pulmonary fibrosis = 25 Pulmonary infiltrate = 20 ARDS = 9 Infection related = 5 Radiation related = 4 Hypersensitivity pneumonitis = 4 Infusion related = 4 Alveolitis = 3 Other = 7
Time to event (n=86):	Median = 35 d, Range 0 – 665 d
Concomitant treatments: (number of cases)	Paclitaxel = 36 Docetaxel = 30 Cyclophosphamide = 11 Doxorubicin = 8 Vinorelbine = 7 Gemcitabine = 4 Fluorouracil = 5 Methotrexate = 3
Indication:	Breast cancer = 88 NSCLC = 4 SCCHN = 1 Ovarian = 1 Unknown = 16

The AERS data search revealed 29 cases of pneumonitis/ILD as a primary event, the demographics reveal the majority of the 110 cases were in women, the chemotherapy most often given as concomitant treatment was paclitaxel and docetaxel, and the most common cancer pulmonary events reported was breast cancer.

The evidence supporting a new safety signal of ILD initially was found in HERA study .Subject (b) (6) who had compelling evidence of a positive rechallenge with trastuzumab. An AERS (adverse event reporting system) data mining report was generated revealing a disproportionate risk ratio of two times the expected incidence of ILD in reporting with trastuzumab use.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All clinical adverse events (AEs) encountered during the conduct of the study up to 28 days after last dose of trial treatment were reported on the AE pages of the Case Report Form. It was a special follow-up requirement of this study to report cardiac or cardiovascular events, as well as related adverse events occurring after completion of the treatment or observation phase (2 years) and beyond the common 28 days safety follow-up. All cardiac and cardiovascular events are to be reported until 10 years after randomization.

Refer to section 6.1.3 for Schedule of Assessment and frequency of follow-up. In addition the design of the HERA study kept the schedule of assessments the same for both arms of the study, however, subjects receiving Herceptin were seen every three weeks for study drug and this introduced a potential for bias increase reporting adverse events in the Herceptin arm.

The data on long-term follow-up in the one year Herceptin arm will be inconclusive as the HERA study allowed for re-randomization of subjects to the two year arm through protocol amendment E, which post dates database closure for the one year arm.

Subjects who were followed in the secondary cardiac endpoint were originally coded to be captured using New York Heart Association (NYHA) classification system. Amendment D, which was approved in November of 2003, changed the coding criteria for the secondary cardiac endpoint. Significant and asymptomatic drops in LVEF would be graded in NCI-CTC version 2 instead of the NYHA classification system. Prior to amendment D 1700 subjects were enrolled into the HERA study per the applicant. The CRF form and instructions to the investigators were not changed to reflect the change in coding with amendment D. This discrepancy was noticed by the Reviewer during coding accuracy check measuring AEs reported in the adverse event dataset against the narratives of the subjects in the cardiac endpoints. As a result, data for asymptomatic subjects that were in the secondary cardiac endpoint continued to be coded in the NYHA classification system, resulting in ongoing protocol violations. Therefore, coding was at the discretion of the investigator. In NCI-CTC version 2, coding would have allowed for a more objective measurement of response based on specific criteria for decrease in LVEF measurement. Asymptomatic subjects in the secondary endpoint did not require confirmation of NYHA class by a cardiologist as required for the symptomatic subjects in the endpoint. The integrity of the data in the secondary endpoint was compromised. The data was not able to be changed post hoc by the applicant and therefore question of validity was discussed with the applicant and the utilization of the information for labeling.

NYHA Classification

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.

Table 35..Applicant Summary of Secondary Cardiac Endpoint

	Observation Only N=1708 n (%)	Herceptin 1 Year N=1678 n (%)
Incidence of Secondary Cardiac Endpoint	9(0.5)	51(3.0)
Exact 95% CI for Incidence[1]	(0.24, 1.00)	(2.27, 3.98)
Difference in Incidence	3	
95% CI for the difference[2]	(1.6, 3.4)	

[1] Exact 95% Confidence Interval for one sample binomial using Pearson-Clopper method
[2] Approximate 95% Confidence Interval for difference of two rates using Hauck-Anderson correction

Not all subjects who meet the criteria for entering the secondary cardiac endpoint entered into the endpoint. The total number of subjects in the secondary endpoint between both arms was 1.8% (60/3386), Table 35. In order to asses true cardiac function for the entire study population LVEF was analyzed for both arms using the EFEXLVEF.xpt dataset.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 7.1. All five hierarchal terms were utilized. Adverse event grading was performed utilizing NCI CTC version 2. A side by side comparison of the verbatim term to MedDRA Lower level Term (LLT) was performed to verify the accuracy of the coding process. Included was a review of approximately 8400 AE line listings. Coding was deemed appropriate in a majority of the events. The events where this reviewers' judgment differed from the coders' were not clinically meaningful and would not have had a significant impact on the study's safety results had they been coded differently.

7.1.5.3 Incidence of common adverse events

The safety database for HERA was comprised of 3386 subjects arm had 1678 subjects and the observation had 1708 subjects. To determine the number of subjects who experienced an adverse event (AE) at any time during the study, the AE.xpt data set was grouped by patient identifier, MedDRA terms from highest level of hierarchy to lowest, treatment arm,

and maximum AE grade. This resulted in a dataset containing one subject per row per AE by maximum grade. The remaining dataset contained only those subjects who experienced at least one AE. These data were then tabulated for the total number of subjects, AE events by grade, and incidence rates per arm. Refer to section 7.1., for overview of AE by intensity (Table 20) and overall incidence of adverse events. Table 36 ,is the highest order of categorization of MedDRA , the system organ class (SOC). Next level of adverse event categorization under SOC is the highest level grouping term (HLGT),

Table 38.

Table 36. Adverse Events by SOC All Grades 1-4

	Observation		Herceptin		Observation		Herceptin	
Adverse Events	**All Grades**		**All Grades**		**Grades 3-4**		**Grades 3-4**	
System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	166	9.72	517	30.81	1	0.06	16	0.95
INFECTIONS AND INFESTATIONS	205	12.00	496	29.56	9	0.53	27	1.61
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	318	18.62	450	26.82	17	1.00	13	0.77
GASTROINTESTINAL DISORDERS	130	7.61	392	23.36	5	0.29	16	0.95
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	91	5.33	318	18.95	2	0.12	1	0.06
NERVOUS SYSTEM DISORDERS	129	7.55	309	18.41	9	0.53	15	0.89
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	102	5.97	249	14.84	8	0.47	4	0.24
VASCULAR DISORDERS	174	10.19	239	14.24	10	0.59	25	1.49
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	128	7.49	153	9.12	5	0.29	5	0.30
CARDIAC DISORDERS	50	2.93	151	9.00	4	0.23	19	1.13
PSYCHIATRIC DISORDERS	98	5.74	148	8.82	3	0.18	7	0.42
INVESTIGATIONS	49	2.87	139	8.28	3	0.18	7	0.42
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	47	2.75	94	5.60	7	0.41	12	0.72
EYE DISORDERS	31	1.81	67	3.99	1	0.06	0	0.00
RENAL AND URINARY DISORDERS	16	0.94	47	2.80	1	0.06	1	0.06
EAR AND LABYRINTH DISORDERS	15	0.88	35	2.09	0	0.00	1	0.06
BLOOD AND LYMPHATIC SYSTEM DISORDERS	12	0.70	31	1.85	4	0.23	3	0.18
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	27	1.58	30	1.79	7	0.41	4	0.24
METABOLISM AND NUTRITION DISORDERS	20	1.17	29	1.73	4	0.23	1	0.06
HEPATOBILIARY DISORDERS	21	1.23	22	1.31	4	0.23	0	0.00
IMMUNE SYSTEM DISORDERS	6	0.35	20	1.19	0	0.00	2	0.12
ENDOCRINE DISORDERS	19	1.11	17	1.01	1	0.06	0	0.00
SURGICAL AND MEDICAL PROCEDURES	11	0.64	10	0.60	1	0.06	1	0.06
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	6	0.35	3	0.18	0	0.00	0	0.00
PREGNANCY, PUERPERIUM AND	5	0.29	2	0.12	2	0.12	1	0.06

	Observation		Herceptin		Observation		Herceptin	
Adverse Events	**All Grades**		**All Grades**		**Grades 3-4**		**Grades 3-4**	
System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
PERINATAL CONDITIONS								

[Refer to appendix D for a complete table of all adverse events in the study BO16348(HERA) by preferred term.]

To provide more categorization of the adverse events MedDRA higher level terms (HLT) was used. Table 37, was sorted by Herceptin grades from largest to smallest using the threshold of ≥ 2% as the lower limit of incidence.

Table 37. Adverse Event by HLT Herceptin ≥ 2% Difference Between Arms

	Observation		Herceptin		Observation		Herceptin	
High Level Term	**All Grades 1-4**		**All Grades 1-4**		**Grade 3-4**		**Grades 3-4**	
Adverse Event	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
UPPER RESPIRATORY TRACT INFECTIONS	81	4.74	249	14.84	0	0.00	1	0.06
MUSCULOSKELETAL AND CONNECTIVE TISSUE SIGNS AND SYMPTOMS NEC	168	9.84	220	13.11	6	0.35	5	0.30
ASTHENIC CONDITIONS	73	4.27	210	12.51	0	0.00	6	0.36
HEADACHES NEC	49	2.87	164	9.77	3	0.18	4	0.24
JOINT RELATED SIGNS AND SYMPTOMS	105	6.15	147	8.76	3	0.18	4	0.24
NAUSEA AND VOMITING SYMPTOMS	24	1.41	146	8.70	3	0.18	7	0.42
DIARRHOEA (EXCL INFECTIVE)	16	0.94	123	7.33	0	0.00	5	0.30
FEBRILE DISORDERS	6	0.35	101	6.02	0	0.00	1	0.06
OEDEMA NEC	45	2.63	96	5.72	0	0.00	1	0.06
BODY TEMPERATURE PERCEPTION	1	0.06	95	5.66	0	0.00	3	0.18
NAIL AND NAIL BED CONDITIONS (EXCL INFECTIONS AND INFESTATIONS)	2	0.12	89	5.30	0	0.00	0	0.00
COUGHING AND ASSOCIATED SYMPTOMS	41	2.40	85	5.07	1	0.06	1	0.06
RASHES, ERUPTIONS AND EXANTHEMS NEC	11	0.64	85	5.07	0	0.00	1	0.06
BREATHING ABNORMALITIES	40	2.34	81	4.83	2	0.12	1	0.06
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	35	2.05	71	4.23	2	0.12	2	0.12
NEUROLOGICAL SIGNS AND SYMPTOMS NEC	31	1.81	71	4.23	1	0.06	3	0.18
GENERAL SIGNS AND SYMPTOMS NEC	14	0.82	70	4.17	0	0.00	0	0.00
INFLUENZA VIRAL INFECTIONS	9	0.53	70	4.17	0	0.00	3	0.18
MUSCLE PAINS	18	1.05	65	3.87	1	0.06	3	0.18
UPPER RESPIRATORY TRACT SIGNS AND SYMPTOMS	11	0.64	63	3.75	0	0.00	0	0.00
CARDIAC FUNCTION DIAGNOSTIC PROCEDURES	12	0.70	61	3.64	0	0.00	0	0.00
URINARY TRACT INFECTIONS	23	1.35	59	3.52	0	0.00	2	0.12
MUSCLE RELATED SIGNS AND SYMPTOMS NEC	8	0.47	51	3.04	0	0.00	0	0.00
PRURITUS NEC	10	0.59	49	2.92	0	0.00	0	0.00
CARDIAC SIGNS AND SYMPTOMS NEC	12	0.70	48	2.86	0	0.00	0	0.00
STOMATITIS AND ULCERATION	2	0.12	43	2.56	0	0.00	0	0.00
NASAL DISORDERS NEC	1	0.06	42	2.50	0	0.00	0	0.00

Table 38. Adverse Events by HLGT with Herceptin Difference ≥ 2% Between Arms

	Observation		Herceptin		Observation		Herceptin	
Adverse Event	**All Grades 1-4**		**All Grades 1-4**		**Grades 3-4**		**Grades 3-4**	
Higher Level Grouping Term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
INFECTIONS - PATHOGEN CLASS UNSPECIFIED	165	9.66	397	23.66	6	0.35	18	1.07
GENERAL SYSTEM DISORDERS NEC	154	9.02	389	23.18	1	0.06	9	0.54
GASTROINTESTINAL SIGNS AND SYMPTOMS	70	4.10	230	13.71	4	0.23	9	0.54
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS NEC	173	10.13	224	13.35	6	0.35	5	0.30
EPIDERMAL AND DERMAL CONDITIONS	62	3.63	214	12.75	1	0.06	1	0.06
RESPIRATORY DISORDERS NEC	87	5.09	199	11.86	3	0.18	2	0.12
BODY TEMPERATURE CONDITIONS	7	0.41	173	10.31	0	0.00	4	0.24
HEADACHES	49	2.87	170	10.13	3	0.18	4	0.24
JOINT DISORDERS	126	7.38	167	9.95	5	0.29	4	0.24
GASTROINTESTINAL MOTILITY AND DEFAECATION CONDITIONS	34	1.99	156	9.30	1	0.06	5	0.30
NEUROLOGICAL DISORDERS NEC	67	3.92	138	8.22	3	0.18	7	0.42
SKIN APPENDAGE CONDITIONS	22	1.29	130	7.75	1	0.06	0	0.00
VIRAL INFECTIOUS DISORDERS	36	2.11	121	7.21	1	0.06	4	0.24
MUSCLE DISORDERS	27	1.58	113	6.73	1	0.06	3	0.18
CARDIAC AND VASCULAR INVESTIGATIONS (EXCL ENZYME TESTS)	19	1.11	91	5.42	1	0.06	1	0.06
CARDIAC DISORDER SIGNS AND SYMPTOMS	12	0.70	57	3.40	0	0.00	0	0.00
UPPER RESPIRATORY TRACT DISORDERS (EXCL INFECTIONS)	8	0.47	56	3.34	1	0.06	0	0.00
ORAL SOFT TISSUE CONDITIONS	2	0.12	49	2.92	0	0.00	0	0.00

(b) (6) these adverse events have been reported in past experience with Herceptin.

Table 39. Common ≥ 5% Adverse Events of Any Grade with Higher Incidence ≥ 2% in the 1-Year Herceptin Arm by Preferred Term

	Observation		Herceptin		Observation		Herceptin	
Preferred Term	**All Grades 1-4**		**All Grades 1-4**		**Grades 3-4**		**Grades 3-4**	
Adverse Event	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
HEADACHE	49	2.87	162	9.65	3	0.18	4	0.24
ARTHRALGIA	98	5.74	137	8.16	3	0.18	4	0.24
NASOPHARYNGITIS	43	2.52	135	8.05	0	0.00	0	0.00
FATIGUE	44	2.58	128	7.63	0	0.00	4	0.24
DIARRHEA	16	0.94	123	7.33	0	0.00	5	0.30
NAUSEA	19	1.11	108	6.44	1	0.06	2	0.12
PYREXIA	6	0.35	100	5.96	0	0.00	1	0.06
BACK PAIN	58	3.40	91	5.42	3	0.18	3	0.18
CHILLS	0	0.00	85	5.07	0	0.00	3	0.18

MedDRA Analysis Tool

	Observation	Herceptin
Adverse Event by Preferred Term	%	%
HYPERTENSION	2	4
*EJECTION FRACTION DECREASED	0.6	3
PALPITATIONS	0.7	3
UPPER RESPIRATORY TRACT INFECTION	1	3
MUSCLE SPASMS	0.2	3
CHEST PAIN	1	3
NAIL DISORDER	0	3
ONYCHORRHEXIS	0.1	2
CONSTIPATION	1	2
*CARDIAC FAILURE CONGESTIVE	0.3	2
ABDOMINAL PAIN UPPER	1	2
*PARAESTHESIA	0.6	2
VERTIGO	0.4	2
EPISTAXIS	0.1	2
RHINORRHOEA	0.3	1
CHEST DISCOMFORT	0.1	1
BLOOD PRESSURE INCREASED	0.2	1
TREMOR	0.1	1
CARDIAC DISORDER	0	0.3
PULMONARY HYPERTENSION	0	0.2
VENTRICULAR DYSFUNCTION	0	0.2

AE subset of adverse event by PT with ranking p-values 0.0000-0.0435
* = In the current label

7.1.5.4 Common adverse event tables

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Table 40, is a comprehensive listing of adverse events in HERA between study arms. The table lists toxicity by MedDRA category of body systems. A MedDRA analysis tool for adverse events was utilized using preferred terms which based on incidence was assigned a p-value for ranking purposes only. This list was crossed referenced against the most commonly reported adverse events ($\geq$ 5% any grade with higher incidence $\geq$ 2% in the 1-year Herceptin arm). More serious but lesser incidence adverse events was also captured and finally adverse events currently in the Herceptin label were compared. A version of this table will be utilized in the updated label of Herceptin.

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Table 40. Overall Summary of Toxicity by Body System

MedDRA (v. 7.1) Adverse Event Preferred Term	1 Year Herceptin (n= 1678)	Observation (n=1708)
Cardiac		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias	42 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	3 (0.2%)	0 (0%)
Cardiomyopathy	2 (0.1%)	0 (0%)
Respiratory Thoracic Mediastinal Disorders		
Nasopharyngitis	135 (8%)	43 (3%)
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
ILD	4 (0.2%)	0 (0%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Rhinorrhea	24 (1%)	5 (0.3%)
Pharyngitis	22 (1%)	9 (0.5%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Gastrointestinal Disorders		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
Musculoskeletal & Connective Tissue Disorders		
Arthralgia	137 (8%)	39 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
Nervous System Disorders		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
Vertigo	25 (1.5%)	7 (0.7%)
Tremor	11 (0.7%)	2 (0.1%)
Skin & Subcutaneous Tissue Disorders		
Rash	70 (4%)	10 (.6%)
Nail Disorders	43 (2%)	0 (0%)

MedDRA (v. 7.1) Adverse Event Preferred Term	**1 Year Herceptin (n= 1678)**	**Observation (n=1708)**
Pruritis	40 (2%)	10 (0.6%)
Onychorrhexis	36 (2%)	1 (0.06%)
Onychomycosis	8 (0.5%)	1 (0%)
General Disorders		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Aesthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Chest Discomfort	20 (1%)	2 (0.1%)
Sudden Death	1 (.06%)	0 (0%)
Infections		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	42 (3%)	13 (0.8%)
Immune System Disorders		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)
Psychiatric Disorders		
Anxiety	40 (2%)	3 (0.2%)

7.1.5.5 Identifying common and drug-related adverse events

Serious adverse events which are probable or definitely due to Herceptin, based on comparison between both arms of the HERA study include congestive heart failure, cardiac failure, decreased ejection fraction, infusion reactions, and pulmonary toxicity associated with and without infusion reactions. The most common adverse events probable or definitely due to Herceptin, based on comparison between both arms of the HERA study include headache, nasopharyngitis, fatigue, diarrhea, nausea, pyrexia, back pain , and chills. Adverse events that are most likely related to Herceptin based on incidence reporting of two times or greater than compared to the Observation arm are the following: hypertension, palpitations, tachycardia, dizziness, vertigo, cough, upper abdominal pain and constipation. Laboratory abnormalities will be discussed later in section 7.1.7.

7.1.6 Less Common Adverse Events

Adverse events interstitial lung disease and sudden death although less common are serious events,

Table 41. These events occurred in the Herceptin group only. Refer to section 7.1.4, for interstitial lung disease and section 7.1.1, for sudden death narrative.

Table 41. Adverse events < 1% in 1-year Herceptin Arm

MedDRA (v. 7.1) Adverse Event Preferred Term	1 Year Herceptin (n= 1678)	Observation (n=1708)
Cardiac		
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	3 (0.2%)	0 (0%)
Respiratory Thoracic Mediastinal Disorders		
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Lung Disease	4 (0.2%)	0 (0%)
Musculoskeletal & Connective Tissue Disorders		
Tremor	11 (0.7%)	2 (0.1%)
Skin & Subcutaneous Tissue Disorders		
Onychomycosis	8 (0.5%)	1 (0%)
General Disorders		
Sudden Death	1 (.06%)	0 (0%)
Immune System Disorders		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

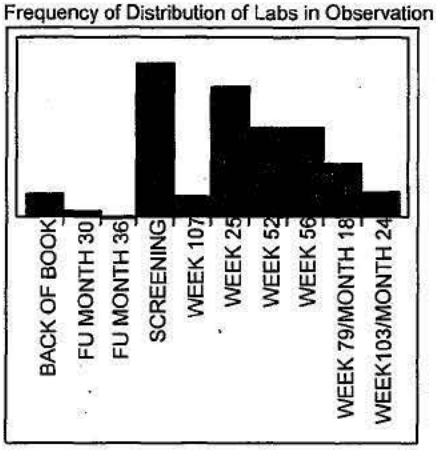
7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The schedule of assessment for laboratory parameters included hematology and biochemistry screens. Hematology labs consisted of,: hemoglobin, total white blood cell count, absolute neutrophil count, and platelet count. Biochemistry labs included: serum creatinine, blood urea nitrogen, electrolytes, AST (SGOT) or ALT (SGPT), ALP, and bilirubin.

The planned schedule of assessment for the laboratory parameters were as follows: baseline, week 25, week 52, week 79, week 103, month 18, month 24 then every six months until month 60, after month 60 every 12 months for 5 years. Unscheduled assessments were captured under the variable "back of the book".

Frequency of Distribution of Labs in Observation Arm

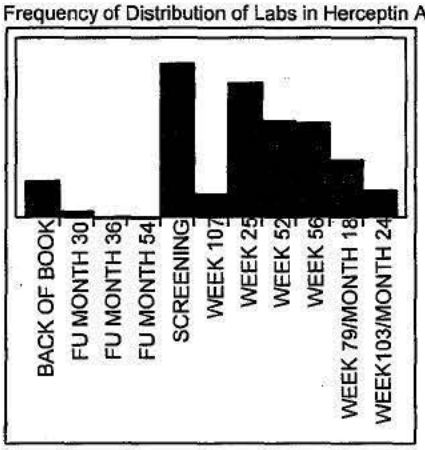


Frequencies

Level	Count	Prob
BACK OF BOOK	3104	0.03818
FU MONTH 30	804	0.00989
FU MONTH 36	26	0.00032
SCREENING	21156	0.26024
WEEK 107	2956	0.03636
WEEK 25	17884	0.21999
WEEK 52	12386	0.15236
WEEK 56	12292	0.15121
WEEK 79/MONTH 18	7265	0.08937
WEEK103/MONTH 24	3420	0.04207
Total	81293	1.00000

N Missing
0
10 Levels

Frequency of Distribution of Labs in Herceptin Arm



Frequencies

Level	Count	Prob
BACK OF BOOK	4888	0.05712
	852	0.00996
FU MONTH 30		
FU MONTH 36	52	0.00061
FU MONTH 54	12	0.00014
SCREENING	20829	0.24341
WEEK 107	3200	0.03740
WEEK 25	18282	0.21364
WEEK 52	13191	0.15415
WEEK 56	12740	0.14888
WEEK 79/MONTH 18	7838	0.09160
WEEK103/MONTH 24	3688	0.04310
Total	85572	1.00000

N Missing
0
11 Levels

7.1.7.3 Standard analyses and explorations of laboratory data

The incidence of grade 1-4 laboratory values in HERA was analyzed. Severity was graded according to the NCI-CTCAE version 2.0. Worst-grade per subject values were determined and compared between treatment groups. Refer to Table 42 through

Table 44.

Table 42. Incidence of Hematologic AEs by CTC Grade

	Observation n=1708		Herceptin n=1678	
	n	%	n	%
Hemoglobin				
Grade 1	439	25.7	540	32.2
Grade 2	37	2.2	45	2.7
Grade 3	1	.06	1	.06
Grade 4	27	1.6	22	1.3
WBC				
Grade 1	538	31.5	549	32.7
Grade 2	106	6.2	120	7.2
Grade 3	7	.41	7	.42
Grade 4	5	.29	4	.24
Platelet				
Grade 1	156	9.1	157	9.4
Grade 2	2	.12	5	.30
Grade 3	4	.23	2	.12
Grade 4	2	.12	1	.06
Neutrophil				
Grade 1	212	12.4	198	11.8
Grade 2	64	3.7	70	4.2
Grade 3	8	.5	8	.5
Grade 4	8	.5	7	.4

Table 43. Incidence of Hepatic AEs by CTC Grade

	Observation n=1708		Herceptin n=1678	
	n	%	n	%
Alkaline Phosphatase				
Grade 1	295	17.3	254	15.1
Grade 2	16	.94	9	.54
Grade 3	8	.47	0	0
Grade 4	-		-	
SGOT				
Grade 1	382	22.4	402	24
Grade 2	29	1.7	21	1.25
Grade 3	11	.64	5	.30
Grade 4	2	.12	0	0
SGPT				
Grade 1	432	25.3	460	27.4
Grade 2	55	3.2	33	2.0
Grade 3	10	.59	4	0.24
Grade 4	2	.12	0	0
Total Bilirubin				
Grade 1	66	3.8	75	4.5
Grade 2	16	.94	19	1.1
Grade 3	5	.3	2	.01
Grade 4	2	.12	0	0

Table 44. Incidence of Chemistry AEs by CTC Grade

	Observation n=1708		**Herceptin n=1678**	
	n	%	n	%
Sodium				
Grade 1	151	8.8	154	9.1
Grade 2	8	.5	12	.71
Grade 3	5	.3	8	.5
Grade 4	7	.4	5	.3
Potassium				
Grade 1	177	10.3	173	10.3
Grade 2	10	.6	24	1.4
Grade 3	14	.8	10	.6
Grade 4	13	.76	15	.9
Serum Creatinine				
Grade 1	86	5	102	6
Grade 2	4	.2	7	.4
Grade 3	-	-	-	-
Grade 4	1	.06	0	0

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

During the study the majority of patients in either study arm did not exhibit a shift from their baseline laboratory test parameter values or exhibited a shift of 2 grades or less between baseline and their worst test value. Fewer patients in the Herceptin 1 year arm experienced a shift of 3 or 4 grades from baseline than in the observation arm. A summary of 3-grade or 4-grade shifts from baseline during the study is shown in Table 45.

Table 45. Summary of Grade 3 or 4 Shifts from Baseline in Laboratory Test Parameters

Parameter	Observation Only N=1708	Herceptin 1 Year N=1678
Hematology		
Hemoglobin g/L (hypo)		
3-grade shift	-	1
4-grade shift	1	-
White Blood Cell (WBC) 10^9/L (hypo)		
3-grade shift	2	1
4-grade shift	2	1
Platelets 10^9/L (hypo)		
3-grade shift	2	2
4-grade shift	1	-
Neutrophils 10^9/L (hypo)		
3-grade shift	4	1
4-grade shift	1	2
Blood Chemistry		
ASAT (SGOT) U/L (hyper)		
3-grade shift	6	5
4-grade shift	2	-
Alkaline Phosphatase U/L (hyper)		
3-grade shift	7	-
4-grade shift	-	-
ALAT (SGPT) U/L (hyper)		
3-grade shift	5	1
4-grade shift	2	-
Total bilirubin µmol/L (hyper)		
3-grade shift	5	1
4-grade shift	2	-
Electrolytes		
Potassium mmol/L (hyper)		
3-grade shift	5	5
4-grade shift	9	7
Potassium mmol/L (hypo)		
3-grade shift	2	2
4-grade shift	4	3
Sodium mmol/L (hyper)		
3-grade shift	-	2
4-grade shift	2	2
Sodium mmol/L (hypo)		
3-grade shift	2	3
4-grade shift	4	2

7.1.7.5 Special assessments

No other special assessments were conducted.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were taken at the screening visit and every 12 weeks corresponding with schedule of assessments follow-up refer to Table 46. The pulse vital sign was only recoded with screening visit and therefore unable to be analyzed over time in relation to changes in blood pressure.

Table 46. Vital Signs for BO 16348 (HERA) (Safety Population)

	Observation					
	N	N Missing	Mean	SD	Median	Range
Screening						
SBP	1604	1147	125	17	121	79-220
DBP	1604	1147	77	10	80	30-115
Pulse Pressure	1604	1147	47	12	45	20-105
Pulse	1604	1147	47	12	45	20-105
Week 13						
SBP	1361	359	125	17	124	80-130
DBP	1361	359	78	10	80	50-120
Pulse Pressure	1367	359	48	12	47	15-110
Pulse		1720				
Week25						
SBP	1268	306	125	16	120	80-200
DBP	169	305	77	10	80	40-126
Pulse Pressure	1268	306	47	12	45	20-100
Pulse		1574				
Week 52						
SBP	855	229	125	16	122	90-185
DBP	855	229	78	10	80	40-130
Pulse Pressure	855	229	47	12	45	20-97
Pulse		1084				
Week 79/Month 18						
SBP	489	137	124	16	122	90-192
DBP	489	127	77	9	80	50-105
Pulse Pressure	489	137	47	12	45	16-94
Pulse		626				
Week 103/Month 24						
SBP	230	69	124	15	120	85-165
DBP	230	69	78	9	80	50-110
Pulse Pressure	230	69	46	11	45	14-101
Pulse		299				
Back of Book	Missing					
SBP						
DBP						

Pulse Pressure
Pulse

	Herceptin					
	N	N Missing	Mean	SD	Median	Range
Screening						
SBP	1617	1079	124	16	120	80-230
DBP	1616	1080	77	10	80	40-134
Pulse Pressure	1616	1080	47	12	45	16-118
Pulse	1576	1120	76	10	76	49-114
Week 13						
SBP	1450	337	126	17	124	75-210
DBP	1450	337	78	10	80	50-130
Pulse Pressure	1450	337	48	12	46	11-107
Pulse		1787				
Week 25						
SBP	1343	290	126	17	124	80-220
DBP	1343	290	78	10	80	40-130
Pulse Pressure	1343	290	48	12	47	17-98
Pulse		1633				
Week 52						
SBP	937	236	126	17	125	80-200
DBP	937	236	78	10	80	46-128
Pulse Pressure	937	236	48	12	48	15-95
Pulse		1173				
Week 79/Month 18						
SBP	535	120	125	16	121	79-180
DBP	535	120	78	10	80	52-120
Pulse Pressure	535	120	47	12	46	15-96
Pulse		655				
Week 103/Month 24						
SBP	251	46	125	17	120	90-180
DBP	251	46	78	10	80	51-110
Pulse Pressure	251	46	46	12	45	20-90
Pulse		297				
Back of Book	Missing					
SBP						
DBP						
Pulse Pressure						

Vital signs (systolic and diastolic blood pressure) were assessed regularly throughout the study. There were no clinically relevant changes from baseline in vital signs and no differences between the study arms with respect to the change from baseline data. A summary of the mean systolic and diastolic blood pressure at baseline and at time points throughout the study is provided in the tables above. Median BP at baseline for the Herceptin arm was 120 mmHg and by week 52 the median BP was up to 125 mmHg. In comparison the observation arm baseline median BP was 121 mmHg and by week 52 remained relatively stable with a median BP of 122 mmHg. The same results can be seen with pulse pressure. The Herceptin arm by week 52 had an increase in the median pulse pressure by three points as compared to the observation arm whose median pulse pressure maintained stable.

Reviewer note: A limitation to the vital signs data is pulse measurements were only collected at baseline and "Back of the Book" measurements which indicated unscheduled measurements of vital signs was coded as missing data. Also, captured in the adverse events datasets (AE.xpt), the incidence of hypertension in the Herceptin arm was 4% (64/1678) vs. observation arm 2% (35/1708).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Drug-control comparisons of laboratory values were limited to the analyses of the differences between the 1-year Herceptin arm and observation arm (see section 7.1.8.3).

7.1.8.3 Standard analyses and explorations of vital signs data

Baseline systolic and diastolic blood pressure and pulse data were analyzed. In addition per schedule of assessment serial blood pressures were analyzed. As stated in section 7.1.81., a limitation to the vital signs data is pulse measurements were only collected at baseline and "Back of the Book" measurements which indicated unscheduled measurements of vital signs was coded as missing data. Long term follow-up data was limited to follow-up out to month 24 and the number of subjects whose data was collected was 231 in the observation arm and 251 in the Herceptin arm. The data for the Herceptin arm shows that the median blood pressure returned to baseline levels at 24 months follow-up.

Blood pressure changes revealed a 5 point increase from baseline median BP in the Herceptin arm, versus a 1 point increase in the observation arm. Clinically meaningful is the correlate of incidence of hypertension reported in the adverse events data where hypertension was reported twice as often in the Herceptin arm than the observation arm.

7.1.8.4 Additional analyses and explorations

None were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Standard 12- Lead electrocardiogram (ECG) was performed for both arms of the study at baseline, weeks 13, 25, and 52. Post drug follow-up of ECG monitoring included months 18, 24, 30, 36, and 60. A limitation to the ECG data was no submission of a electronic dataset but as a line by line submission. Section 7.1.9.3, contains the analysis of ECG abnormalities reported as AEs in the AE.xpt datatset.

7.1.9.3 Standard analyses and explorations of ECG data

The total number of subjects reporting ECG abnormalities as AEs in the observation arm was 0.23% (4/1708) compared to 0.54% (9/1678) in the Herceptin arm, Table 47. No grade 3-4 abnormalities were reported, however the incidence of T-wave inversion reported between arms is clinically meaningful. The Herceptin arm was reported the event of T-wave inversion four times higher than the observation arm.

Table 47. ECG abnormalities reported as AEs Between Arms

	Observation (n=1708)		**Herceptin (n=1678)**	
	All Grades		**All Grades**	
Preferred Term	**n**	**%**	**n**	**%**
ECG P WAVE INVERTED	0	0.00	1	0.06
ELECTROCARDIOGRAM ABNORMAL	1	0.06	3	0.18
ELECTROCARDIOGRAM CHANGE	0	0.00	1	0.06
ELECTROCARDIOGRAM QT PROLONGED	1	0.06	0	0.00
ELECTROCARDIOGRAM T WAVE INVERSION	1	0.06	4	0.24
QRS AXIS ABNORMAL	1	0.06	0	0.00

7.1.9.4 Additional analyses and explorations

None were performed.

7.1.10 Immunogenicity

The HERA study was not designed to collect serum samples in order to determine the incidence of human anti-human antibody (HAHA) to trastuzumab. Data to immunogenecity is limited to legacy data in the metastatic setting. The incidence of immune responses (HAHA) to trastuzumab in the setting of metastatic disease is low. The impact on HAHA, if any, is of minimal risk and does not offset the benefits of the effects on DFS.

7.1.11 Human Carcinogenicity

Human carcinogenicity studies were not required and therefore not conducted or included in the application in support of this proposed labeling extension.

7.1.12 Special Safety Studies

No special safety studies were conducted in support of this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal phenomenon is known. Trastuzumab has no expected abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

Oligohydramnios was initially identified five post marketing cases in 2004. Changes made to the label were based on three cases and the addition of oligohydramnios identified in the post marketing setting was added. The pregnancy category remained a "B". In 2007 post marketing reports through the adverse events reporting system (AERS) identified 18 cases of oligohydramnios. A consult was placed to the Maternal Heath Team at the FDA to review the post marketing data.

Review of the published literature and MedWatch forms submitted to FDA reveal ten reported and unique pregnancies in women with breast cancer who used Herceptin during some portion of their pregnancy, nine of whom developed oligohydramnios. In one other case, a woman received two doses of Herceptin just prior to conception. Table 1 summarizes the key features of these 11 cases including the gestational ages at which Herceptin was given, the gestational age at which oligo- or anhydramnios was diagnosed, concomitant chemotherapies, whether the patient was dechallenged or rechallenged with Herceptin, and the pregnancy outcome.

RECOMMENDATIONS

1. The pregnancy category for Herceptin (trastuzumab) should be changed to a "D" based on the available human data that suggest a possible teratogenic effect leading to oligohydramnios.

2. The pregnancy portion of the Herceptin label should include information about the known cases of oligohydramnios that occurred with use of Herceptin during pregnancy.

3. The label should recommend that pregnant women using Herceptin undergo screening for oligohydramnios with obstetrical ultrasound examination at regular intervals.

4. If oligohydramnios occurs, the obstetrician should begin fetal testing appropriate for the gestational age of the fetus and consistent with the standards of care for the community. This testing should continue on a regular basis until one of two conditions is met:

    a. Herceptin therapy is discontinued and oligohydramnios resolves
    b. Delivery.

5. In cases where the physician and patient decide to continue Herceptin therapy for maternal reasons despite the presence of oligohydramnios, additional intravenous hydration should be considered. With other forms of chemotherapy during pregnancy, transient oligohydramnios has been observed, and extra hydration sometimes mitigates this effect.

6. Include contact information for the Cancer and Childbirth Registry and encourage enrollment of pregnant patients using Herceptin.

   (Refer to Appendix E for consult)

7.1.15 Assessment of Effect on Growth

There is no information on the use of this drug in children. The indication supported by this application occurs exclusively in adults.

7.1.16 Overdose Experience

There was no report of overdose in the sBLA application.

7.1.17 Postmarketing Experience

See section 7.1.14.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Raw and Derived Datasets Reviewed	
Safety Review	Efficacy Review
AE (adverse event)	EFEX (Efficacy and special safety assessments)
CAB (Cardiac Advisory Board Review)	EFEXLVEF (LVEF)
CHEMOTX (Prior chemotherapy)	EFEXRE (radiological exam)
DEMO (demographic data)	EFFEXSURV (disease recurrence and survival)
DIAG (previous and current diseases)	* CARDIAC (cardiac\LVEF data)
DIED (Death information)	* CARDIC 2 (secondary cardiac LVEF, CAB)
EFEXCE (Cardiac Event)	*PAT (efficacy analysis data)
EFEXCQ (cardiac questionnaire)	
EXCL (Exclusions)	
EXIT (study completion/discontinuation	
HORMTX (hormone therapy)	
LABP (Laboratory results)	
MEDO (previous and concomitant treatment)	
MEDT (Study drug	

administration)	

* Derived data

In addition source documentation included CRFs and narrative summaries.
Exposure data to drug was adequate to provide safety information. Refer to section 1.3.3.

7.2.1.1 Study type and design/patient enumeration

Refer to section 6.1.3 Study Design

7.2.1.2 Demographics

The characteristics of both the 1-year Herceptin and observation group were well balanced. Most patients were a median age of 49 years (range 21-80), Caucasian (83%), postmenopausal (45%), and had node negative disease with no neoadjuvant chemotherapy (33%). Tumor characteristics were mostly commonly reported was infiltrating ductal (95%), tumor grade 3 (60%), estrogen and progesterone receptor negative (48%), and HER2 status IHC 3+ (79%). Primary surgery most often performed was a modified radical mastectomy (48%). Median clinical tumor size was 40 mm and median pathological size was 22 mm. The chemotherapy most commonly received was anthracyclines with no taxanes (68%) and radiotherapy (77%). Tamoxifen alone was the most commonly received adjuvant endocrine therapy (31%).

7.2.1.3 Extent of exposure (dose/duration)

Refer to section 1.3.3 Safety, Table 1. Duration of Herceptin in the Randomized Treatment for Efficacy.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Post-marketing/AERS (adverse events reporting system) reports were reviewed for this application. Cross-reference section 7.1.4 Interstitial Lung Disease (ILD) and section 7.1.14 Human Reproduction and Pregnancy Data and oligohydramnios.

7.2.2.1 Other studies

There are no other studies.

7.2.2.2 Postmarketing experience

A periodic safety update report (PSUR) was included in the submission for Herceptin. The dates of surveillance spanned February 14, 2006-November 16, 2006. Summary of changes included new indication for use in early breast cancer in node0positive disease following doxorubicin and cyclophosphamide. From this adjuvant study information was updated regarding LVEF assessment, adverse events were updated. No new safety signals were reported. Information of the risk of cardiac dysfunction in patients over 65 was updated . Dose modification section was added to include information on dose modification performed during early breast cancer trials.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects had exposure to drug to provide safety information.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing
Not applicable to this efficacy supplement.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate. Refer to section 6.1.3 Schedule of Assessments.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No drug-drug interactions were conducted or necessary during study BO16348 (HERA).

7.2.8 Assessment of Quality and Completeness of Data

The following statements regarding data quality and completeness with regard to adverse event evaluation and toxicity grading are pertinent to the review of this application:

- The study was open labeled, which could lead to over and/or under reporting of toxicities in both treatment arms. The extent to which observed toxicities concurred with the investigator's pre-study bias, whether seen on the treatment or observation arm could have influenced reporting. It is not possible to estimate the magnitude of this potential bias.

- Although the schedule of assessments was identical to both arms, subjects in the Herceptin arm had the opportunity to report symptoms more often in conjunction with the infusion appointment (every three weeks).

- Collection of data post 52 weeks dropped off considerably and unable to draw clinically meaningful conclusions.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted a 120-day safety update at the FDA's request. The safety update of subjects who experienced adverse events after the data cutoff period of the original 21 December 2006 sBLA submission. This safety update included subsequent safety data on subjects from the HERA clinical trial who were randomized to the observation and 1-year Herceptin arms as captured in the 31 October 2006 F. Hoffman-La Roche clinical database. Revised narratives and corresponding case report forms (CRFs) for 31 patients who experienced adverse events were included in the update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Cardiac

Adverse events considered to be related to study drug and consistent with known toxicity include; ejection fraction decreased Herceptin arm 3.5% (54/1678) in comparison to observation 0.6% (11/1708), cardiac failure congestive Herceptin 2% (30/1678) in comparison to observation 0.3% (5/1708), cardiac failure Herceptin arm 0.55% (9/1678) in comparison to observation 0.2% (4/1708). Cardiomyopathy reported in the Herceptin arm only, as 0.12% (2/1678). In addition the incidence of hypertension on study drug was twice that of the observation arm 4% (64/1708) in comparison to 2% (35/1708).

Limitation of Data
The data on long-term follow-up in the one year Herceptin arm will be inconclusive as the HERA study allowed for re-randomization of subjects to the two year arm through protocol amendment E, which post dates database closure for the one year arm.

Subjects who were followed in the secondary cardiac endpoint were originally coded to be captured using New York Heart Association (NYHA) classification system. Amendment D, which was approved in November of 2003, changed the coding criteria for the secondary cardiac endpoint. Significant and asymptomatic drops in LVEF would be graded in NCI-CTC version 2 instead of the NYHA classification system. Prior to amendment D 1700 subjects were enrolled into the HERA study per the applicant. The CRF form and instructions to the investigators were not changed to reflect the change in coding with amendment D. This discrepancy was noticed by the Reviewer during coding accuracy check measuring AEs reported in the adverse event dataset against the narratives of the subjects in the cardiac endpoints. As a result, data for asymptomatic subjects that were in the secondary cardiac endpoint continued to be coded in the NYHA classification system, resulting in ongoing protocol violations. Therefore, coding was at the discretion of the investigator. In NCI-CTC version 2, coding would have allowed for a more objective measurement of response based on specific criteria for decrease in LVEF measurement. Asymptomatic subjects in the secondary endpoint did not require confirmation of NYHA class by a cardiologist as required for the symptomatic subjects in the endpoint. The integrity of the data in the secondary endpoint was compromised. The data was not able to be changed post hoc by the applicant and therefore question of validity was discussed with the applicant and the utilization of the information for labeling.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Data from BO16348 (HERA) were reviewed to assess the overall frequency of adverse events for subjects treated with Herceptin as contrasted with those in the observation comparator arm. In addition, these results were compared to summaries of data from the legacy studies, the current product label, and post marketing safety updates. There was no pooling of data from these sources.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The basis for this regimen relies heavily on the applicant's identification of the minimum effective trough level in non-clinical animal models; the doses selected to be administered every three weeks were designed to achieve and maintain trough levels at or above this proposed threshold. The sponsor did not provide clinical study data to address the dose-response or dose-toxicity relationships according to this every 21 day schedule. However there is substantial experience with this regimen off-label which indicate that this schedule is tolerable. This is the first clinical trial reviewed by FDA to establish the safety and

efficacy of this every three week dosing regimen. The application does not contain the results of clinical studies evaluating the comparative safety and activity of this regimen with the approved regimen.

In addition to the clinical study results characterizing safety and efficacy of this dosing regimen, the application contains pharmacokinetic data from three trials (see table below, reproduced from Dr. Angela Men's) which characterize the pharmacokinetic profile of this dosing regimen, assess for pharmacokinetic interactions between Herceptin and taxane chemotherapeutic agents, and assess for pharmacokinetic interactions between the Herceptin and serum levels of shed target antigen (extracellular domain of the HER2/*neu* receptor).

Table Clinical Studies for which Pharmacokinetic Data were provided in the Application

Study	Design	Subjects	N	Dose/Schedule
BO16348 (HERA)	Phase 3, open-label, randomized, multi-center	Women with HER2(+), early-stage, node+ or high-risk node- breast cancer	3386 (PK-44)	8 mg/kg loading dose followed by 6mg/kg q3w
WO16229	Phase 2, open-label, single-arm	Women with metastatic breast cancer with HER2 overexpression/amplification (IHC3+ and/or FISH+)	105	8 mg/kg loading dose followed by 6mg/kg q3w
BO15935	Phase 1/2 open-label,	Women with metastatic breast cancer with HER2 overexpression/amplification (IHC2+ or 3+ or FISH+)	32	8 mg/kg loading dose on Day1 followed by 6mg/kg q3w with/without paclitaxel

8.2 Drug-Drug Interactions

No drug-drug interactions were conducted or necessary during study BO16348 (HERA)..

8.3 Special Populations

This efficacy supplement contained no specific studies to evaluate dosing based on race, gender, age or major organ impairment. No data from study BO16348 (HERA) suggested dosing should be modified based on demographic characteristics.

8.4 Pediatrics

A waiver for pediatric studies under PREA is granted in this application because the indication sought is for a condition which does not occur in children.

8.5 Advisory Committee Meeting

The review team, including this reviewer, decided not to present the findings in the application to the Oncologic Drugs Advisory Committee for the following reasons: 1)the effects of Herceptin on the primary endpoint, DFS, and related secondary endpoints were both clinically relevant, highly significant, and internally consistent across relevant subgroups. In addition, this study replicates the findings of an early supplemental application (BL STN 103792.5150) for essentially the same indication; 2) the primary endpoint, prolongation of disease-free survival, is considered an appropriate and feasible measure of clinical benefit for adjuvant treatment of solid tumors, including breast cancer; and 3) there were no safety signals that were considered to outweigh the clinical benefit demonstrated.

8.6 Literature Review

A review of published literature was performed to identify cases of pregnancy in women receiving Herceptin therapy. These data are reviewed in detail in the consultant review memo of August 17, 2007, by Dr. Karen Feibus of the Maternal/Fetal Health team and are summarized /abstracted in Section 7.1.14 of this review.

8.7 Postmarketing Risk Management Plan

Consultation provided by the Office of Surveillance and Epidemiology (Dr. Allen Brinker) and by the Maternal and Fetal Health Team (Dr. Karen Feibus). Upon review of the post-marketing information and identification of additional cases of oligohydramnios both in the literature and in spontaneous post-marketing reports submitted to AERS, and as summarized in Section 7.1.14 of this review, both the consultants and the clinical reviewers requested that Genentech provide a post-marketing commitment to further investigate the outcomes and management of the pregnancy in women taking Herceptin. Genentech originally proposed (b) (4)
The clinical reviewer and consultants agreed that such a study would be useful but would not be sufficient to provide data on outcomes due to the expected low incidence of Herceptin use in pregnancy women and (b) (4)

In subsequent discussions, Genentech modified their plan (b) (6) and agreeing to develop a protocol for data collection through an established registry system. The PMC is summarized in Section 1.2.1.

In addition, product labeling has been revised to include the available data and to provide guidance on additional monitoring for the presence and progression of oligohydramnios in pregnant women receiving Herceptin.

8.8 Other Relevant Materials

There were no additional studies, including actual use, labeling comprehension studies and marketing studies, were considered in this review.

Consultation on product labeling was requested from the Division of Division of Drug Marketing, Advertising, and Communication (DDMAC). For details, refer to the consult memo generated by Carole Broadnax Ph.D. All of the recommended changes to product labeling were incorporated into final product labeling.

Protocols have been requested for the evaluation of the impact of Herceptin on the QTc interval and for the evaluation of effects of current/recent Herceptin use on pregnancy. These protocols will be submitted post-approval, under PMCs described in Section 1 of this review. Consultation on these proposed studies will be obtained upon submission of the draft/final protocols.

9. OVERALL ASSESSMENT

9.1 Conclusions

The recommendation for approval is based on the results of two arms out of a three arm study BO16348 (HERA), 1-year Herceptin versus observation only. HERA is single, randomized, open label, phase III, multicenter study conducted outside the United States. A total of 3386 women were randomized between the two arms and demonstrated clinically important and statistically significant prolongation to disease free survival (DFS). Two years of survival follow-up demonstrated a statistically significant advantage of an absolute difference in 2-year K-M estimated DFS as 7.6% advantage to the 1-year Herceptin arm ($p<0.0001$ based on log-rank test; hazard ratio=0.54, 95%CI=[0.44, 0.67]).

9.2 Recommendation on Regulatory Action

Approval is recommended for the following indication: Herceptin for use as a single agent, for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR negative or with one high-risk feature) or node-positive breast cancer, following multi-modality anthracycline based therapy.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Post marketing identification of an increased number of cases of oligohydramnios in pregnancy with trastuzumab and level of evidence in case reports (positive dechallenge and rechallenge) was cause to change the pregnancy category from B to D. A post marketing commitment by the applicant was agreed upon to submit a protocol for a prospectively and actively enrolled pregnancy registry that will collect information assessing pregnancy complications, and birth outcomes in women with breast cancer exposed to a Herceptin containing regimen (refer to section 1.2.1).

9.3.2 Required Phase 4 Commitments

The Applicant is to provide a final clinical study report (CSR) of the safety and efficacy of 2-years of Trastuzumab treatment in Study BO16348 (HERA)in order to provide a final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility (refer to section 1.2.3)

To conduct a QT study according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in approximately 50 subjects receiving trastuzumab (refer to section 1.2.3).

9.4 Labeling Review

Implementation of the Physician's Labeling Rule (21 CFR 201.57) required extensive format and content changes to the label. A copy of the original proposed label is attached as an appendix. There were labeling negotiations with the Applicant, and the final version of the label is also attached.

Summary of the Major Changes to Herceptin Label

Highlights Section

- Condensed to half a page

Black Box Warning

- Addition of interstitial pnuemonitis

Indications and Usage

- Revised to include adjuvant breast cancer as a single agent for node positive and node negative (ER/PR negative or with one high risk feature) following multi- modality anthracyclines based therapy

Dosage and Administration

- New dose and schedule of administration added to adjuvant breast cancer (2.1)
- Revised instructions for overall dose modification (2.2)

Warning and Precautions

- Under Cardiomyopathy; hypertension and arrhythmias added, revised cardiac monitoring (5.1)
- Table 1: Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies. And Table 2: Incidence of Cardiac Dysfunction* in Metastatic Breast Cancer Studies replaced text in Cardiomyopathy (5.1)
- Under pulmonary toxicity; interstitial pnuemonitis added (5.4)
- Embryo-fetal toxicity pregnancy category changed to D and updated information on oligohydramnios (5.6)

Adverse Reactions

- New Table 3, updated adverse reactions by MedDRA preferred term (6.1)
- New Table 5, Per-patient Incidence of New Onset Myocardial Dysfunction (by LVEF) Studies 1, 2 and 3 (6.1)
- New Figure 1, Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of $\geq$10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Even (6.1)

- New Figure 2, Study 3: Cumulative Incidence of Time to First LVEF Decline of ≥10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Even (6.1)

Postmarketing Experience
- Oligohydramnios (6.3)

Use in Specific Populations
- Pregnancy category changed to D (8.1)

Clinical Studies
- Study 3, BO16348 (HERA) added (14.1)
- Table 6, Efficacy Results from Adjuvant Treatment of Breast Cancer (Studies 1 + 2 and Study 3) (combined information across adjuvant studies into one table). (14.1)
- Table 7, Treatment Outcomes in Studies 2 and 3 as a Function of HER2 Overexpression or Amplification (combined information across adjuvant studies into one table). (14.1)
- Table 8. Study 4: Efficacy Results in First-Line Treatment for Metastatic Breast Cancer (replaced former table 12). (14(b)(4))

(b) (4)

Patient Counseling information section 17 new:
- Encourage pregnant women who are using Herceptin to enroll in the Cancer and Childbirth Registry

9.5 Comments to Applicant
No additional comments to the applicant were provided.

10.0 APPENDICES

10.1 Review of Individual Study Reports
Study BO16348 (HERA) was the only study with supporting datasets reviewed for this application. The review discusses the data from this study in depth. FDA reviews of legacy study reports were also reviewed (STN 103792.0, STN 103792/5150).

10.2 Line-by-Line Labeling Review
Substantive changes are summarized in section 9.4. FDA has recommended the following major changes in the content of the originally proposed label for this submission: (Refer to Appendix F and G)

Overall changes in the content of most sections, including (b) (4) were made pursuant to the Physician Labeling Rule (21 CFR 201.57)

Black Box Warning inclusive of interstitial pneumonitits under Infusion reactions, Pulmonary Toxciity:
Infusion reactions, Pulmonary toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Indications and Usage in section 1.1 revised to include use as a single agent in adjuvant breast cancer.
As a single agent, for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR negative or with one high-risk feature) or node-positive breast cancer, following multi-modality anthracycline based therapy.

Dosage and Administration in section 2.1 revised to include new dose schedule in adjuvant breast cancer.
New dose and schedule of administration added to adjuvant breast cancer (2.1)
Initiate Herceptin following completion of all chemotherapy. Administer Herceptin at an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg every three weeks for a total of 17 doses (52 weeks of therapy). Administer all doses ≥4 mg/kg as 90 minute intravenous infusions.

Dose modification section 2.2, for cardiomyopathy revised for clarity:
Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the following:

- *≥ 16% absolute decrease in LVEF from pre-treatment values*
- *LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.*
- *Herceptin may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤ 15%.*
- *Permanently discontinue Herceptin for a persistent (> 8 weeks) LVEF decline or for suspension of Herceptin dosing on more than 3 occasions for cardiomyopathy.*

Warnings and precautions section 5.1, added Table 1 and 2 in place of text

Table 1
Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

		Incidence	
Study	Event	Herceptin	Control
1 & 2	Congestive heart failure*	2% (32/1677)	0.4% (7/1600)
3	Congestive heart failure	2% (30/1678)	0.3% (5/1708)

*Includes 1 patient with fatal cardiomyopathy.

Table 2
Incidence of Cardiac Dysfunction* in Metastatic Breast Cancer Studies

		Incidence			
		NYHA I-IV		NYHA III-IV	
Study	Event	Herceptin	Control	Herceptin	Control
4 (AC)	Cardiac Dysfunction	28%	7%	19%	3%
4 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
5	Cardiac Dysfunction**	7%	N/A	5%	N/A

* Congestive heart failure or significant asymptomatic decrease in LVEF

** Includes 1 patient with fatal cardiomyopathy.

Warnings and precautions section, 5.4 Pulmonary Toxicity, added new safety finding interstitial pnuemonitis:
Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis.

Warning and Precautions section, 5.6 Embryo-Fetal Toxicity, pregnancy category changed from B to D and updated information on oligohydramnios:

Embryo-Fetal Toxicity (Pregnancy Category D)
Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case reports suggest that Herceptin use during pregnancy increases the risk of oligohydramnios during the second and third trimesters. If Herceptin is used during pregnancy or if a woman becomes pregnant while taking Herceptin, she should be apprised of the potential hazard to a fetus.

Adverse Reactions section, 6.1 Clinical trials experience, new Table 3 of updated adverse reactions by MedDRA preferred term.

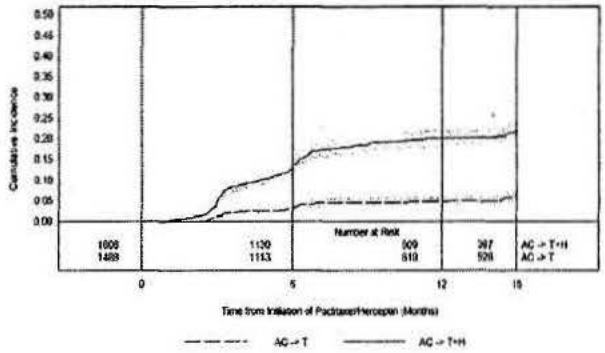
Adverse Reactions section, 6.1 Clinical trials experience, new Table 5, Per-patient Incidence of New Onset Myocardial Dysfunction (by LVEF) Studies 1, 2 and 3:

Table 5
Per-patient Incidence of New Onset
Myocardial Dysfunction (by LVEF) Studies 1, 2 and 3

Criteria	Studies 1 and 2		Study 3	
	AC-TH (n=1606)	AC-T (n=1488)	Herceptin (n=1678)	Observation (n=1708)
Post-baseline LVEF <50%	22.8% (366)	9.1% (136)	8.6% (144)	2.7% (46)
LVEF<50% and ≥10% decrease from baseline	18.3% (294)	5.4% (81)	7.0% (118)	2.0% (35)
LVEF<50% and ≥16% decrease from baseline	11.7% (188)	2.2% (33)	3.8% (64)	1.2% (20)
LVEF absolute decrease of ≥10%, <20%	33.4% (536)	18.3% (272)	22.4% (376)	11.9% (204)
LVEF absolute decrease ≥20%	9.2% (148)	2.4% (36)	3.5% (59)	1.2% (21)

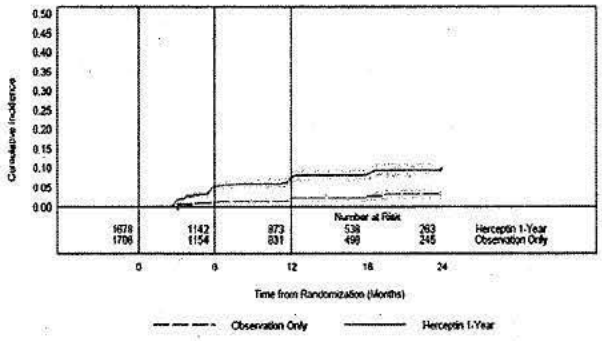
Adverse Reactions section, 6.1 Clinical trials experience, new Figure 1, Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of ≥10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event:

Figure 1
Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of ≥10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Adverse Reactions section, 6.1 Clinical trials experience, new Figure 2, Study 3: Cumulative Incidence of Time to First LVEF Decline of ≥10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event:

Figure 2
Study 3: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Postmarketing Experience section 6.3, oligohydramnios added.

Use in Specific Populations, section 8.1 Pregnancy Category, changed to D:

Pregnancy
Teratogenic Effects: Category D [see Warnings and Precautions (5.6)]

Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case reports suggest that Herceptin use during pregnancy increases the risk for oligohydramnios during the second and third trimester. If Herceptin is used during pregnancy or if a woman becomes pregnant while taking Herceptin, she should be apprised of the potential hazard to a fetus.

In the postmarketing setting, oligohydramnios was reported in women who received Herceptin during pregnancy, either alone or in combination with chemotherapy. In half of these women, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin was resumed after the amniotic fluid index improved, and oligohydramnios recurred.

Women using Herceptin during pregnancy should be monitored for oligohydramnios. If oligohydramnios occurs, fetal testing should be done that is appropriate for gestational age and consistent with community standards of care. Additional intravenous (IV) hydration has been helpful when oligohydramnios has occurred following administration of other chemotherapy agents, however the effects of additional IV hydration with Herceptin treatment are not known.

Clinical Studies section 14.1, Study 3, BO16348 (HERA) added:
In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory. Patients with node-negative disease were required to have ≥ T1c primary tumor. Patients with a history of congestive heart failure or LVEF <55%, uncontrolled arrhythmias, angina requiring medication clinically significant valvular heart disease, evidence of transmural infarction on ECG, poorly controlled hypertension (systolic > 180 mm Hg or diastolic > 100 mm Hg) were not eligible.

Patients were randomized (1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy; to receive no additional treatment (n = 1693) or 1 year of Herceptin treatment (n = 1693). Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator discretion. Herceptin was administered with an initial dose of 8 mg/kg followed by

subsequent doses of 6 mg/kg once every three weeks for a total of 52 weeks. The primary endpoint was disease-free survival (DFS), defined as in Studies 1 and 2.

Among the 3386 patients randomized to the two treatment arms, the median age was 49 years (range 21–80), 83% were Caucasian, and 13% were Asian. Disease characteristics: 94% infiltrating ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32% node negative, and in 11% of patients, nodal status was not assessable due to prior neo-adjuvant chemotherapy. Ninety-six percent (1055/1098 of patients with node-negative disease had high-risk features: among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and 47% (512) were ER and or PgR + and had at least one of the following high-risk features: pathological tumor size greater than 2 cm, Grade 2–3, or age < 35 years. Prior to randomization, 94% of patients had received anthracycline-based chemotherapy regimens.

Clinical Studies section 14.1 Table 6, Efficacy Results from Adjuvant Treatment of Breast Cancer (Studies 1 + 2 and Study 3). Combined information across adjuvant studies into one table:

Table 6
Efficacy Results from Adjuvant Treatment of
Breast Cancer (Studies 1 + 2 and Study 3)

	Study 1 + 2		Study 3	
	AC→ Herceptin + T (n =1872)	AC→ T (n = 1880)	Chemo→ Herceptin (n =1693)	Chemo→ Observation (n = 1693)
Primary Endpoint				
DFS events	133	261	127	219
Hazard ratio (95% CI)	0.48[a] (0.39, 0.59)		0.54 (0.44, 0.67)	
p-value	< 0.0001[b]		< 0.0001[c]	
Secondary Endpoints				
Deaths	62	92	31	40
Hazard ratio 95% CI	0.67		0.75	
p-value	NS[d]		NS[d]	

CI = confidence interval.
[a] Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.
[b] stratified log-rank test.
[c] log-rank test.
[d] NS= non-significant.

Clinical Studies section 14 Table 7, Treatment Outcomes in Studies 2 and 3 as a Function of HER2 Overexpression or Amplification. Combined information across adjuvant studies into one table:

Table 7
Treatment Outcomes in Studies 2 and 3 as a Function of HER2 Overexpression or Amplification

HER2 Assay Result*	Study 2 Number of Patients	Study 2 Hazard Ratio DFS (95% CI)	Study 3 Number of Patients	Study 3 Hazard Ratio DFS (95% CI)
IHC 3+				
FISH (+)	1170	0.42 (0.27, 0.64)	91	0.56 (0.13, 2.50)
FISH (−)	51	0.71 (0.04, 11.79)	8	----
FISH Unknown	51	0.69 (0.09, 5.14)	2258	0.53 (0.41, 0.69)
IHC < 3+ / FISH (+)	174	1.01 (0.18, 5.65)	299 ^	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	----	------	724	0.59 (0.38, 0.93)

* IHC by HercepTest, FISH by PathVysion as performed at a central laboratory.

^ All cases in this category in study 3 were IHC 2+ .

Clinical Studies section 14 Table 8. Study 4: Efficacy Results in First-Line Treatment for Metastatic Breast Cancer (replaced former table (b)(4):

Table 8
Study 4: Efficacy Results in
First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemo-therapy (n = 235)	All Chemo-therapy (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC[a] (n = 143)	AC (n = 138)
Primary Endpoint						
Median TTP(mos)[b,c]	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value[d]	< 0.0001		< 0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value[e]	< 0.001		< 0.001		0.10	
Median Resp Duration (mos)[b,c]	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% quartile	6, 15	4, 8	5 ,11	4, 7	6, 15	4, 8
Med Survival (mos)[c]	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value[d]	0.05		0.17		0.16	

[a] AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate.
[d] log-rank test.
[e] $\chi 2$-test.

(b) (4)

Patient Counseling Information section 17, new:

- Advise patients to contact a health care profession immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of morethan 5 pounds in 24 hours, dizziness or loss of consciousness.
- Advise women with reproductive potential to use effective contraceptive methods during treatment and for a minimum of six months following Herceptin.
- Encourage pregnant women who are using Herceptin to enroll in the Cancer and Childbirth Registry .

Appendix A Correspondence to Applicant from Breast International Group (B.I.G.)

B.I.G.-aisbl Secretariat
Jules Bordet Institute
Boulevard de Waterloo 121, 7th Fl
1000 Brussels Belgium
Tel: 32 2 541 33 04
Fax: 32 541 3199
BIG@bordet.be
www.breastinternationalgroup.org

Dr. Leonard Reyno
Medical Director
Herceptin
Genentech Inc.
460 Point San Bruno Blvd
South San Francisco (California) 94080-4990
United States of America

Brussels 30 June 2006

Dear Dr. Reyno,

It was nice to talk to you on the phone.
We truly want to help Genentech as much as we can with the filing of adjuvant trastuzumab in the US. Unfortunately, complying with the FDA request would require us to go against the charter and recommendations of our own IDMC.

Currently,
1) The IDMC minutes are confidential. They were written and approved by the members of the committee with this understanding. We would have to convene a special session of the IDMC to consider the request and prepare excerpted minutes, as the trial is still ongoing for the 1-year versus 2-year comparison. This would violate the terms of the IDMC charter and require substantial effort and inconvenience for all concerned.
2) The IDMC has recommended that the 2-year trastuzumab arm data remain blinded. Release of 2- year data by the Executive and Steering Committees would be contrary to the recommendation of the IDMC.

The next meeting of our HERA IDMC will take place in December 2006. There is a plan to look at interim efficacy data of the 2-year versus 1-year comparison at that time.

I am sorry that I can not be of greater help at this time.

Please do not hesitate to contact me again if needed.

Yours sincerely,

Martine Piccart, MD, PhD
Breast International Group (BIG)-aisbl
Jules Bordet Institute
Boulevard de Waterloo 121/7th floor
1000 Brussels-Belgium
tel: +32 (0)2 541 33 04
fax:+32 (0)2 541 31 99

CC: Richard Gelber, Carolyn Straehle, Stella Dolci, Eleanor McFadden

DEC2006

Appendix B Footnotes to study BO16348 (HERA) Inclusion Criteria

[A] Margins of the resected specimen had to be histologically free of invasive adeno-carcinoma and ductal carcinoma in situ (DCIS). Lobular carcinoma in situ (LCIS) did not count as a positive margin. Exception: Patients who had 'non-resectable' deep margin invasion were eligible provided they had had radiotherapy encompassing the region concerned. Patients with histologically documented infiltration of the skin (pT4) were eligible provided they had undergone radiotherapy encompassing the tumor bed.
[B] Node positive patients/adjuvant chemotherapy: Axillary dissection was mandatory. Sentinel node sampling was allowed provided that axillary dissection followed confirmation of a positive sentinel node(s). Node positive patients/neo-adjuvant chemotherapy: Axillary dissection was also mandatory in patients achieving "complete clinical response" after neo-adjuvant chemotherapy. Sentinel node sampling alone was NOT acceptable after neo-adjuvant chemotherapy; if used it must always have been followed by a complete axillary dissection. In patients receiving neo-adjuvant chemotherapy lymph node status was to be considered unknown, regardless of the results of post-chemotherapy axillary dissection.
[C] Node negative patients: Sentinel node and/or axillary dissection were acceptable.
[D] All locally positive HER2 tests must have been reconfirmed by the central laboratory prior to patient entry, by submission of a tumor block or slides from the participating sites. The central lab used the following methods for confirmation: Local 2+ by IHC or local FISH confirmed by FISH (PathVysion, Vysis); local IHC 3+ confirmed by IHC (HercepTest, DAKO).
[E] As part of screening patients did not need to consent to central reconfirmation of HER2 status. A written informed consent had to be obtained prior to randomization in the actual HERA study.
[F] Primary surgery aiming at resection of the tumor bed was also mandatory for patients achieving a "clinical complete response" after neo-adjuvant chemotherapy.
[G] Patients receiving neoadjuvant therapy had to have HER2 confirmation on a sample of their tumor that was obtained PRIOR to starting neoadjuvant chemotherapy. Post/during chemotherapy tissue samples were not to be used to establish HER2 over-expression for eligibility.
[H] Applied only for patients with negative nodes.

Appendix C Footnotes to study BO16348 (HERA) Exclusion Criteria

[A] Previous history of ductal carcinoma in situ (DCIS) of the breast was not an exclusion criterion.
[B] For radiotherapy planning and dose details, please refer to Protocol Section 5.1.4
[C] Clinical suspicion of supraclavicular lymph node involvement must be accompanied by a negative fine needle aspirate (FNA) or biopsy in order to be eligible.
[D] Patients may have participated in a (neo-) adjuvant chemotherapy trial prior to enrollment in the HERA trial, provided that the chemotherapy trial was approved by the HERA Executive Committee, and that patients comply with the HERA treatment and follow-up schedule.
[E] As judged by the investigator.
[F] Patients with hypertension which was well controlled on medication were eligible.
[G] Women of child bearing potential must have had a negative pregnancy test (urine or serum) within 7 days prior to randomization and/or Herceptin treatment (see Protocol section 7.2.5 and 7.5.4 for details).
[H] Examples of adequate contraceptive measures are intra-uterine device, barrier method (condoms, diaphragm), also in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives were not indicated in this patient population.

Appendix D Adverse Events Table for BO16348 (HERA) by Preferred Term

All Adverse events Grades 1-4 for HERA Study by Preferred Term

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
HEADACHE	49	2.87	162	9.65	3	0.18	4	0.24
ARTHRALGIA	98	5.74	137	8.16	3	0.18	4	0.24
NASOPHARYNGITIS	43	2.52	135	8.05	0	0.00	0	0.00
FATIGUE	44	2.58	128	7.63	0	0.00	4	0.24
DIARRHOEA	16	0.94	123	7.33	0	0.00	5	0.30
NAUSEA	19	1.11	108	6.44	1	0.06	2	0.12
PYREXIA	6	0.35	100	5.96	0	0.00	1	0.06
HOT FLUSH	84	4.92	98	5.84	2	0.12	5	0.30
BACK PAIN	58	3.40	91	5.42	3	0.18	3	0.18
CHILLS	0	0.00	85	5.07	0	0.00	3	0.18
COUGH	34	1.99	81	4.83	0	0.00	1	0.06
OEDEMA PERIPHERAL	37	2.17	79	4.71	0	0.00	1	0.06
ASTHENIA	30	1.76	75	4.47	0	0.00	1	0.06
INFLUENZA	9	0.53	70	4.17	0	0.00	3	0.18
RASH	10	0.59	70	4.17	0	0.00	0	0.00
HYPERTENSION	35	2.05	64	3.81	5	0.29	11	0.66
MYALGIA	17	1.00	63	3.75	1	0.06	3	0.18
PAIN IN EXTREMITY	45	2.63	60	3.58	0	0.00	1	0.06
DIZZINESS	29	1.70	60	3.58	1	0.06	3	0.18
VOMITING	10	0.59	58	3.46	2	0.12	6	0.36
EJECTION FRACTION DECREASED	11	0.64	58	3.46	0	0.00	0	0.00
INSOMNIA	31	1.81	58	3.46	0	0.00	1	0.06
DYSPNOEA	26	1.52	57	3.40	1	0.06	1	0.06
DEPRESSION	35	2.05	51	3.04	1	0.06	5	0.30
BONE PAIN	26	1.52	49	2.92	1	0.06	1	0.06
PALPITATIONS	12	0.70	48	2.86	0	0.00	0	0.00
UPPER RESPIRATORY TRACT INFECTION	20	1.17	46	2.74	0	0.00	0	0.00
MUSCLE SPASMS	3	0.18	46	2.74	0	0.00	0	0.00
CHEST PAIN	22	1.29	45	2.68	0	0.00	2	0.12
NAIL DISORDER	0	0.00	43	2.56	0	0.00	0	0.00
URINARY TRACT INFECTION	13	0.76	42	2.50	0	0.00	2	0.12
LYMPHOEDEMA	40	2.34	42	2.50	0	0.00	1	0.06
ABDOMINAL PAIN	16	0.94	41	2.44	2	0.12	1	0.06
INFLUENZA LIKE ILLNESS	3	0.18	40	2.38	0	0.00	0	0.00
ANXIETY	19	1.11	40	2.38	1	0.06	0	0.00
PRURITUS	10	0.59	40	2.38	0	0.00	0	0.00
RHINITIS	6	0.35	36	2.15	0	0.00	0	0.00
ONYCHORRHEXIS	1	0.06	36	2.15	0	0.00	0	0.00
CONSTIPATION	17	1.00	33	1.97	1	0.06	0	0.00
PHARYNGOLARYNGEAL PAIN	8	0.47	32	1.91	0	0.00	0	0.00
CARDIAC FAILURE	5	0.29	30	1.79	0	0.00	7	0.42

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
CONGESTIVE								
DYSPEPSIA	9	0.53	30	1.79	0	0.00	0	0.00
SHOULDER PAIN	28	1.64	30	1.79	1	0.06	1	0.06
ABDOMINAL PAIN UPPER	15	0.88	29	1.73	0	0.00	1	0.06
WEIGHT INCREASED	17	1.00	29	1.73	1	0.06	1	0.06
PARAESTHESIA	11	0.64	29	1.73	0	0.00	0	0.00
STOMATITIS	1	0.06	26	1.55	0	0.00	0	0.00
SINUSITIS	5	0.29	26	1.55	0	0.00	1	0.06
CHEST WALL PAIN	24	1.41	26	1.55	1	0.06	0	0.00
VERTIGO	7	0.41	25	1.49	0	0.00	0	0.00
BREAST PAIN	19	1.11	25	1.49	0	0.00	0	0.00
EPISTAXIS	1	0.06	25	1.49	0	0.00	0	0.00
RHINORRHOEA	5	0.29	24	1.43	0	0.00	0	0.00
ERYTHEMA	7	0.41	24	1.43	0	0.00	0	0.00
PHARYNGITIS	9	0.53	22	1.31	0	0.00	0	0.00
DYSPNOEA EXERTIONAL	15	0.88	21	1.25	1	0.06	0	0.00
TACHYCARDIA	5	0.29	20	1.19	0	0.00	1	0.06
GASTRITIS	11	0.64	20	1.19	0	0.00	0	0.00
CHEST DISCOMFORT	2	0.12	20	1.19	0	0.00	0	0.00
BRONCHITIS	9	0.53	19	1.13	0	0.00	0	0.00
CYSTITIS	11	0.64	19	1.13	0	0.00	0	0.00
OEDEMA	7	0.41	18	1.07	0	0.00	0	0.00
HERPES ZOSTER	9	0.53	18	1.07	1	0.06	1	0.06
MUSCULOSKELETAL PAIN	11	0.64	17	1.01	2	0.12	0	0.00
DYSURIA	2	0.12	17	1.01	0	0.00	0	0.00
DRY SKIN	2	0.12	16	0.95	0	0.00	0	0.00
PAIN	8	0.47	15	0.89	1	0.06	0	0.00
OSTEOPOROSIS	13	0.76	15	0.89	2	0.12	0	0.00
NECK PAIN	12	0.70	15	0.89	0	0.00	0	0.00
ACNE	2	0.12	15	0.89	0	0.00	0	0.00
CONJUNCTIVITIS	5	0.29	14	0.83	0	0.00	0	0.00
AXILLARY PAIN	11	0.64	14	0.83	0	0.00	0	0.00
BLOOD PRESSURE INCREASED	3	0.18	14	0.83	1	0.06	1	0.06
OSTEOARTHRITIS	9	0.53	14	0.83	1	0.06	0	0.00
LETHARGY	7	0.41	14	0.83	0	0.00	1	0.06
SCAR PAIN	10	0.59	14	0.83	0	0.00	0	0.00
DRY MOUTH	6	0.35	13	0.77	0	0.00	0	0.00
MALAISE	0	0.00	13	0.77	0	0.00	1	0.06
NASAL DRYNESS	0	0.00	13	0.77	0	0.00	0	0.00
ECZEMA	5	0.29	13	0.77	0	0.00	0	0.00
MUCOSAL INFLAMMATION	0	0.00	12	0.72	0	0.00	0	0.00
ERYSIPELAS	5	0.29	12	0.72	0	0.00	2	0.12
LOWER RESPIRATORY TRACT INFECTION	9	0.53	12	0.72	1	0.06	1	0.06
ANOREXIA	10	0.59	12	0.72	2	0.12	0	0.00
HYPERHIDROSIS	5	0.29	12	0.72	0	0.00	0	0.00
MOUTH ULCERATION	1	0.06	11	0.66	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
CELLULITIS	5	0.29	11	0.66	1	0.06	2	0.12
LOCALISED INFECTION	1	0.06	11	0.66	0	0.00	1	0.06
HERPES SIMPLEX	5	0.29	11	0.66	0	0.00	0	0.00
TREMOR	2	0.12	11	0.66	0	0.00	0	0.00
HYPOAESTHESIA	13	0.76	11	0.66	0	0.00	0	0.00
VAGINAL DISCHARGE	6	0.35	11	0.66	0	0.00	0	0.00
VISION BLURRED	4	0.23	10	0.60	0	0.00	0	0.00
ABDOMINAL DISTENSION	4	0.23	10	0.60	0	0.00	0	0.00
HAEMORRHOIDS	5	0.29	10	0.60	0	0.00	0	0.00
HYPERSENSITIVITY	1	0.06	10	0.60	0	0.00	1	0.06
MASTITIS	6	0.35	10	0.60	0	0.00	1	0.06
MENOPAUSAL SYMPTOMS	4	0.23	10	0.60	0	0.00	2	0.12
VAGINAL HAEMORRHAGE	7	0.41	10	0.60	0	0.00	0	0.00
CARDIAC FAILURE	4	0.23	9	0.54	1	0.06	4	0.24
LACRIMATION INCREASED	0	0.00	9	0.54	0	0.00	0	0.00
TOOTHACHE	3	0.18	9	0.54	0	0.00	0	0.00
SEASONAL ALLERGY	1	0.06	9	0.54	0	0.00	0	0.00
CONTUSION	4	0.23	9	0.54	0	0.00	0	0.00
MIGRAINE	0	0.00	9	0.54	0	0.00	0	0.00
DYSGEUSIA	2	0.12	9	0.54	0	0.00	0	0.00
PERIPHERAL SENSORY NEUROPATHY	4	0.23	9	0.54	0	0.00	0	0.00
BREAST CYST	5	0.29	9	0.54	0	0.00	0	0.00
BREAST MASS	12	0.70	9	0.54	0	0.00	0	0.00
ENDOMETRIAL HYPERPLASIA	6	0.35	9	0.54	0	0.00	0	0.00
RHINITIS ALLERGIC	1	0.06	9	0.54	0	0.00	0	0.00
HYPOTENSION	3	0.18	9	0.54	1	0.06	2	0.12
ANAEMIA	3	0.18	8	0.48	1	0.06	0	0.00
LYMPHADENOPATHY	2	0.12	8	0.48	0	0.00	0	0.00
ANGINA PECTORIS	4	0.23	8	0.48	0	0.00	1	0.06
APHTHOUS STOMATITIS	0	0.00	8	0.48	0	0.00	0	0.00
FEELING COLD	1	0.06	8	0.48	0	0.00	0	0.00
ONYCHOMYCOSIS	0	0.00	8	0.48	0	0.00	0	0.00
TOOTH ABSCESS	2	0.12	8	0.48	0	0.00	0	0.00
VAGINAL INFECTION	6	0.35	8	0.48	0	0.00	0	0.00
WOUND INFECTION	3	0.18	8	0.48	0	0.00	2	0.12
PARONYCHIA	0	0.00	8	0.48	0	0.00	1	0.06
CENTRAL LINE INFECTION	1	0.06	8	0.48	0	0.00	4	0.24
AMNESIA	0	0.00	8	0.48	0	0.00	0	0.00
MENORRHAGIA	5	0.29	8	0.48	1	0.06	1	0.06
NASAL DISCOMFORT	0	0.00	8	0.48	0	0.00	0	0.00
URTICARIA	4	0.23	8	0.48	0	0.00	0	0.00
ARRHYTHMIA	0	0.00	7	0.42	0	0.00	0	0.00
MUCOSAL DRYNESS	0	0.00	7	0.42	0	0.00	0	0.00
TONSILLITIS	1	0.06	7	0.42	0	0.00	0	0.00
VIRAL UPPER RESPIRATORY TRACT	3	0.18	7	0.42	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
INFECTION								
JOINT SPRAIN	1	0.06	7	0.42	0	0.00	1	0.06
OVARIAN CYST	8	0.47	7	0.42	0	0.00	0	0.00
VULVOVAGINAL DRYNESS	11	0.64	7	0.42	1	0.06	0	0.00
EXANTHEM	0	0.00	7	0.42	0	0.00	0	0.00
PHLEBITIS	4	0.23	7	0.42	0	0.00	0	0.00
LEUKOPENIA	3	0.18	6	0.36	1	0.06	2	0.12
NEUTROPENIA	3	0.18	6	0.36	2	0.12	2	0.12
HEPATIC STEATOSIS	5	0.29	6	0.36	0	0.00	0	0.00
GASTROENTERITIS	6	0.35	6	0.36	0	0.00	0	0.00
TOOTH INFECTION	0	0.00	6	0.36	0	0.00	0	0.00
INFECTION	5	0.29	6	0.36	1	0.06	0	0.00
RESPIRATORY TRACT INFECTION	4	0.23	6	0.36	0	0.00	1	0.06
PNEUMONIA	1	0.06	6	0.36	0	0.00	0	0.00
NAIL INFECTION	0	0.00	6	0.36	0	0.00	0	0.00
LARYNGITIS	1	0.06	6	0.36	0	0.00	0	0.00
WEIGHT DECREASED	8	0.47	6	0.36	0	0.00	0	0.00
SCIATICA	6	0.35	6	0.36	0	0.00	0	0.00
ASTHMA	4	0.23	6	0.36	2	0.12	1	0.06
ALOPECIA	1	0.06	6	0.36	0	0.00	0	0.00
FLUSHING	7	0.41	6	0.36	0	0.00	0	0.00
CARDIAC DISORDER	0	0.00	5	0.30	0	0.00	0	0.00
EAR PAIN	0	0.00	5	0.30	0	0.00	0	0.00
TINNITUS	4	0.23	5	0.30	0	0.00	0	0.00
HYPOTHYROIDISM	9	0.53	5	0.30	0	0.00	0	0.00
CATARACT	5	0.29	5	0.30	0	0.00	0	0.00
EYE PAIN	0	0.00	5	0.30	0	0.00	0	0.00
RECTAL HAEMORRHAGE	2	0.12	5	0.30	0	0.00	0	0.00
GASTROOESOPHAGEAL REFLUX DISEASE	1	0.06	5	0.30	0	0.00	0	0.00
ABDOMINAL PAIN LOWER	4	0.23	5	0.30	0	0.00	0	0.00
STOMACH DISCOMFORT	0	0.00	5	0.30	0	0.00	0	0.00
CHOLELITHIASIS	6	0.35	5	0.30	1	0.06	0	0.00
VAGINAL CANDIDIASIS	6	0.35	5	0.30	0	0.00	1	0.06
GASTROINTESTINAL INFECTION	0	0.00	5	0.30	0	0.00	0	0.00
EAR INFECTION	1	0.06	5	0.30	0	0.00	0	0.00
EYE INFECTION	2	0.12	5	0.30	0	0.00	0	0.00
ARTHROPOD BITE	3	0.18	5	0.30	0	0.00	0	0.00
FALL	5	0.29	5	0.30	1	0.06	1	0.06
OSTEOPENIA	4	0.23	5	0.30	0	0.00	0	0.00
JOINT STIFFNESS	4	0.23	5	0.30	0	0.00	0	0.00
JOINT SWELLING	2	0.12	5	0.30	0	0.00	0	0.00
MUSCULOSKELETAL DISCOMFORT	3	0.18	5	0.30	0	0.00	0	0.00
UTERINE LEIOMYOMA	5	0.29	5	0.30	0	0.00	0	0.00
SOMNOLENCE	1	0.06	5	0.30	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
SYNCOPE	1	0.06	5	0.30	1	0.06	2	0.12
CARPAL TUNNEL SYNDROME	3	0.18	5	0.30	0	0.00	0	0.00
SLEEP DISORDER	5	0.29	5	0.30	0	0.00	0	0.00
POLLAKIURIA	3	0.18	5	0.30	0	0.00	0	0.00
BREAST FIBROSIS	3	0.18	5	0.30	2	0.12	1	0.06
BREAST DISCOMFORT	5	0.29	5	0.30	0	0.00	0	0.00
DERMATITIS	5	0.29	5	0.30	0	0.00	0	0.00
DERMATITIS ALLERGIC	1	0.06	5	0.30	0	0.00	0	0.00
RASH PRURITIC	0	0.00	5	0.30	0	0.00	0	0.00
RASH MACULAR	0	0.00	5	0.30	0	0.00	0	0.00
NIGHT SWEATS	9	0.53	5	0.30	1	0.06	0	0.00
LYMPHANGITIS	1	0.06	5	0.30	0	0.00	1	0.06
PERICARDIAL EFFUSION	4	0.23	4	0.24	0	0.00	0	0.00
AUTOIMMUNE THYROIDITIS	0	0.00	4	0.24	0	0.00	0	0.00
HYPERTHYROIDISM	3	0.18	4	0.24	1	0.06	0	0.00
EYELID OEDEMA	0	0.00	4	0.24	0	0.00	0	0.00
EYE IRRITATION	1	0.06	4	0.24	0	0.00	0	0.00
VISUAL DISTURBANCE	1	0.06	4	0.24	0	0.00	0	0.00
GINGIVITIS	1	0.06	4	0.24	0	0.00	0	0.00
IRRITABLE BOWEL SYNDROME	1	0.06	4	0.24	0	0.00	0	0.00
ABDOMINAL DISCOMFORT	2	0.12	4	0.24	0	0.00	0	0.00
DYSPHAGIA	0	0.00	4	0.24	0	0.00	0	0.00
ODYNOPHAGIA	0	0.00	4	0.24	0	0.00	0	0.00
INFUSION RELATED REACTION	0	0.00	4	0.24	0	0.00	0	0.00
INFLAMMATION	0	0.00	4	0.24	0	0.00	0	0.00
FOLLICULITIS	0	0.00	4	0.24	0	0.00	0	0.00
FUNGAL INFECTION	0	0.00	4	0.24	0	0.00	0	0.00
FUNGAL SKIN INFECTION	1	0.06	4	0.24	0	0.00	0	0.00
CATHETER SITE INFECTION	1	0.06	4	0.24	0	0.00	0	0.00
BRONCHITIS ACUTE	5	0.29	4	0.24	0	0.00	0	0.00
RASH PUSTULAR	0	0.00	4	0.24	0	0.00	1	0.06
HERPES VIRUS INFECTION	0	0.00	4	0.24	0	0.00	0	0.00
GASTROENTERITIS VIRAL	0	0.00	4	0.24	0	0.00	0	0.00
POST PROCEDURAL PAIN	4	0.23	4	0.24	0	0.00	1	0.06
ELECTROCARDIOGRAM T WAVE INVERSION	1	0.06	4	0.24	0	0.00	0	0.00
BODY TEMPERATURE INCREASED	0	0.00	4	0.24	0	0.00	0	0.00
ARTHRITIS	2	0.12	4	0.24	1	0.06	0	0.00
BURSITIS	2	0.12	4	0.24	0	0.00	0	0.00
OSTEOCHONDROSIS	1	0.06	4	0.24	0	0.00	0	0.00
TENDONITIS	5	0.29	4	0.24	0	0.00	0	0.00
BENIGN BREAST NEOPLASM	0	0.00	4	0.24	0	0.00	0	0.00
DISTURBANCE IN	0	0.00	4	0.24	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
ATTENTION								
NEUROPATHY PERIPHERAL	3	0.18	4	0.24	0	0.00	0	0.00
BREAST OEDEMA	4	0.23	4	0.24	0	0.00	0	0.00
PELVIC PAIN	2	0.12	4	0.24	0	0.00	0	0.00
DYSPAREUNIA	1	0.06	4	0.24	0	0.00	0	0.00
PULMONARY HYPERTENSION	0	0.00	4	0.24	0	0.00	0	0.00
PRODUCTIVE COUGH	4	0.23	4	0.24	1	0.06	0	0.00
NASAL ULCER	0	0.00	4	0.24	0	0.00	0	0.00
SKIN FISSURES	0	0.00	4	0.24	0	0.00	0	0.00
RASH ERYTHEMATOUS	1	0.06	4	0.24	0	0.00	0	0.00
ONYCHOLYSIS	0	0.00	4	0.24	0	0.00	0	0.00
DEEP VEIN THROMBOSIS	1	0.06	4	0.24	1	0.06	3	0.18
HAEMATOMA	1	0.06	4	0.24	0	0.00	0	0.00
TACHYARRHYTHMIA	0	0.00	3	0.18	0	0.00	2	0.12
CARDIOVASCULAR DISORDER	0	0.00	3	0.18	0	0.00	0	0.00
MITRAL VALVE INCOMPETENCE	3	0.18	3	0.18	0	0.00	0	0.00
VENTRICULAR DYSFUNCTION	0	0.00	3	0.18	0	0.00	0	0.00
EAR DISCOMFORT	1	0.06	3	0.18	0	0.00	0	0.00
HIATUS HERNIA	0	0.00	3	0.18	0	0.00	1	0.06
HAEMATOCHEZIA	1	0.06	3	0.18	0	0.00	0	0.00
FLATULENCE	1	0.06	3	0.18	0	0.00	0	0.00
CATHETER RELATED COMPLICATION	0	0.00	3	0.18	0	0.00	2	0.12
INJECTION SITE PAIN	0	0.00	3	0.18	0	0.00	0	0.00
FEELING HOT	0	0.00	3	0.18	0	0.00	0	0.00
FACE OEDEMA	1	0.06	3	0.18	0	0.00	0	0.00
TENDERNESS	2	0.12	3	0.18	0	0.00	0	0.00
CLOSTRIDIUM COLITIS	0	0.00	3	0.18	0	0.00	0	0.00
BREAST ABSCESS	1	0.06	3	0.18	0	0.00	1	0.06
POSTOPERATIVE INFECTION	2	0.12	3	0.18	1	0.06	0	0.00
SUBCUTANEOUS ABSCESS	1	0.06	3	0.18	0	0.00	0	0.00
VIRAL INFECTION	2	0.12	3	0.18	0	0.00	0	0.00
JOINT DISLOCATION	0	0.00	3	0.18	0	0.00	0	0.00
FOOT FRACTURE	1	0.06	3	0.18	0	0.00	0	0.00
RIB FRACTURE	3	0.18	3	0.18	1	0.06	0	0.00
RADIATION PNEUMONITIS	0	0.00	3	0.18	0	0.00	0	0.00
SEROMA	0	0.00	3	0.18	0	0.00	0	0.00
CARDIAC MURMUR	0	0.00	3	0.18	0	0.00	0	0.00
ELECTROCARDIOGRAM ABNORMAL	1	0.06	3	0.18	0	0.00	0	0.00
DECREASED APPETITE	1	0.06	3	0.18	0	0.00	0	0.00
FLUID RETENTION	3	0.18	3	0.18	0	0.00	0	0.00
HYPERTRIGLYCERIDAEMIA	0	0.00	3	0.18	0	0.00	0	0.00
ARTHROPATHY	0	0.00	3	0.18	0	0.00	1	0.06

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
SPINAL OSTEOARTHRITIS	3	0.18	3	0.18	0	0.00	0	0.00
INTERVERTEBRAL DISC PROTRUSION	1	0.06	3	0.18	0	0.00	0	0.00
SCOLIOSIS	1	0.06	3	0.18	0	0.00	0	0.00
LIMB DISCOMFORT	1	0.06	3	0.18	0	0.00	0	0.00
MUSCULOSKELETAL STIFFNESS	6	0.35	3	0.18	0	0.00	0	0.00
AXILLARY MASS	1	0.06	3	0.18	0	0.00	0	0.00
GANGLION	0	0.00	3	0.18	0	0.00	1	0.06
LIPOMA	1	0.06	3	0.18	0	0.00	0	0.00
CEREBROVASCULAR ACCIDENT	0	0.00	3	0.18	0	0.00	2	0.12
DYSAESTHESIA	1	0.06	3	0.18	0	0.00	0	0.00
NEUROPATHIC PAIN	1	0.06	3	0.18	0	0.00	0	0.00
SENSORY DISTURBANCE	0	0.00	3	0.18	0	0.00	0	0.00
AGITATION	0	0.00	3	0.18	0	0.00	0	0.00
NERVOUSNESS	1	0.06	3	0.18	0	0.00	0	0.00
NEPHROLITHIASIS	0	0.00	3	0.18	0	0.00	0	0.00
BREAST DISORDER	5	0.29	3	0.18	0	0.00	0	0.00
CERVICAL POLYP	1	0.06	3	0.18	0	0.00	0	0.00
VAGINITIS ATROPHIC	0	0.00	3	0.18	0	0.00	0	0.00
DYSMENORRHOEA	2	0.12	3	0.18	0	0.00	0	0.00
METRORRHAGIA	1	0.06	3	0.18	0	0.00	0	0.00
GENITAL DISCHARGE	1	0.06	3	0.18	0	0.00	0	0.00
UTERINE POLYP	0	0.00	3	0.18	0	0.00	0	0.00
WHEEZING	1	0.06	3	0.18	0	0.00	0	0.00
PNEUMOTHORAX	1	0.06	3	0.18	1	0.06	1	0.06
DYSPHONIA	0	0.00	3	0.18	0	0.00	0	0.00
NASAL CONGESTION	3	0.18	3	0.18	0	0.00	0	0.00
SWELLING FACE	0	0.00	3	0.18	0	0.00	0	0.00
RASH PAPULAR	0	0.00	3	0.18	0	0.00	0	0.00
PRURITUS GENERALISED	0	0.00	3	0.18	0	0.00	0	0.00
SCAR	0	0.00	3	0.18	0	0.00	0	0.00
HAIR GROWTH ABNORMAL	0	0.00	3	0.18	0	0.00	0	0.00
THROMBOPHLEBITIS	3	0.18	3	0.18	0	0.00	1	0.06
LYMPHOSTASIS	1	0.06	3	0.18	0	0.00	0	0.00
HYPERTENSIVE CRISIS	0	0.00	3	0.18	0	0.00	1	0.06
THROMBOCYTOPENIA	1	0.06	2	0.12	1	0.06	0	0.00
EXTRASYSTOLES	0	0.00	2	0.12	0	0.00	0	0.00
ATRIAL FIBRILLATION	1	0.06	2	0.12	1	0.06	0	0.00
VENTRICULAR EXTRASYSTOLES	1	0.06	2	0.12	0	0.00	0	0.00
CARDIOTOXICITY	0	0.00	2	0.12	0	0.00	0	0.00
MYOCARDIAL ISCHAEMIA	0	0.00	2	0.12	0	0.00	0	0.00
CARDIOMYOPATHY	0	0.00	2	0.12	0	0.00	1	0.06
VENTRICULAR HYPOKINESIA	0	0.00	2	0.12	0	0.00	0	0.00
GOITRE	5	0.29	2	0.12	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
MADAROSIS	0	0.00	2	0.12	0	0.00	0	0.00
DRY EYE	0	0.00	2	0.12	0	0.00	0	0.00
EYE DISCHARGE	0	0.00	2	0.12	0	0.00	0	0.00
INGUINAL HERNIA	1	0.06	2	0.12	0	0.00	0	0.00
ANAL FISSURE	0	0.00	2	0.12	0	0.00	0	0.00
PRURITUS ANI	0	0.00	2	0.12	0	0.00	0	0.00
GINGIVAL BLEEDING	0	0.00	2	0.12	0	0.00	0	0.00
GASTROINTESTINAL HAEMORRHAGE	0	0.00	2	0.12	0	0.00	0	0.00
OESOPHAGITIS	3	0.18	2	0.12	0	0.00	0	0.00
REFLUX OESOPHAGITIS	1	0.06	2	0.12	0	0.00	0	0.00
ABDOMINAL RIGIDITY	0	0.00	2	0.12	0	0.00	0	0.00
GASTRIC ULCER	1	0.06	2	0.12	0	0.00	0	0.00
HAEMORRHOIDAL HAEMORRHAGE	0	0.00	2	0.12	0	0.00	0	0.00
HYPOAESTHESIA ORAL	0	0.00	2	0.12	0	0.00	0	0.00
CATHETER SITE PAIN	0	0.00	2	0.12	0	0.00	0	0.00
CATHETER SITE RELATED REACTION	0	0.00	2	0.12	0	0.00	0	0.00
INFUSION SITE PAIN	0	0.00	2	0.12	0	0.00	0	0.00
HYPERTHERMIA	0	0.00	2	0.12	0	0.00	0	0.00
FEELING ABNORMAL	0	0.00	2	0.12	0	0.00	0	0.00
ILL-DEFINED DISORDER	1	0.06	2	0.12	0	0.00	0	0.00
THIRST	3	0.18	2	0.12	0	0.00	0	0.00
GRANULOMA	1	0.06	2	0.12	0	0.00	0	0.00
GENERALISED OEDEMA	0	0.00	2	0.12	0	0.00	0	0.00
CYST	1	0.06	2	0.12	0	0.00	0	0.00
MASS	1	0.06	2	0.12	0	0.00	0	0.00
HEPATIC PAIN	3	0.18	2	0.12	0	0.00	0	0.00
BREAST CELLULITIS	6	0.35	2	0.12	1	0.06	0	0.00
ORAL FUNGAL INFECTION	0	0.00	2	0.12	0	0.00	1	0.06
VAGINAL MYCOSIS	3	0.18	2	0.12	0	0.00	0	0.00
APPENDICITIS	0	0.00	2	0.12	0	0.00	2	0.12
DENTAL CARIES	1	0.06	2	0.12	0	0.00	0	0.00
OTITIS MEDIA	0	0.00	2	0.12	0	0.00	0	0.00
FEBRILE INFECTION	0	0.00	2	0.12	0	0.00	0	0.00
FURUNCLE	3	0.18	2	0.12	0	0.00	0	0.00
NAIL BED INFECTION	0	0.00	2	0.12	0	0.00	0	0.00
SKIN INFECTION	2	0.12	2	0.12	0	0.00	0	0.00
ACUTE TONSILLITIS	0	0.00	2	0.12	0	0.00	0	0.00
LARYNGOPHARYNGITIS	0	0.00	2	0.12	0	0.00	0	0.00
TRACHEITIS	1	0.06	2	0.12	0	0.00	0	0.00
RESPIRATORY TRACT INFECTION VIRAL	3	0.18	2	0.12	0	0.00	0	0.00
VIRAL PHARYNGITIS	1	0.06	2	0.12	0	0.00	0	0.00
LOWER LIMB FRACTURE	0	0.00	2	0.12	0	0.00	2	0.12
WRIST FRACTURE	1	0.06	2	0.12	0	0.00	1	0.06
RADIATION SKIN INJURY	1	0.06	2	0.12	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
SUNBURN	0	0.00	2	0.12	0	0.00	0	0.00
THERMAL BURN	1	0.06	2	0.12	0	0.00	0	0.00
ANIMAL BITE	1	0.06	2	0.12	0	0.00	0	0.00
ARTHROPOD STING	1	0.06	2	0.12	0	0.00	0	0.00
WOUND	1	0.06	2	0.12	0	0.00	0	0.00
BACK INJURY	1	0.06	2	0.12	1	0.06	0	0.00
SKIN LACERATION	0	0.00	2	0.12	0	0.00	1	0.06
ECHOCARDIOGRAM ABNORMAL	1	0.06	2	0.12	0	0.00	0	0.00
HEART RATE INCREASED	0	0.00	2	0.12	0	0.00	0	0.00
HEART RATE IRREGULAR	0	0.00	2	0.12	0	0.00	0	0.00
BLOOD ALKALINE PHOSPHATASE INCREASED	0	0.00	2	0.12	0	0.00	0	0.00
ALANINE AMINOTRANSFERASE INCREASED	1	0.06	2	0.12	0	0.00	2	0.12
ASPARTATE AMINOTRANSFERASE INCREASED	1	0.06	2	0.12	0	0.00	1	0.06
BLOOD GLUCOSE INCREASED	0	0.00	2	0.12	0	0.00	0	0.00
HYPERGLYCAEMIA	0	0.00	2	0.12	0	0.00	1	0.06
HYPERURICAEMIA	0	0.00	2	0.12	0	0.00	0	0.00
SPINAL DISORDER	0	0.00	2	0.12	0	0.00	0	0.00
JOINT RANGE OF MOTION DECREASED	1	0.06	2	0.12	0	0.00	0	0.00
FIBROMYALGIA	1	0.06	2	0.12	0	0.00	0	0.00
MUSCLE TIGHTNESS	3	0.18	2	0.12	0	0.00	0	0.00
NIGHT CRAMPS	2	0.12	2	0.12	0	0.00	0	0.00
MUSCULAR WEAKNESS	1	0.06	2	0.12	0	0.00	1	0.06
INTERVERTEBRAL DISC DISORDER	1	0.06	2	0.12	0	0.00	0	0.00
TENOSYNOVITIS	1	0.06	2	0.12	1	0.06	0	0.00
BREAST CANCER	2	0.12	2	0.12	1	0.06	2	0.12
SKIN PAPILLOMA	0	0.00	2	0.12	0	0.00	0	0.00
MALIGNANT MELANOMA	0	0.00	2	0.12	0	0.00	1	0.06
TRANSIENT ISCHAEMIC ATTACK	0	0.00	2	0.12	0	0.00	0	0.00
TENSION HEADACHE	0	0.00	2	0.12	0	0.00	0	0.00
BALANCE DISORDER	0	0.00	2	0.12	0	0.00	0	0.00
SYNCOPE VASOVAGAL	0	0.00	2	0.12	0	0.00	1	0.06
HYPERAESTHESIA	1	0.06	2	0.12	0	0.00	0	0.00
HYPERTONIA	0	0.00	2	0.12	0	0.00	0	0.00
PERIPHERAL MOTOR NEUROPATHY	0	0.00	2	0.12	0	0.00	1	0.06
STRESS	1	0.06	2	0.12	0	0.00	0	0.00
DEPRESSED MOOD	4	0.23	2	0.12	0	0.00	0	0.00
AFFECT LABILITY	1	0.06	2	0.12	0	0.00	0	0.00
IRRITABILITY	2	0.12	2	0.12	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
LIBIDO DECREASED	4	0.23	2	0.12	1	0.06	0	0.00
CYSTITIS HAEMORRHAGIC	0	0.00	2	0.12	0	0.00	0	0.00
STRESS INCONTINENCE	0	0.00	2	0.12	0	0.00	0	0.00
URINARY INCONTINENCE	1	0.06	2	0.12	0	0.00	0	0.00
HAEMATURIA	3	0.18	2	0.12	0	0.00	0	0.00
RENAL COLIC	0	0.00	2	0.12	0	0.00	0	0.00
RENAL PAIN	0	0.00	2	0.12	0	0.00	0	0.00
NIPPLE EXUDATE BLOODY	0	0.00	2	0.12	0	0.00	0	0.00
NIPPLE PAIN	0	0.00	2	0.12	0	0.00	0	0.00
MENSTRUATION IRREGULAR	1	0.06	2	0.12	0	0.00	0	0.00
ENDOMETRIOSIS	1	0.06	2	0.12	0	0.00	1	0.06
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0.00	2	0.12	0	0.00	0	0.00
PLEURAL EFFUSION	1	0.06	2	0.12	0	0.00	0	0.00
HYPERVENTILATION	0	0.00	2	0.12	0	0.00	0	0.00
THROAT TIGHTNESS	0	0.00	2	0.12	0	0.00	0	0.00
BLISTER	0	0.00	2	0.12	0	0.00	0	0.00
PAIN OF SKIN	1	0.06	2	0.12	0	0.00	0	0.00
SKIN REACTION	0	0.00	2	0.12	0	0.00	0	0.00
DERMATITIS CONTACT	2	0.12	2	0.12	0	0.00	0	0.00
SKIN EXFOLIATION	1	0.06	2	0.12	0	0.00	0	0.00
RASH GENERALISED	0	0.00	2	0.12	0	0.00	1	0.06
RASH MACULO-PAPULAR	1	0.06	2	0.12	0	0.00	0	0.00
PANNICULITIS	0	0.00	2	0.12	0	0.00	0	0.00
SKIN NODULE	1	0.06	2	0.12	0	0.00	0	0.00
DERMATITIS ACNEIFORM	0	0.00	2	0.12	0	0.00	0	0.00
NAIL RIDGING	0	0.00	2	0.12	0	0.00	0	0.00
PETECHIAE	0	0.00	2	0.12	0	0.00	0	0.00
CATHETER REMOVAL	1	0.06	2	0.12	0	0.00	0	0.00
CENTRAL VENOUS CATHETERISATION	0	0.00	2	0.12	0	0.00	0	0.00
CIRCULATORY COLLAPSE	0	0.00	2	0.12	0	0.00	0	0.00
ORTHOSTATIC HYPOTENSION	0	0.00	2	0.12	0	0.00	0	0.00
THROMBOSIS	0	0.00	2	0.12	0	0.00	0	0.00
THROMBOPHLEBITIS SUPERFICIAL	0	0.00	2	0.12	0	0.00	0	0.00
ANGIOPATHY	1	0.06	2	0.12	0	0.00	0	0.00
HYPERAEMIA	0	0.00	2	0.12	0	0.00	0	0.00
VASCULITIS	0	0.00	2	0.12	0	0.00	0	0.00
HAEMORRHAGIC DIATHESIS	0	0.00	1	0.06	0	0.00	0	0.00
LYMPHADENITIS	0	0.00	1	0.06	0	0.00	0	0.00
LYMPHOID TISSUE HYPERPLASIA	0	0.00	1	0.06	0	0.00	0	0.00
EOSINOPHILIA	0	0.00	1	0.06	0	0.00	0	0.00
LYMPHOPENIA	2	0.12	1	0.06	0	0.00	0	0.00
BUNDLE BRANCH BLOCK	0	0.00	1	0.06	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
LEFT								
BUNDLE BRANCH BLOCK RIGHT	0	0.00	1	0.06	0	0.00	0	0.00
SINUS ARRHYTHMIA	0	0.00	1	0.06	0	0.00	0	0.00
SINUS BRADYCARDIA	2	0.12	1	0.06	0	0.00	0	0.00
SINUS TACHYCARDIA	4	0.23	1	0.06	0	0.00	0	0.00
SUPRAVENTRICULAR TACHYCARDIA	1	0.06	1	0.06	0	0.00	1	0.06
CARDIAC VENTRICULAR DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
HEART VALVE INSUFFICIENCY	0	0.00	1	0.06	0	0.00	0	0.00
CORONARY ARTERY DISEASE	0	0.00	1	0.06	0	0.00	0	0.00
CORONARY ARTERY STENOSIS	0	0.00	1	0.06	0	0.00	1	0.06
ACUTE CORONARY SYNDROME	1	0.06	1	0.06	1	0.06	1	0.06
VENTRICULAR DYSFUNCTION	0	0.00	1	0.06	0	0.00	0	0.00
CARDIOMEGALY	1	0.06	1	0.06	0	0.00	0	0.00
PERICARDITIS LUPUS	0	0.00	1	0.06	0	0.00	1	0.06
MIXED HYPERLIPIDAEMIA	1	0.06	1	0.06	0	0.00	0	0.00
EPIDERMAL NAEVUS	0	0.00	1	0.06	0	0.00	0	0.00
NAEVUS HAEMORRHAGE	0	0.00	1	0.06	0	0.00	0	0.00
DEAFNESS	0	0.00	1	0.06	0	0.00	0	0.00
SUDDEN HEARING LOSS	0	0.00	1	0.06	0	0.00	1	0.06
MIDDLE EAR EFFUSION	0	0.00	1	0.06	0	0.00	0	0.00
ENDOCRINOPATHY DIENCEPHALIC	0	0.00	1	0.06	0	0.00	0	0.00
THYROIDITIS	1	0.06	1	0.06	0	0.00	0	0.00
XEROPHTHALMIA	0	0.00	1	0.06	0	0.00	0	0.00
LACRIMATION DECREASED	0	0.00	1	0.06	0	0.00	0	0.00
EYELID DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
CONJUNCTIVITIS ALLERGIC	1	0.06	1	0.06	0	0.00	0	0.00
BLEPHARITIS	0	0.00	1	0.06	0	0.00	0	0.00
ERYTHEMA OF EYELID	0	0.00	1	0.06	0	0.00	0	0.00
EYE INFLAMMATION	0	0.00	1	0.06	0	0.00	0	0.00
EYE PRURITUS	0	0.00	1	0.06	0	0.00	0	0.00
OCULAR HYPERAEMIA	0	0.00	1	0.06	0	0.00	0	0.00
ABNORMAL SENSATION IN EYE	0	0.00	1	0.06	0	0.00	0	0.00
FOREIGN BODY SENSATION IN EYES	0	0.00	1	0.06	0	0.00	0	0.00
VITREOUS DETACHMENT	0	0.00	1	0.06	0	0.00	0	0.00
VITREOUS FLOATERS	3	0.18	1	0.06	0	0.00	0	0.00
VISUAL ACUITY REDUCED	1	0.06	1	0.06	0	0.00	0	0.00
MYOPIA	0	0.00	1	0.06	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
COLONIC POLYP	1	0.06	1	0.06	0	0.00	0	0.00
PERIODONTITIS	1	0.06	1	0.06	0	0.00	0	0.00
TOOTH DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
TOOTH FRACTURE	0	0.00	1	0.06	0	0.00	0	0.00
SENSITIVITY OF TEETH	0	0.00	1	0.06	0	0.00	0	0.00
PANCREATITIS	1	0.06	1	0.06	1	0.06	0	0.00
GASTRIC DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
ANAL HAEMORRHAGE	1	0.06	1	0.06	0	0.00	0	0.00
COLITIS	0	0.00	1	0.06	0	0.00	0	0.00
GASTRITIS ATROPHIC	0	0.00	1	0.06	0	0.00	0	0.00
PROCTITIS	1	0.06	1	0.06	0	0.00	0	0.00
BOWEL SOUNDS ABNORMAL	0	0.00	1	0.06	0	0.00	0	0.00
EPIGASTRIC DISCOMFORT	2	0.12	1	0.06	0	0.00	0	0.00
ERUCTATION	0	0.00	1	0.06	0	0.00	0	0.00
ABNORMAL FAECES	0	0.00	1	0.06	0	0.00	0	0.00
GASTROINTESTINAL PAIN	0	0.00	1	0.06	0	0.00	0	0.00
OESOPHAGEAL PAIN	0	0.00	1	0.06	0	0.00	0	0.00
ILEUS	0	0.00	1	0.06	0	0.00	1	0.06
PEPTIC ULCER	0	0.00	1	0.06	0	0.00	0	0.00
ORAL MUCOSAL DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
ORAL PAIN	0	0.00	1	0.06	0	0.00	0	0.00
ORAL MUCOSAL BLISTERING	0	0.00	1	0.06	0	0.00	0	0.00
PERITONITIS	0	0.00	1	0.06	0	0.00	1	0.06
SALIVARY GLAND PAIN	0	0.00	1	0.06	0	0.00	0	0.00
GLOSSITIS	0	0.00	1	0.06	0	0.00	0	0.00
VENIPUNCTURE SITE PAIN	0	0.00	1	0.06	0	0.00	0	0.00
CATHETER SITE INFLAMMATION	0	0.00	1	0.06	0	0.00	0	0.00
IMPLANT SITE RASH	0	0.00	1	0.06	0	0.00	0	0.00
MIGRATION OF IMPLANT	0	0.00	1	0.06	0	0.00	0	0.00
INJECTION SITE EXTRAVASATION	0	0.00	1	0.06	0	0.00	0	0.00
INJECTION SITE HAEMORRHAGE	0	0.00	1	0.06	0	0.00	0	0.00
INJECTION SITE RASH	0	0.00	1	0.06	0	0.00	0	0.00
INJECTION SITE REACTION	0	0.00	1	0.06	0	0.00	0	0.00
HYPERPYREXIA	0	0.00	1	0.06	0	0.00	0	0.00
SUDDEN DEATH	0	0.00	1	0.06	0	0.00	1	0.06
EXTRAVASATION	0	0.00	1	0.06	0	0.00	0	0.00
PERFORMANCE STATUS DECREASED	0	0.00	1	0.06	0	0.00	0	0.00
SWELLING	0	0.00	1	0.06	0	0.00	0	0.00
UNEVALUABLE EVENT	0	0.00	1	0.06	0	0.00	0	0.00
XEROSIS	0	0.00	1	0.06	0	0.00	0	0.00
INFLAMMATION OF WOUND	0	0.00	1	0.06	0	0.00	0	0.00
DISCOMFORT	1	0.06	1	0.06	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
NON-CARDIAC CHEST PAIN	0	0.00	1	0.06	0	0.00	0	0.00
ADVERSE DRUG REACTION	1	0.06	1	0.06	0	0.00	1	0.06
BILIARY COLIC	1	0.06	1	0.06	1	0.06	0	0.00
CHOLECYSTITIS CHRONIC	1	0.06	1	0.06	0	0.00	0	0.00
BILIARY DYSKINESIA	0	0.00	1	0.06	0	0.00	0	0.00
GALLBLADDER DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
JAUNDICE	0	0.00	1	0.06	0	0.00	0	0.00
PORTAL VEIN THROMBOSIS	0	0.00	1	0.06	0	0.00	0	0.00
HEPATITIS	0	0.00	1	0.06	0	0.00	0	0.00
HEPATITIS TOXIC	0	0.00	1	0.06	0	0.00	0	0.00
HEPATOTOXICITY	0	0.00	1	0.06	0	0.00	0	0.00
GALLBLADDER POLYP	2	0.12	1	0.06	0	0.00	0	0.00
HEPATIC CYST	2	0.12	1	0.06	0	0.00	0	0.00
DRUG HYPERSENSITIVITY	3	0.18	1	0.06	0	0.00	1	0.06
CATHETER SITE CELLULITIS	0	0.00	1	0.06	0	0.00	0	0.00
VAGINITIS BACTERIAL	0	0.00	1	0.06	0	0.00	0	0.00
PERTUSSIS	0	0.00	1	0.06	0	0.00	0	0.00
SALMONELLOSIS	0	0.00	1	0.06	0	0.00	1	0.06
STAPHYLOCOCCAL SEPSIS	0	0.00	1	0.06	0	0.00	0	0.00
SCARLET FEVER	0	0.00	1	0.06	0	0.00	0	0.00
CANDIDIASIS	1	0.06	1	0.06	0	0.00	0	0.00
ORAL CANDIDIASIS	0	0.00	1	0.06	0	0.00	0	0.00
GENITAL INFECTION FUNGAL	0	0.00	1	0.06	0	0.00	0	0.00
TINEA PEDIS	0	0.00	1	0.06	0	0.00	0	0.00
TINEA VERSICOLOUR	0	0.00	1	0.06	0	0.00	0	0.00
ENTEROBIASIS	0	0.00	1	0.06	0	0.00	0	0.00
ABDOMINAL WALL ABSCESS	0	0.00	1	0.06	0	0.00	1	0.06
RECTAL ABSCESS	0	0.00	1	0.06	0	0.00	1	0.06
BREAST INFECTION	3	0.18	1	0.06	0	0.00	0	0.00
GINGIVAL ABSCESS	0	0.00	1	0.06	0	0.00	0	0.00
LABYRINTHITIS	2	0.12	1	0.06	1	0.06	0	0.00
HORDEOLUM	0	0.00	1	0.06	0	0.00	0	0.00
CERVICITIS	1	0.06	1	0.06	0	0.00	0	0.00
VULVOVAGINITIS	0	0.00	1	0.06	0	0.00	0	0.00
ABSCESS	1	0.06	1	0.06	0	0.00	0	0.00
ABSCESS LIMB	0	0.00	1	0.06	0	0.00	0	0.00
CATHETER RELATED INFECTION	0	0.00	1	0.06	0	0.00	0	0.00
INFECTED INSECT BITE	0	0.00	1	0.06	0	0.00	0	0.00
BRONCHITIS CHRONIC	1	0.06	1	0.06	0	0.00	0	0.00
LOBAR PNEUMONIA	1	0.06	1	0.06	0	0.00	0	0.00
PNEUMONIA PRIMARY ATYPICAL	0	0.00	1	0.06	0	0.00	0	0.00
INFECTIVE TENOSYNOVITIS	0	0.00	1	0.06	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
CATHETER SEPSIS	0	0.00	1	0.06	0	0.00	1	0.06
SEPSIS	0	0.00	1	0.06	0	0.00	0	0.00
CARBUNCLE	0	0.00	1	0.06	0	0.00	0	0.00
ACUTE SINUSITIS	0	0.00	1	0.06	0	0.00	0	0.00
PHARYNGOTONSILLITIS	0	0.00	1	0.06	0	0.00	0	0.00
PULMONARY TUBERCULOSIS	0	0.00	1	0.06	0	0.00	0	0.00
TUBERCULOSIS	0	0.00	1	0.06	0	0.00	0	0.00
HERPETIC STOMATITIS	0	0.00	1	0.06	0	0.00	0	0.00
VARICELLA	0	0.00	1	0.06	0	0.00	0	0.00
LARYNGITIS VIRAL	0	0.00	1	0.06	0	0.00	0	0.00
VIRAL LABYRINTHITIS	1	0.06	1	0.06	0	0.00	0	0.00
LIMB INJURY	2	0.12	1	0.06	0	0.00	0	0.00
FIBULA FRACTURE	1	0.06	1	0.06	0	0.00	0	0.00
PATELLA FRACTURE	1	0.06	1	0.06	0	0.00	0	0.00
TIBIA FRACTURE	0	0.00	1	0.06	0	0.00	0	0.00
PUBIC RAMI FRACTURE	0	0.00	1	0.06	0	0.00	0	0.00
DISLOCATION OF VERTEBRA	0	0.00	1	0.06	0	0.00	0	0.00
FRACTURED SACRUM	0	0.00	1	0.06	0	0.00	0	0.00
UPPER LIMB FRACTURE	1	0.06	1	0.06	0	0.00	0	0.00
POISONING	0	0.00	1	0.06	0	0.00	0	0.00
THERAPEUTIC AGENT TOXICITY	0	0.00	1	0.06	0	0.00	1	0.06
RADIATION ASSOCIATED PAIN	1	0.06	1	0.06	0	0.00	0	0.00
RADIATION INJURY	0	0.00	1	0.06	0	0.00	0	0.00
PNEUMOTHORAX TRAUMATIC	0	0.00	1	0.06	0	0.00	1	0.06
EPICONDYLITIS	0	0.00	1	0.06	0	0.00	0	0.00
MUSCLE STRAIN	0	0.00	1	0.06	0	0.00	1	0.06
TENDON RUPTURE	0	0.00	1	0.06	0	0.00	0	0.00
WHIPLASH INJURY	1	0.06	1	0.06	0	0.00	0	0.00
EXCORIATION	1	0.06	1	0.06	0	0.00	0	0.00
FOREIGN BODY TRAUMA	0	0.00	1	0.06	0	0.00	0	0.00
INJURY	1	0.06	1	0.06	0	0.00	0	0.00
INJURY ASPHYXIATION	1	0.06	1	0.06	0	0.00	0	0.00
PAIN TRAUMA ACTIVATED	1	0.06	1	0.06	0	0.00	0	0.00
ROAD TRAFFIC ACCIDENT	0	0.00	1	0.06	0	0.00	0	0.00
WOUND COMPLICATION	1	0.06	1	0.06	0	0.00	0	0.00
FAILURE OF IMPLANT	0	0.00	1	0.06	0	0.00	1	0.06
MEDICAL DEVICE PAIN	0	0.00	1	0.06	0	0.00	0	0.00
POST PROCEDURAL VOMITING	0	0.00	1	0.06	0	0.00	0	0.00
INCISION SITE COMPLICATION	1	0.06	1	0.06	0	0.00	0	0.00
POST PROCEDURAL COMPLICATION	1	0.06	1	0.06	0	0.00	0	0.00
POST PROCEDURAL	0	0.00	1	0.06	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
HAEMORRHAGE								
POST PROCEDURAL OEDEMA	0	0.00	1	0.06	0	0.00	0	0.00
POSTOPERATIVE WOUND COMPLICATION	0	0.00	1	0.06	0	0.00	0	0.00
WOUND DECOMPOSITION	0	0.00	1	0.06	0	0.00	0	0.00
WOUND DEHISCENCE	0	0.00	1	0.06	0	0.00	1	0.06
MULTIPLE GATED ACQUISITION SCAN ABNORMAL	0	0.00	1	0.06	0	0.00	0	0.00
ECG P WAVE INVERTED	0	0.00	1	0.06	0	0.00	0	0.00
ELECTROCARDIOGRAM CHANGE	0	0.00	1	0.06	0	0.00	0	0.00
PULSE ABNORMAL	0	0.00	1	0.06	0	0.00	0	0.00
BLOOD PRESSURE ABNORMAL	0	0.00	1	0.06	0	0.00	0	0.00
BLOOD PRESSURE SYSTOLIC INCREASED	0	0.00	1	0.06	0	0.00	0	0.00
PLATELET COUNT	0	0.00	1	0.06	0	0.00	0	0.00
HAEMOGLOBIN DECREASED	0	0.00	1	0.06	0	0.00	1	0.06
WHITE BLOOD CELL COUNT INCREASED	0	0.00	1	0.06	0	0.00	0	0.00
ASPARTATE AMINOTRANSFERASE	0	0.00	1	0.06	0	0.00	0	0.00
GAMMA-GLUTAMYLTRANSFERASE INCREASED	0	0.00	1	0.06	0	0.00	1	0.06
BLOOD CHOLESTEROL INCREASED	0	0.00	1	0.06	0	0.00	0	0.00
LIPIDS INCREASED	0	0.00	1	0.06	0	0.00	0	0.00
BLOOD UREA INCREASED	0	0.00	1	0.06	0	0.00	0	0.00
BIOPSY BREAST	0	0.00	1	0.06	0	0.00	0	0.00
BLOOD MAGNESIUM DECREASED	0	0.00	1	0.06	0	0.00	0	0.00
BLOOD POTASSIUM INCREASED	1	0.06	1	0.06	0	0.00	0	0.00
HYPOKALAEMIA	0	0.00	1	0.06	0	0.00	0	0.00
ALCOHOL INTOLERANCE	0	0.00	1	0.06	0	0.00	0	0.00
FOOD INTOLERANCE	0	0.00	1	0.06	0	0.00	0	0.00
LACTOSE INTOLERANCE	0	0.00	1	0.06	0	0.00	0	0.00
DIABETES MELLITUS INADEQUATE CONTROL	0	0.00	1	0.06	0	0.00	0	0.00
DIABETES MELLITUS NON-INSULIN-DEPENDENT	0	0.00	1	0.06	0	0.00	0	0.00
DYSLIPIDAEMIA	0	0.00	1	0.06	0	0.00	0	0.00
HAEMARTHROSIS	0	0.00	1	0.06	0	0.00	0	0.00
MONARTHRITIS	3	0.18	1	0.06	1	0.06	0	0.00
GOUTY ARTHRITIS	0	0.00	1	0.06	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
JOINT EFFUSION	0	0.00	1	0.06	0	0.00	0	0.00
RHEUMATOID ARTHRITIS	2	0.12	1	0.06	0	0.00	0	0.00
MYOSITIS	0	0.00	1	0.06	0	0.00	0	0.00
MUSCLE DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
MUSCLE RIGIDITY	0	0.00	1	0.06	0	0.00	0	0.00
LOWER LIMB DEFORMITY	0	0.00	1	0.06	0	0.00	0	0.00
TOE DEFORMITY	1	0.06	1	0.06	1	0.06	0	0.00
INTERVERTEBRAL DISC DISPLACEMENT	0	0.00	1	0.06	0	0.00	1	0.06
FLANK PAIN	5	0.29	1	0.06	0	0.00	0	0.00
MUSCLE CONTRACTURE	1	0.06	1	0.06	0	0.00	0	0.00
GROIN PAIN	4	0.23	1	0.06	0	0.00	0	0.00
SYNOVIAL CYST	0	0.00	1	0.06	0	0.00	0	0.00
TENDON DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
FIBROADENOMA OF BREAST	0	0.00	1	0.06	0	0.00	0	0.00
ACROCHORDON	0	0.00	1	0.06	0	0.00	0	0.00
BENIGN NEOPLASM OF SKIN	0	0.00	1	0.06	0	0.00	0	0.00
PITUITARY TUMOUR BENIGN	0	0.00	1	0.06	0	0.00	0	0.00
THYROID NEOPLASM	2	0.12	1	0.06	0	0.00	0	0.00
COLON ADENOMA	0	0.00	1	0.06	0	0.00	0	0.00
ADENOMA BENIGN	0	0.00	1	0.06	0	0.00	0	0.00
FIBROADENOMA	0	0.00	1	0.06	0	0.00	0	0.00
ACOUSTIC NEUROMA	0	0.00	1	0.06	0	0.00	0	0.00
OVARIAN ADENOMA	0	0.00	1	0.06	0	0.00	0	0.00
UTERINE CANCER	1	0.06	1	0.06	1	0.06	1	0.06
LUNG NEOPLASM	0	0.00	1	0.06	0	0.00	0	0.00
BENIGN MUSCLE NEOPLASM	0	0.00	1	0.06	0	0.00	0	0.00
CEREBRAL HAEMORRHAGE	0	0.00	1	0.06	0	0.00	1	0.06
VASCULAR ENCEPHALOPATHY	1	0.06	1	0.06	0	0.00	0	0.00
FACIAL PALSY	0	0.00	1	0.06	0	0.00	0	0.00
ANOSMIA	0	0.00	1	0.06	0	0.00	0	0.00
PAROSMIA	1	0.06	1	0.06	0	0.00	0	0.00
MEMORY IMPAIRMENT	0	0.00	1	0.06	0	0.00	0	0.00
AKATHISIA	0	0.00	1	0.06	0	0.00	0	0.00
HYPOKINESIA	0	0.00	1	0.06	0	0.00	0	0.00
PARESIS	2	0.12	1	0.06	1	0.06	0	0.00
COORDINATION ABNORMAL	0	0.00	1	0.06	0	0.00	1	0.06
LOSS OF CONSCIOUSNESS	0	0.00	1	0.06	0	0.00	0	0.00
NERVOUS SYSTEM DISORDER	2	0.12	1	0.06	1	0.06	0	0.00
AGEUSIA	0	0.00	1	0.06	0	0.00	0	0.00
HEAD DISCOMFORT	0	0.00	1	0.06	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
APHONIA	0	0.00	1	0.06	0	0.00	0	0.00
OPTIC NEURITIS RETROBULBAR	0	0.00	1	0.06	0	0.00	1	0.06
VISUAL FIELD DEFECT	0	0.00	1	0.06	0	0.00	0	0.00
POLYNEUROPATHY	1	0.06	1	0.06	0	0.00	0	0.00
GRAND MAL CONVULSION	0	0.00	1	0.06	0	0.00	0	0.00
CERVICOBRACHIAL SYNDROME	1	0.06	1	0.06	0	0.00	0	0.00
NERVE ROOT COMPRESSION	0	0.00	1	0.06	0	0.00	0	0.00
CEREBELLAR ATROPHY	0	0.00	1	0.06	0	0.00	1	0.06
ECTOPIC PREGNANCY	0	0.00	1	0.06	0	0.00	0	0.00
PREGNANCY	5	0.29	1	0.06	2	0.12	1	0.06
ADJUSTMENT DISORDER WITH DEPRESSED MOOD	0	0.00	1	0.06	0	0.00	0	0.00
BEREAVEMENT REACTION	0	0.00	1	0.06	0	0.00	0	0.00
ANTICIPATORY ANXIETY	0	0.00	1	0.06	0	0.00	0	0.00
PANIC ATTACK	0	0.00	1	0.06	0	0.00	0	0.00
RESTLESSNESS	0	0.00	1	0.06	0	0.00	0	0.00
DYSTHYMIC DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
TEARFULNESS	0	0.00	1	0.06	0	0.00	0	0.00
DELUSION	0	0.00	1	0.06	0	0.00	1	0.06
MOOD SWINGS	1	0.06	1	0.06	0	0.00	0	0.00
LOSS OF LIBIDO	1	0.06	1	0.06	0	0.00	0	0.00
CYSTITIS NONINFECTIVE	0	0.00	1	0.06	0	0.00	0	0.00
LUPUS NEPHRITIS	0	0.00	1	0.06	0	0.00	0	0.00
RENAL CYST	0	0.00	1	0.06	0	0.00	0	0.00
HYDRONEPHROSIS	1	0.06	1	0.06	0	0.00	1	0.06
BLADDER PAIN	0	0.00	1	0.06	0	0.00	0	0.00
MICTURITION DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
MICTURITION URGENCY	0	0.00	1	0.06	0	0.00	0	0.00
CHROMATURIA	0	0.00	1	0.06	0	0.00	0	0.00
URINE ODOUR ABNORMAL	0	0.00	1	0.06	0	0.00	0	0.00
NOCTURIA	0	0.00	1	0.06	0	0.00	0	0.00
BREAST HYPERPLASIA	0	0.00	1	0.06	0	0.00	0	0.00
BREAST DISCHARGE	1	0.06	1	0.06	0	0.00	0	0.00
BREAST HAEMORRHAGE	0	0.00	1	0.06	0	0.00	0	0.00
CERVICAL DYSPLASIA	0	0.00	1	0.06	0	0.00	0	0.00
POSTMENOPAUSAL HAEMORRHAGE	1	0.06	1	0.06	0	0.00	0	0.00
MENSTRUAL DISORDER	1	0.06	1	0.06	0	0.00	0	0.00
HYPOMENORRHOEA	0	0.00	1	0.06	0	0.00	0	0.00
MENOMETRORRHAGIA	0	0.00	1	0.06	0	0.00	0	0.00
POLYMENORRHAGIA	0	0.00	1	0.06	0	0.00	0	0.00
OVARIAN DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
OVARIAN HYPERFUNCTION	0	0.00	1	0.06	0	0.00	0	0.00
OVULATION PAIN	0	0.00	1	0.06	0	0.00	0	0.00
GENITAL HAEMORRHAGE	2	0.12	1	0.06	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
GENITAL RASH	0	0.00	1	0.06	0	0.00	0	0.00
ENDOMETRIAL DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
UTERINE DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
UTERINE HAEMORRHAGE	1	0.06	1	0.06	0	0.00	0	0.00
VAGINAL DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
VAGINAL DYSPLASIA	0	0.00	1	0.06	0	0.00	0	0.00
GENITAL PRURITUS FEMALE	1	0.06	1	0.06	0	0.00	0	0.00
VAGINAL BURNING SENSATION	1	0.06	1	0.06	0	0.00	0	0.00
VAGINAL PAIN	0	0.00	1	0.06	0	0.00	0	0.00
VULVOVAGINAL DISCOMFORT	1	0.06	1	0.06	0	0.00	0	0.00
BRONCHOSPASM	0	0.00	1	0.06	0	0.00	0	0.00
PNEUMONITIS	0	0.00	1	0.06	0	0.00	0	0.00
HYPOPNOEA	0	0.00	1	0.06	0	0.00	0	0.00
HYPOVENTILATION	0	0.00	1	0.06	0	0.00	0	0.00
TACHYPNOEA	0	0.00	1	0.06	0	0.00	0	0.00
HAEMOPTYSIS	3	0.18	1	0.06	0	0.00	0	0.00
HICCUPS	0	0.00	1	0.06	0	0.00	0	0.00
PLEURITIC PAIN	0	0.00	1	0.06	0	0.00	0	0.00
RESPIRATORY TRACT CONGESTION	0	0.00	1	0.06	0	0.00	0	0.00
RESPIRATORY TRACT IRRITATION	0	0.00	1	0.06	0	0.00	0	0.00
POSTNASAL DRIP	0	0.00	1	0.06	0	0.00	0	0.00
RHINALGIA	0	0.00	1	0.06	0	0.00	0	0.00
SNEEZING	0	0.00	1	0.06	0	0.00	0	0.00
THROAT IRRITATION	0	0.00	1	0.06	0	0.00	0	0.00
NASAL DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
SINUS CONGESTION	0	0.00	1	0.06	0	0.00	0	0.00
SINUS POLYP	0	0.00	1	0.06	0	0.00	0	0.00
PHARYNGEAL OEDEMA	0	0.00	1	0.06	0	0.00	0	0.00
TRACHEAL PAIN	0	0.00	1	0.06	0	0.00	0	0.00
XERODERMA	0	0.00	1	0.06	0	0.00	0	0.00
DERMATOSIS	1	0.06	1	0.06	0	0.00	0	0.00
SKIN DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
SKIN FIBROSIS	1	0.06	1	0.06	0	0.00	0	0.00
SKIN LESION	2	0.12	1	0.06	0	0.00	0	0.00
NEURODERMATITIS	0	0.00	1	0.06	0	0.00	0	0.00
PRURIGO	0	0.00	1	0.06	0	0.00	0	0.00
SKIN IRRITATION	0	0.00	1	0.06	0	0.00	0	0.00
DRUG ERUPTION	1	0.06	1	0.06	1	0.06	0	0.00
PITYRIASIS ROSEA	0	0.00	1	0.06	0	0.00	0	0.00
PHOTOSENSITIVITY ALLERGIC REACTION	1	0.06	1	0.06	0	0.00	0	0.00
ITCHING SCAR	0	0.00	1	0.06	0	0.00	0	0.00
RASH VESICULAR	0	0.00	1	0.06	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
SKIN CHAPPED	0	0.00	1	0.06	0	0.00	0	0.00
PIGMENTATION DISORDER	1	0.06	1	0.06	0	0.00	0	0.00
PYODERMA GANGRENOSUM	0	0.00	1	0.06	0	0.00	0	0.00
SKIN ULCER	0	0.00	1	0.06	0	0.00	0	0.00
INTERTRIGO	0	0.00	1	0.06	0	0.00	0	0.00
HYPOTRICHOSIS	1	0.06	1	0.06	0	0.00	0	0.00
DYSHIDROSIS	0	0.00	1	0.06	0	0.00	0	0.00
HEAT RASH	0	0.00	1	0.06	0	0.00	0	0.00
INGROWING NAIL	0	0.00	1	0.06	0	0.00	0	0.00
KOILONYCHIA	0	0.00	1	0.06	0	0.00	0	0.00
NAIL DYSTROPHY	0	0.00	1	0.06	0	0.00	0	0.00
NAIL PSORIASIS	0	0.00	1	0.06	0	0.00	0	0.00
ONYCHOMADESIS	0	0.00	1	0.06	0	0.00	0	0.00
ONYCHOMALACIA	0	0.00	1	0.06	0	0.00	0	0.00
TRICHORRHEXIS	0	0.00	1	0.06	0	0.00	0	0.00
INCREASED TENDENCY TO BRUISE	2	0.12	1	0.06	0	0.00	0	0.00
HAEMORRHAGE SUBCUTANEOUS	0	0.00	1	0.06	0	0.00	0	0.00
SKIN OEDEMA	1	0.06	1	0.06	0	0.00	0	0.00
TELANGIECTASIA	0	0.00	1	0.06	0	0.00	0	0.00
BREAST OPERATION	0	0.00	1	0.06	0	0.00	0	0.00
BREAST RECONSTRUCTION	2	0.12	1	0.06	1	0.06	0	0.00
CATARACT OPERATION	0	0.00	1	0.06	0	0.00	1	0.06
ENDODONTIC PROCEDURE	0	0.00	1	0.06	0	0.00	0	0.00
SALPINGO-OOPHORECTOMY	0	0.00	1	0.06	0	0.00	0	0.00
MOLE EXCISION	0	0.00	1	0.06	0	0.00	0	0.00
ISCHAEMIA	0	0.00	1	0.06	0	0.00	0	0.00
VENOUS OCCLUSION	0	0.00	1	0.06	0	0.00	0	0.00
DIABETIC VASCULAR DISORDER	0	0.00	1	0.06	0	0.00	0	0.00
PERIPHERAL COLDNESS	0	0.00	1	0.06	0	0.00	0	0.00
SUBCLAVIAN VEIN THROMBOSIS	2	0.12	1	0.06	1	0.06	0	0.00
VENOUS THROMBOSIS LIMB	0	0.00	1	0.06	0	0.00	0	0.00
VEIN PAIN	0	0.00	1	0.06	0	0.00	0	0.00
VENOUS STASIS	0	0.00	1	0.06	0	0.00	0	0.00
VARICOSE VEIN	3	0.18	1	0.06	0	0.00	0	0.00
LYMPH NODE PAIN	1	0.06	0	0.00	0	0.00	0	0.00
BRADYCARDIA	2	0.12	0	0.00	1	0.06	0	0.00
ATRIAL TACHYCARDIA	1	0.06	0	0.00	0	0.00	0	0.00
AORTIC VALVE INCOMPETENCE	1	0.06	0	0.00	0	0.00	0	0.00
TRICUSPID VALVE INCOMPETENCE	3	0.18	0	0.00	0	0.00	0	0.00
VENTRICULAR	1	0.06	0	0.00	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
DYSKINESIA								
ARNOLD-CHIARI MALFORMATION	1	0.06	0	0.00	0	0.00	0	0.00
DERMOID CYST OF OVARY	1	0.06	0	0.00	0	0.00	0	0.00
DERMOID CYST	1	0.06	0	0.00	0	0.00	0	0.00
PIGMENTED NAEVUS	2	0.12	0	0.00	0	0.00	0	0.00
HYPOACUSIS	1	0.06	0	0.00	0	0.00	0	0.00
CUPULOLITHIASIS	1	0.06	0	0.00	0	0.00	0	0.00
VERTIGO POSITIONAL	1	0.06	0	0.00	0	0.00	0	0.00
TYMPANIC MEMBRANE DISORDER	1	0.06	0	0.00	0	0.00	0	0.00
HYPERPARATHYROIDISM	1	0.06	0	0.00	0	0.00	0	0.00
GLAUCOMA	1	0.06	0	0.00	0	0.00	0	0.00
CONJUNCTIVAL HAEMORRHAGE	1	0.06	0	0.00	0	0.00	0	0.00
UVEITIS	1	0.06	0	0.00	0	0.00	0	0.00
MEIBOMIANITIS	1	0.06	0	0.00	0	0.00	0	0.00
SCLERITIS	1	0.06	0	0.00	0	0.00	0	0.00
EYELID PTOSIS	2	0.12	0	0.00	0	0.00	0	0.00
ASTHENOPIA	1	0.06	0	0.00	0	0.00	0	0.00
VITREOUS DEGENERATION	1	0.06	0	0.00	0	0.00	0	0.00
RETINAL DETACHMENT	2	0.12	0	0.00	1	0.06	0	0.00
RETINAL DYSTROPHY	1	0.06	0	0.00	0	0.00	0	0.00
ABDOMINAL HERNIA	2	0.12	0	0.00	0	0.00	0	0.00
PROCTALGIA	1	0.06	0	0.00	0	0.00	0	0.00
GASTRIC POLYPS	1	0.06	0	0.00	0	0.00	0	0.00
RECTAL POLYP	1	0.06	0	0.00	0	0.00	0	0.00
GINGIVAL PAIN	1	0.06	0	0.00	0	0.00	0	0.00
FOOD POISONING	2	0.12	0	0.00	0	0.00	0	0.00
COLITIS ULCERATIVE	1	0.06	0	0.00	0	0.00	0	0.00
GASTRODUODENITIS	1	0.06	0	0.00	0	0.00	0	0.00
INTESTINAL SPASM	1	0.06	0	0.00	0	0.00	0	0.00
DUODENAL ULCER	1	0.06	0	0.00	0	0.00	0	0.00
IMPLANT SITE INFLAMMATION	1	0.06	0	0.00	0	0.00	0	0.00
INDURATION	1	0.06	0	0.00	0	0.00	0	0.00
LOCAL SWELLING	3	0.18	0	0.00	0	0.00	0	0.00
ULCER	1	0.06	0	0.00	0	0.00	0	0.00
MUCOUS MEMBRANE DISORDER	1	0.06	0	0.00	0	0.00	0	0.00
PITTING OEDEMA	1	0.06	0	0.00	0	0.00	0	0.00
FACIAL PAIN	1	0.06	0	0.00	0	0.00	0	0.00
SUPRAPUBIC PAIN	1	0.06	0	0.00	0	0.00	0	0.00
DRUG THERAPEUTIC INCOMPATIBILITY	1	0.06	0	0.00	0	0.00	0	0.00
DRUG INTOLERANCE	1	0.06	0	0.00	0	0.00	0	0.00
NODULE	1	0.06	0	0.00	0	0.00	0	0.00
CHOLECYSTITIS	1	0.06	0	0.00	1	0.06	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
HEPATIC FUNCTION ABNORMAL	1	0.06	0	0.00	1	0.06	0	0.00
FOOD ALLERGY	1	0.06	0	0.00	0	0.00	0	0.00
BORRELIA INFECTION	1	0.06	0	0.00	0	0.00	0	0.00
HELICOBACTER GASTRITIS	1	0.06	0	0.00	0	0.00	0	0.00
BRONCHOPULMONARY ASPERGILLOSIS	1	0.06	0	0.00	0	0.00	0	0.00
GENITAL CANDIDIASIS	1	0.06	0	0.00	0	0.00	0	0.00
NAIL CANDIDA	1	0.06	0	0.00	0	0.00	0	0.00
NAIL TINEA	1	0.06	0	0.00	0	0.00	0	0.00
DIVERTICULITIS	2	0.12	0	0.00	1	0.06	0	0.00
ORAL INFECTION	1	0.06	0	0.00	0	0.00	0	0.00
PAROTITIS	1	0.06	0	0.00	1	0.06	0	0.00
GENITAL INFECTION FEMALE	1	0.06	0	0.00	0	0.00	0	0.00
VULVITIS	2	0.12	0	0.00	0	0.00	0	0.00
MUSCLE ABSCESS	1	0.06	0	0.00	0	0.00	0	0.00
UROSEPSIS	1	0.06	0	0.00	0	0.00	0	0.00
SOFT TISSUE INFECTION	1	0.06	0	0.00	0	0.00	0	0.00
DENGUE FEVER	1	0.06	0	0.00	0	0.00	0	0.00
HEPATITIS B	1	0.06	0	0.00	0	0.00	0	0.00
CONDYLOMA ACUMINATUM	1	0.06	0	0.00	0	0.00	0	0.00
FRACTURE	1	0.06	0	0.00	0	0.00	0	0.00
MENISCUS LESION	1	0.06	0	0.00	0	0.00	0	0.00
ANKLE FRACTURE	2	0.12	0	0.00	2	0.12	0	0.00
FEMUR FRACTURE	1	0.06	0	0.00	0	0.00	0	0.00
THORACIC VERTEBRAL FRACTURE	1	0.06	0	0.00	0	0.00	0	0.00
RADIUS FRACTURE	1	0.06	0	0.00	1	0.06	0	0.00
ANAEMIA POSTOPERATIVE	1	0.06	0	0.00	1	0.06	0	0.00
INCISIONAL HERNIA	1	0.06	0	0.00	0	0.00	0	0.00
POST PROCEDURAL FISTULA	1	0.06	0	0.00	0	0.00	0	0.00
POST PROCEDURAL HAEMATOMA	1	0.06	0	0.00	0	0.00	0	0.00
ELECTROCARDIOGRAM QT PROLONGED	1	0.06	0	0.00	0	0.00	0	0.00
QRS AXIS ABNORMAL	1	0.06	0	0.00	0	0.00	0	0.00
TRANSAMINASES INCREASED	2	0.12	0	0.00	1	0.06	0	0.00
BONE DENSITY DECREASED	1	0.06	0	0.00	0	0.00	0	0.00
SMEAR CERVIX ABNORMAL	1	0.06	0	0.00	0	0.00	0	0.00
BLOOD CHLORIDE INCREASED	1	0.06	0	0.00	0	0.00	0	0.00
DEHYDRATION	1	0.06	0	0.00	1	0.06	0	0.00
DIABETES MELLITUS	3	0.18	0	0.00	1	0.06	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
IRON DEFICIENCY	1	0.06	0	0.00	0	0.00	0	0.00
HYPERLIPIDAEMIA	1	0.06	0	0.00	0	0.00	0	0.00
BONE DISORDER	2	0.12	0	0.00	0	0.00	0	0.00
OSTEOSCLEROSIS	1	0.06	0	0.00	0	0.00	0	0.00
PERIOSTITIS	1	0.06	0	0.00	0	0.00	0	0.00
COCCYDYNIA	1	0.06	0	0.00	0	0.00	0	0.00
PAIN IN JAW	2	0.12	0	0.00	0	0.00	0	0.00
PERIARTHRITIS	3	0.18	0	0.00	0	0.00	0	0.00
SHOULDER PAIN	1	0.06	0	0.00	0	0.00	0	0.00
SPONDYLITIS	1	0.06	0	0.00	0	0.00	0	0.00
BUTTOCK PAIN	2	0.12	0	0.00	0	0.00	0	0.00
CHEST WALL MASS	2	0.12	0	0.00	0	0.00	0	0.00
NODULE ON EXTREMITY	1	0.06	0	0.00	0	0.00	0	0.00
SACRAL PAIN	1	0.06	0	0.00	0	0.00	0	0.00
SENSATION OF HEAVINESS	1	0.06	0	0.00	0	0.00	0	0.00
TENOSYNOVITIS STENOSANS	1	0.06	0	0.00	0	0.00	0	0.00
TRIGGER FINGER	1	0.06	0	0.00	0	0.00	0	0.00
BREAST CANCER IN SITU	1	0.06	0	0.00	1	0.06	0	0.00
SEBORRHOEIC KERATOSIS	1	0.06	0	0.00	0	0.00	0	0.00
PAPILLARY THYROID CANCER	1	0.06	0	0.00	1	0.06	0	0.00
GASTROINTESTINAL TRACT ADENOMA	1	0.06	0	0.00	0	0.00	0	0.00
COLON CANCER	1	0.06	0	0.00	1	0.06	0	0.00
PANCREATIC CARCINOMA	1	0.06	0	0.00	1	0.06	0	0.00
HAEMANGIOMA	1	0.06	0	0.00	0	0.00	0	0.00
TERATOMA BENIGN	1	0.06	0	0.00	0	0.00	0	0.00
NEOPLASM MALIGNANT	1	0.06	0	0.00	0	0.00	0	0.00
SQUAMOUS CELL CARCINOMA	1	0.06	0	0.00	0	0.00	0	0.00
NEOPLASM	1	0.06	0	0.00	0	0.00	0	0.00
MENINGIOMA	1	0.06	0	0.00	0	0.00	0	0.00
CERVIX CARCINOMA	1	0.06	0	0.00	1	0.06	0	0.00
ENDOMETRIAL CANCER	2	0.12	0	0.00	0	0.00	0	0.00
CHONDROMA	1	0.06	0	0.00	0	0.00	0	0.00
BASAL CELL CARCINOMA	1	0.06	0	0.00	0	0.00	0	0.00
CEREBRAL ISCHAEMIA	1	0.06	0	0.00	1	0.06	0	0.00
CAROTID ARTERY ATHEROMA	1	0.06	0	0.00	0	0.00	0	0.00
VERTEBROBASILAR INSUFFICIENCY	2	0.12	0	0.00	1	0.06	0	0.00
COGNITIVE DISORDER	1	0.06	0	0.00	0	0.00	0	0.00
MOVEMENT DISORDER	1	0.06	0	0.00	0	0.00	0	0.00
HEMIPARESIS	1	0.06	0	0.00	1	0.06	0	0.00
NYSTAGMUS	2	0.12	0	0.00	0	0.00	0	0.00
FORMICATION	1	0.06	0	0.00	0	0.00	0	0.00
DYSARTHRIA	1	0.06	0	0.00	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
MEDIAN NERVE LESION	1	0.06	0	0.00	0	0.00	0	0.00
NEUROPATHY	1	0.06	0	0.00	0	0.00	0	0.00
CONVULSION	2	0.12	0	0.00	0	0.00	0	0.00
RADICULITIS LUMBOSACRAL	1	0.06	0	0.00	0	0.00	0	0.00
ADJUSTMENT DISORDER	1	0.06	0	0.00	0	0.00	0	0.00
ANXIETY DISORDER	1	0.06	0	0.00	0	0.00	0	0.00
COGNITIVE DETERIORATION	1	0.06	0	0.00	0	0.00	0	0.00
MAJOR DEPRESSION	1	0.06	0	0.00	0	0.00	0	0.00
MOOD ALTERED	2	0.12	0	0.00	0	0.00	0	0.00
EMOTIONAL DISTRESS	2	0.12	0	0.00	0	0.00	0	0.00
MENTAL DISORDER	1	0.06	0	0.00	0	0.00	0	0.00
COMPLETED SUICIDE	0	0.00	0	0.00	0	0.00	0	0.00
NEPHRITIS	1	0.06	0	0.00	1	0.06	0	0.00
INCONTINENCE	1	0.06	0	0.00	0	0.00	0	0.00
POLYURIA	1	0.06	0	0.00	0	0.00	0	0.00
CALCULUS URINARY	3	0.18	0	0.00	0	0.00	0	0.00
FIBROCYSTIC BREAST DISEASE	1	0.06	0	0.00	0	0.00	0	0.00
BREAST DYSPLASIA	1	0.06	0	0.00	0	0.00	0	0.00
BREAST MICROCALCIFICATION	2	0.12	0	0.00	1	0.06	0	0.00
BREAST INDURATION	1	0.06	0	0.00	0	0.00	0	0.00
BREAST SWELLING	3	0.18	0	0.00	0	0.00	0	0.00
BREAST TENDERNESS	7	0.41	0	0.00	0	0.00	0	0.00
GALACTORRHOEA	1	0.06	0	0.00	0	0.00	0	0.00
MENOPAUSAL DISORDER	1	0.06	0	0.00	0	0.00	0	0.00
POLYMENORRHOEA	1	0.06	0	0.00	0	0.00	0	0.00
PELVIC DISCOMFORT	1	0.06	0	0.00	0	0.00	0	0.00
SEXUAL DYSFUNCTION	1	0.06	0	0.00	0	0.00	0	0.00
UTERINE PROLAPSE	1	0.06	0	0.00	0	0.00	0	0.00
ADNEXA UTERI MASS	1	0.06	0	0.00	0	0.00	0	0.00
ENDOMETRIAL HYPERTROPHY	1	0.06	0	0.00	0	0.00	0	0.00
PLEURISY	1	0.06	0	0.00	0	0.00	0	0.00
PULMONARY EMBOLISM	1	0.06	0	0.00	1	0.06	0	0.00
ORTHOPNOEA	1	0.06	0	0.00	0	0.00	0	0.00
ALLERGIC RESPIRATORY SYMPTOM	1	0.06	0	0.00	0	0.00	0	0.00
PAINFUL RESPIRATION	1	0.06	0	0.00	0	0.00	0	0.00
DIAPHRAGMATIC HERNIA	1	0.06	0	0.00	0	0.00	0	0.00
VOCAL CORD POLYP	2	0.12	0	0.00	1	0.06	0	0.00
NASOPHARYNGEAL DISORDER	1	0.06	0	0.00	0	0.00	0	0.00
HYPERKERATOSIS	2	0.12	0	0.00	0	0.00	0	0.00
ACTINIC KERATOSIS	1	0.06	0	0.00	0	0.00	0	0.00
DERMAL CYST	2	0.12	0	0.00	0	0.00	0	0.00
HAND DERMATITIS	1	0.06	0	0.00	0	0.00	0	0.00

Adverse Event MedDRA PT	Observation All Grades		Herceptin All Grades		Observation Grades 3-4		Herceptin Grades 3-4	
	n	%	n	%	n	%	n	%
SKIN INFLAMMATION	1	0.06	0	0.00	0	0.00	0	0.00
PSORIASIS	1	0.06	0	0.00	0	0.00	0	0.00
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1	0.06	0	0.00	0	0.00	0	0.00
HIRSUTISM	2	0.12	0	0.00	0	0.00	0	0.00
NAIL DISCOLOURATION	1	0.06	0	0.00	0	0.00	0	0.00
ECCHYMOSIS	1	0.06	0	0.00	0	0.00	0	0.00
FOOT OPERATION	1	0.06	0	0.00	0	0.00	0	0.00
BREAST PROSTHESIS IMPLANTATION	1	0.06	0	0.00	0	0.00	0	0.00
APPENDICECTOMY	1	0.06	0	0.00	0	0.00	0	0.00
LYMPHADENECTOMY	1	0.06	0	0.00	0	0.00	0	0.00
OOPHORECTOMY BILATERAL	1	0.06	0	0.00	0	0.00	0	0.00
SCAR EXCISION	1	0.06	0	0.00	0	0.00	0	0.00
NERVE BLOCK	1	0.06	0	0.00	0	0.00	0	0.00
HOSPITALISATION	1	0.06	0	0.00	0	0.00	0	0.00
SURGERY	1	0.06	0	0.00	0	0.00	0	0.00
ATHEROSCLEROSIS	1	0.06	0	0.00	0	0.00	0	0.00
LYMPHOCELE	1	0.06	0	0.00	0	0.00	0	0.00
HAEMORRHAGE	2	0.12	0	0.00	1	0.06	0	0.00

Appendix E FDA Maternal Health Team Consult

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

M E M O R A N D U M

Date: August 17, 2007 (amended 09/07/07) **Date Consulted:** May 29, 2007

From: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Through: Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

Sandra Kweder, MD
Deputy Director, Office of New Drugs

To: Division of Biological Oncology Products

Drug: Trastuzumab (Herceptin®)

Subject: Case reports of oligohydramnios associated with Herceptin use during pregnancy. Are changes needed in the pregnancy section of labeling?

Materials Reviewed:

- 19 MedWatch reports that reported on eight unique cases of oligohydramnios
- Published literature on oligohydramnios associated with Herceptin use during pregnancy
- Published literature on oligohydramnios associated with pregnancies in patients with cancer or pregnancies in patients with cancer receiving chemotherapy
- Published literature on the role of epidermal growth factor in renal development.

Consult Question:

Should available information on the 18 case reports of oligohydramnios with Herceptin® use during pregnancy lead to changes in labeling of the drug for use during pregnancy?

EXECUTIVE SUMMARY

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the Erb-2/Her2/neu receptor (epithelial growth factor 2 protein). In 1998, FDA approved Herceptin (BLA 103792) alone and in combination with paclitaxel (chemotherapy-nieve patients only) for the treatment of metastatic breast cancer in women with HER2-overexpressing metastatic breast cancer. On November 16, 2006, FDA approved Herceptin as part of an adjuvant treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel in women with HER2-overexpressing, node-positive breast cancer. Up to one in 3000 live births is complicated by breast cancer.[7]

The Division of Biologic Oncology Products (DBOP) consulted the Maternal Health Team (MHT) regarding the potential need for changes in labeling based on 18 case reports of oligohydramnios associated with Herceptin use during pregnancy. The Pregnancy and Lactation Labeling Team (PLT, now the Maternal Health Team) reviewed this issue in September 2004, when there were five known cases of oligohydramnios associated with Herceptin use in pregnancy, and at that time, PLT felt that the data was confounded and not robust enough to include in labeling. The current label mentions the existence of a limited number of post-marketing cases of oligohydramnios and states that no association between oligohydramnios and the use of Herceptin has been established. DBOP would like MHT to revisit this issue in light of additional reported oligohydramnios cases and the drug's relatively new indication as adjuvant therapy for breast cancer. DBOP is concerned about potential increased use of Herceptin among women of reproductive age women with breast cancer.

Currently, there are nine unique reports of oligohydramnios associated with Herceptin use in pregnancy both in the published literature and post-marketing reports in the AERS database. In four, and possibly five, of these cases, the amniotic fluid volume has recovered following discontinuation of Herceptin therapy. There is one case with both a positive dechallenge and rechallenge. Transient oligohydramnios has occasionally been reported following courses of chemotherapy with other agents, but the amniotic fluid volume has generally recovered in a short period of time. Sometimes clinicians have used additional intravenous hydration in an attempt to compensate for fluid compartment shifts and blunt this effect following chemotherapy.

Pre-clinical data suggest an important role for epidermal growth factor in renal development. Human renal tubular development continues until 36 weeks gestation. Data from studies in organ culture, where an antibody is used to block the epidermal growth factor receptor, suggest that blocking the EGF receptor may interfere with normal nephron development. It seems scientifically plausible, based on the drug's mechanism of action that Herceptin could potentially increase the likelihood of oligohydramnios.

At this time, the data are not robust enough to conclude that a clear association exists between the use of Herceptin during pregnancy and the occurrence of oligohydramnios; however, the data do suggest a possible association that deserves monitoring. Additional data are needed to more clearly define and understand this possible relationship. Based on a woman's individual disease

state and course of progression and on risk/benefit counseling between physician and patient, some women may continue Herceptin when oligohydramnios occurs and some may stop. Some women who continue therapy may be delivered depending on the gestational age of the fetus and other factors, and some may continue their pregnancy with fetal monitoring and ultrasound examinations. In order to optimize the clinical outcomes for pregnant women with breast cancer and their babies, women using Herceptin during pregnancy should be monitored for oligohydramnios. If and when oligohydramnios occurs, risk/benefit counseling should occur and fetal testing should begin.

While oligohydramnios is not a classically teratogenic effect, the oligohydramnios may be caused by an untoward effect of Herceptin on nephron growth and function.

RECOMMENDATIONS

2. The pregnancy category for Herceptin (trastuzumab) should be changed to a "D" based on the available human data that suggest a possible teratogenic effect leading to oligohydramnios.

3. The pregnancy portion of the Herceptin label should include information about the known cases of oligohydramnios that occurred with use of Herceptin during pregnancy.

4. The label should recommend that pregnant women using Herceptin undergo screening for oligohydramnios with obstetrical ultrasound examination at regular intervals.

5. If oligohydramnios occurs, the obstetrician should begin fetal testing appropriate for the gestational age of the fetus and consistent with the standards of care for the community. This testing should continue on a regular basis until one of two conditions is met:

    a. Herceptin therapy is discontinued and oligohydramnios resolves
    b. Delivery.

6. In cases where the physician and patient decide to continue Herceptin therapy for maternal reasons despite the presence of oligohydramnios, additional intravenous hydration should be considered. With other forms of chemotherapy during pregnancy, transient oligohydramnios has been observed, and extra hydration sometimes mitigates this effect.

7. Include contact information for the Cancer and Childbirth Registry and encourage enrollment of pregnant patients using Herceptin.

8. Please see Appendix B for suggested draft language for the pregnancy and nursing mothers portions of the label.

INTRODUCTION

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that

targets the extracellular domain of the Erb-2/Her2/neu receptor (epithelial growth factor receptor 2 protein). It is indicated as single agent therapy in metastatic, Her2-overexpressing breast cancer and as part of a chemotherapy regimen for Her2-overexpressing, node positive breast cancer. The Division of Biologic Oncology Products (DBOP) consulted the Maternal Health Team (MHT) regarding the potential need for changes in labeling based on 18 case reports of oligohydramnios associated with Herceptin use during pregnancy. While the Pregnancy and Lactation Labeling Team (PLT, now the Maternal Health Team) reviewed this issue in September 2004, DBOP would like the issue revisited in light of additional reported oligohydramnios cases and the drug's relatively new indication as adjuvant therapy for breast cancer. DBOP is concerned about potential increased use of Herceptin among women of reproductive age women with breast cancer.

BACKGROUND

While breast cancer is primarily a disease of older women, with a median age at diagnosis of 61 years, seven to 14% of breast cancers are diagnosed in women less than 40 years of age. [7,10] With delay of childbearing by many women into their 30's and even 40's, breast cancer (treated, recurrent, or newly diagnosed) is seen with increasing frequency in pregnancy. Up to one in 3000 live births is complicated by breast cancer, and this number does not include pregnancy terminations done for the mother's condition. [7] Breast cancer tumors in women under the age of 40 years tend to be larger, more aggressive, less differentiated, and lymph-node positive. Younger women with breast cancer tend to have tumors that are more likely to be estrogen and progesterone receptor negative and Her-2/neu positive. They experience higher disease-related mortality and shorter disease-free survival. [10]

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the Erb-2/Her2/neu receptor. In 1998, FDA approved Herceptin (BLA 103792) alone and in combination with paclitaxel (chemotherapy-nieve patients only) for the treatment of metastatic breast cancer in women with HER2-overexpressing metastatic breast cancer. On November 16, 2006, FDA approved Herceptin as part of an adjuvant treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel in women with HER2-overexpressing, node-positive breast cancer.

In 2004, the Division consulted PLT on whether information on five cases of oligohydramnios that occurred with Herceptin use during pregnancy should be included in labeling. At that time, Gerard Nahum MD, medical officer, reviewed information submitted by the sponsor on 23 women with breast cancer exposed to Herceptin during pregnancy. In all cases, the women were also exposed to other chemotherapeutic agents concurrently. Among 12 pregnancies that resulted in live births, eight of the women had metastatic disease (one of these women had two pregnancies), and three used Herceptin off-label in the adjuvant setting. The timing of exposure during pregnancy varied. Oligohydramnios occurred in five of these 12 pregnancies, and two of these cases involved another factor that could have contributed to the occurrence of oligohydramnios – one case of trisomy-21 and one case of severe intra-uterine growth restriction (IUGR). At that time, the PLT did not recommend including information on the isolated case reports of oligohydramnios in drug product labeling. The concomitant chemotherapy, the variable time of exposure during pregnancy, and an adverse selection testing bias based on

maternal disease combined with a probability of a false-positive diagnosis of oligohydramnios were all variables that supported PLT's conclusion that this information should not be included in product labeling. The team felt that the data was not robust enough to support a potential association between the occurrence of oligohydramnios and the use of Herceptin in these women. The most recently approved label (November 2006) includes the following statement:

> **In the postmarketing setting, oligohydramnios has been reported in women who received Herceptin during pregnancy, either in combination with chemotherapy or as a single agent. Given the limited number of reported cases, the high background rate of occurrence of oligohydramnios, the lack of clear temporal relationships between drug use and clinical findings, and the lack of supportive findings in animal studies, an association between Herceptin and oligohydramnios has not been established.**

Oligohydramnios is a reduced volume of amniotic fluid around the fetus, and anhydramnios is the absence of fluid around the fetus. In utero, the placenta is primarily responsible for maintaining fetal homeostasis. Fetal urine formation begins by 12 weeks of gestation and is the main constituent of amniotic fluid.[2] Amniotic fluid volume peaks at an average of one liter at 36 weeks gestation and then slowly declines. Often, decreased fluid volume occurs in pregnancies that continue post-term (beyond 40 weeks gestation), and in this situation, oligohydramnios is a reason to deliver the patient. Prior to term, oligohydramnios is far less common and is often associated with a poor prognosis. Different ultrasound methods have been used to assess the amount of amniotic fluid. Phelan et al (1987) described quantifying amniotic fluid by adding the vertical depths of the largest pocket of fluid in each of four equal uterine quadrants. This measurement is called the amniotic fluid index (AFI) and is widely used in clinical practice and as part of the biophysical profile (BPP), a form of antenatal testing that evaluates AFI, fetal tone, fetal movement, fetal breathing, and fetal heart rate pattern (nonstress test, NST) over a 30 minute period of time. An AFI < 5 cm is defined as oligohydramnios. The other widely accepted ultrasonographic method of defining oligohydramnios is the lack of a vertical pocket of amniotic fluid at least 2 cm deep. A number of studies suggest that while the AFI is a more accurate way of estimating actual amniotic fluid volume, none of the ultrasound assessments of amniotic fluid volume accurately predict fetal tolerance of labor or neonatal outcomes.[14]

Decreased amniotic fluid may be associated with maternal or fetal problems. Such maternal conditions include preterm premature rupture of membranes (PPROM) or conditions that affect placental function or vascularization (postterm pregnancy, preeclampsia). Maternal use of ACE inhibitors can also cause oligohydramnios. Fetal conditions almost always associated with oligohydramnios include fetal urinary tract obstruction or renal agenesis (Potter syndrome). Fifteen to 25% of cases of preterm oligohydramnios are associated with fetal anomalies. However, otherwise normal fetuses may experience the following consequences of early-onset, severe oligohydramnios: musculoskeletal deformities (like clubfoot, limb contractures), pulmonary hypoplasia, and/or serious deformities due to fetal part entrapment in amniotic bands. When oligohydramnios is accompanied by intrauterine growth restriction, the risk of fetal

morbidity is increased. In these situations, fetal surveillance is important and delivery is often recommended for fetal or maternal indications. While gestational age is a consideration, in these situations, fetal or maternal compromise usually overrides the potential complications from preterm delivery.[14]

Oligohydramnios detected before 36 weeks gestation with normal fetal anatomy by ultrasound can be managed expectantly along with antepartum fetal testing.[14] Antepartum fetal testing is most often performed once or twice weekly using a combination of NSTs and BPPs. The contraction stress test (CST) has the best predictive values for fetal well being during the seven days following testing but most often is not used routinely due to the possible increased risk of preterm labor.

Four of five studies suggest that maternal hydration can increase AFI, but the effect dissipates by 24 hours following fluid administration. Fluid restriction or dehydration can lower the AFI.

REVIEW OF DATA

To complete this consult, this reviewer reviewed and/or looked for the following information:

- 19 MedWatch reports that reported on eight unique cases of oligohydramnios
- Published literature on oligohydramnios associated with Herceptin use during pregnancy
- Published literature on oligohydramnios associated with pregnancies in patients with cancer or pregnancies in patients with cancer receiving chemotherapy
- Published literature on the role of epidermal growth factor in renal development.

Renal development and epidermal growth factor

Based on current data about the role that epithelial growth factor plays in renal development, some scientists and clinicians suspect that Herceptin has a potential to cause fetal adverse effects with in-utero exposure.

During embryonic development, three sets of renal organs develop sequentially: the pronephros, the mesonephros, and finally, the metanephros, which persist to become the mature kidneys. The ureteric bud grows from the mesonephric duct after the fourth week of gestation. The Wolffian duct grows caudally, passing the pronephros and mesonephros to approach the metanephric mesenchyme. As this occurs, growth factor signaling from the metanephric mesenchyme transitions from insulin growth factor-II (IGF-II) to glial-derived neurotrophic factor (GDNF). Wilm's tumor gene expression begins, suppresses IGF-II, and helps convert metanephric mesenchymal cells to epithelial cells. GDNF appears essential for promoting outpouching of the ureteric bud from the mesonephric duct. Retinoids also play an important but incompletely understood role in ureteric bud formation. Stimulation of the angiotension II receptor AT2 leads to mesenchymal apoptosis needed for ureteric bud development.[9]

The ureteric bud produces a number of soluble agents that work together to promote cellular condensation and differentiation.[9] One of these agents is epithelial growth factor (EGF), also called transforming growth factor-α (TGF-α). TGF-α is synthesized and secreted in the embryonic kidney where it binds to the EGF receptor. The TGF-α peptide and receptors are present in the fetal human metanephros. Studies in cultured embryonic organ show that adding anti-TGF-α antibodies inhibits morphogenesis and tubulogenesisis. This suggests that TGF-α plays a role in early ureteric bud development. EGF/ TGF-α also appears to participate in rescuing uninduced mesenchymal cells from apoptosis. While the role of EGF/ TGF-α is not completely defined, it appears to play an important part in kidney organogenesis.[6]

Nephrons develop in successive stages from the inner to the outer area of the fetal kidney, in parallel with the vascular system. In humans, nephrogenesis is not completed until the 36th week of gestation. In preterm infants, the process continues following delivery. EGF/ TGF-α is one of the many factors involved in the promotion and control of nephrogenesis.[2]

Reviewer comment:

Herceptin is an IgG monoclonal antibody that blocks the human epidermal growth factor receptor 2 protein and is known to cross the placenta. Organ culture studies suggest that blocking the EGF receptor may interfere with normal nephron development.

Oligohydramnios and Herceptin use during pregnancy

Review of the published literature and MedWatch forms submitted to FDA reveal ten reported and unique pregnancies in women with breast cancer who used Herceptin during some portion of their pregnancy, nine of whom developed oligohydramnios. In one other case, a woman received two doses of Herceptin just prior to conception. Table 1 summarizes the key features of these 11 cases including the gestational ages at which Herceptin was given, the gestational age at which oligo- or anhydramnios was diagnosed, concomitant chemotherapies, whether the patient was dechallenged or rechallenged with Herceptin, and the pregnancy outcome. These cases are presented in tabular form in greater detail in Appendix A.

In cases 1 – 6, Herceptin was discontinued during pregnancy. In cases 1 – 5, the therapy was stopped due to oligohydramnios or anhydramnios. In four of these cases, there was documented reaccumulation of amniotic fluid following discontinuation of Herceptin therapy. After improvement in or resolution of oligohydramnios, one of these patients was re-challenged with Herceptin. One week after resumption of Herceptin therapy, the patient was delivered by cesarean with oligohydramnios. The fifth patient in whom Herceptin was discontinued (Case 4) received her last dose at 24 weeks gestation, and she delivered at 34 weeks by cesarean section. The MedWatch report did not include information about the reason for cesarean section at that time or the amount of amniotic fluid present prior to or at delivery. The fact that she remained pregnant for about two months following the diagnosis of oligohydramnios suggests that the amniotic fluid volume likely recovered after Herceptin therapy was stopped. The sixth patient (Case 6) discontinued Herceptin therapy during pregnancy for a maternal reason. On transthoracic echocardiography, she had a mildly reduced ventricular ejection fraction, a known cardiotoxic effect associated with Herceptin. At 25 weeks gestation, AFI was normal in this pregnancy even though Herceptin therapy was continued up until 24 weeks.[11]

In Cases 7 and 8, the patients had apparently normal pregnancies until 26 and 27 weeks respectively when the patients were diagnosed with recurrent metastatic breast cancer. In both cases, Herceptin therapy was started in combination with paclitaxel or vinorelbine and continued until delivery. In case 7, the patient received Herceptin and paclitaxel at 26 and 29 weeks

Table 1: Summary of 11 reported cases of Herceptin exposure during pregnancy: nine with oligohydramnios and two without oligohydramnios

Case	Gestational age (weeks)		Other chemo	De-challenge	Re-challenge	Outcome
	Herceptin exposure	Oligo- or anhydramnios				
1	0 – 26	26	None	Yes	Yes	AFI increased after dechallenge. Delivered at 29 wks by C/S with oligohydramnios one week after rechallenge.
2	0 – 7; 14 – 32	32	Zoladex	Yes	No	At 36 weeks, spontaneous labor and normal vaginal delivery. Trisomy 21.
3	0 – 20	23	None	Yes	No	AF reappeared at 25 weeks and normal at 32 weeks. Normal delivery at 37.5 wks.
4	0 – 24	25+	None	Yes	No	Delivered by C/S at 34 wks. Unknown reason for C/S.
5	0 – 24	None	None	Yes	No	Herceptin treatment through 24 wks gestation. Normal AFI at 25 wks. Normal infant delivered by C/S at 37 wks.
6	23 – 27	30	Docetaxel	Yes	No	At 33 wks, reaccumulating AF. Delivered by C/S for maternal reasons at 36 wks. Normal infant.
7	26 – 29	31 – 32	Paclitaxel	No	No	Due to anhydramnios with IUGR, fetal lung maturation with steroids and C/S at 32 weeks. Decreased neonatal renal function.
8	27 – del	After starting treatment	Vinorelbine	No	No	Treatment continued for maternal reasons. Extra IV hydration with weekly tx. Oligohydramnios persistent. Induction and delivery 35 wks

Table 1: Summary of 11 reported cases of Herceptin exposure during pregnancy: nine with oligohydramnios and two without oligohydramnios						
	Gestational age (weeks)					
9	0 – del	26	None	No	No	C/S at 36 weeks. Baby with limb deformities. Died of pulmonary hypoplasia at 6 hrs
10	0 – 24	24	? Vinorelbine	No	No	Therapeutic abortion twin gestation at 24 weeks. "Lungs not developing properly"
11	-4 - 0	None	None	No	No	Normal pregnancy

gestation.[1] Within a couple of weeks of the last Herceptin dose, anhydramnios was diagnosed by ultrasound. The physicians administered steroids to mature the fetal lungs and delivered the baby by cesarean section at 32 weeks gestation, three weeks after the last dose of Herceptin. The baby had decreased renal function, which normalized over the first four weeks of life.

Reviewer comment:

Based on the severity of the mother's disease and rates of morbidity and mortality for a 32 week premature infant with anhydramnios, the obstetrician and oncologist may have decided that it was in the best interest of the mother and baby to proceed with delivery. In a different disease state situation, the clinicians may have opted for discontinuation of Herception therapy and expectant management with antepartum surveillance. Based on other cases reviewed here, it is possible that amniotic fluid may have reaccumulated with this more conservative management plan. It is interesting to note that this infant had compromised renal function at the time of delivery. This was not seen in the other Herceptin-exposed infants. While it is scientifically plausible that the decrease in renal function could be related to epithelial growth factor receptor blockade by Herceptin, there are not enough data to support such a conclusion.

In Case 8, the mother was also diagnosed with metastatic recurrence of breast cancer mid-pregnancy.[4] She began Herceptin and vinorelbine therapy at 27 weeks gestation and developed oligohydramnios shortly thereafter. Due to her condition, weekly Herceptin and vinorelbine therapy continued up to and through delivery but she received extra IV hydration with each treatment. The oligohydramnios persisted but was not progressive, and the patient underwent induction of labor at 35 weeks. She delivered a healthy infant by vaginal delivery and there were no complications.

In cases 9 and 10, the mothers received Herceptin therapy throughout the course of their pregnancies, and both had poor pregnancy outcomes. One mother continued Herceptin mono-therapy from prior to conception through delivery at 36 weeks. Oligohydramnios was diagnosed at 26 weeks gestation. Following counseling, the patient decided to continue the pregnancy and Herceptin therapy. The baby was delivered by cesarean at 36 weeks gestation with limb deformities and pulmonary hypoplasia. It died at six hours of life. Case 10 was a woman with a

twin gestation receiving Herceptin monotherapy. At 24 weeks gestation, ultrasound revealed olighohydramnios and evidence that the "lungs were not developing properly." She chose to undergo therapeutic abortion at that time.

Case 11 is a published case of a woman who received two doses of Herceptin four weeks prior to and three days prior to conception. She did not receive any additional chemotherapy during her pregnancy. She had a normal pregnancy and delivery, and the baby had no complications.[12]

Chemotherapy and Pregnancy

A toxnet search found the word "oligohydramnios" associated with the following drugs: captopril, quinapril, losartan, indomethacin, enalapril, celcoxib, benazepril, rofecoxib, valdecoxib, and lisinopril. Other than ACE inhibitors and NSAIDs, no other drugs were associated with oligohydramnios in the Toxnet search.

A Toxnet search with the terms "vinorelbine and oligohydramnios" and "cancer and oligohydramnios" yielded only one informative and relevant article not already presented in this review. In 1997, Cuvier et al reported on three women with breast cancer treated with 5-fluorouracil (5-FU) and vinorelbine during pregnancy. The women began therapy at 24 – 29 weeks gestation. After two rounds of 5-FU and vinorelbine chemotherapy, one woman received six courses of cyclophosphamide and epidoxorubicin due to disease progression. Two women had spontaneous labor and vaginal deliveries at 37 and 41 weeks, and the third woman (the one who received four chemotherapeutic agents) delivered at 34 weeks by cesarean section. It appears that none of these women developed oligohydramnios; however, the reason for the cesarean delivery at 34 weeks was not provided in the article. All three children had normal development at 23 – 35 months of age.[3]

A PubMed search using the search terms "paclitaxel and oligohydramnios", " docetaxel and oligohydramnios", and "vinorelbine and oligohydramnios," found only the article by Bader et al that reports one of the oligohydramnios cases associated with Herceptin use with paclitaxel during pregnancy. A search with the terms "cancer and oligohydramnios" found three relevant articles. Two involved Herceptin cases already discussed in this review (Watson and Bader) and the other was a case report of a woman diagnosed with acute lymphocytic leukemia at 25 weeks gestation.[5] A detailed obstetrical ultrasound at that time revealed fetal growth at the 35th percentile, a normal AFI, and normal umbilical artery Doppler systolic-diastolic ratio. At 26 weeks gestation, the patient began intensive multi-agent chemotherapy: cyclophosphamide, intrathecal methotrexate, daunorubicin, vincristine, 6-mercaptopurine, cytarabine, L-asparaginase, and prednisone. After each course of chemotherapy, transient oligohydramnios occurred with the AFI decreasing to 2.0 – 3.4 cm and recovering to normal over 6-7 days. The patient went into labor spontaneously at 36 2/7 weeks gestation. There was thick meconium at rupture of membranes. This patient underwent extensive fetal monitoring during the pregnancy. Weekly non-stress tests began at 28 weeks gestation and were done twice weekly starting at 32 weeks. Ultrasound assessments of amniotic fluid were done weekly once chemotherapy began. Additional factors during this pregnancy included maternal anemia (transfusion for a hematocrit of 22%) and antibiotic treatment for a MRSA infection of indwelling Hickman catheter.[5]

Kelly et al[7] published a review article in 2006 on the options for systemic therapy in pregnant patients with breast cancer. The authors included eight studies that reported outcomes for women treated with chemotherapy during pregnancy for a variety of cancers. Three percent of babies had a congenital anomaly, which is the same as the background rate in the population. Fetal death, spontaneous abortion, prematurity, and fetal complications occurred more often in babies born to leukemic patients compared to those born to women with other tumor types. No cases of oligohydramnios were reported, but this reviewer did not review all of the original articles in this series. The largest included series was by Germann et al (2004) and did not describe any diagnoses of oligohydramnios or anhydramnios.

The Cancer and Childbirth Registry has enrolled about 92 pregnant women with breast cancer. This reviewer spoke with the registry director, Dr. Elyce Cardonick, a maternal-fetal-medicine specialist. Dr. Cardonick stated that she has seen cases of borderline oligohydramnios in pregnant women with breast cancer following a round of chemotherapy but additional IV hydration administered with the chemotherapy reversed the process. She has not seen severe oligohydramnios or anhydramnios associated with chemotherapy treatment for breast cancer during pregnancy.

DISCUSSION/CONCLUSIONS

Herceptin (trastuzumab) is a recombinant IgG humanized monoclonal antibody that binds to the epidermal growth receptor 2. It is effective for the treatment of Her-2 overexpressing metastatic breast cancers as monotherapy and for primary node-positive breast cancers as part of an adjuvant chemotherapy regimen. There are nine unique reports of oligohydramnios associated with Herceptin use in pregnancy both in the published literature and post-marketing reports in the AERS database. In four, and possibly five, of these cases, the amniotic fluid volume has recovered following discontinuation of Herceptin therapy. There is one case with both a positive dechallenge and rechallenge. The current label mentions the existence of a limited number of post-marketing cases of oligohydramnios and states that no association between oligohydramnios and the use of Herceptin has been established.

Pre-clinical data suggest an important role for epidermal growth factor in renal development. Human renal tubular development continues until 36 weeks gestation. Data from studies in organ culture, where an antibody is used to block the epidermal growth factor receptor, suggest that blocking the EGF receptor may interfere with normal nephron development. It seems scientifically plausible, based on the drug's mechanism of action that Herceptin could potentially increase the likelihood of oligohydramnios.

Oligohydramnios (decreased amniotic fluid volume) and anhydramnios (no amniotic fluid), in the absence of premature rupture of membranes, can be related to chronic fetal hypoxia, decreased or absent fetal renal function, poor placental function, and some fetal anomalies. In preterm pregnancies, the presence of oligohydramnios is associated with increased fetal morbidity, which is due in part to an increased risk of cord compression and due in part to the underlying condition that caused the oligohydramnios.

At this time, the data are not robust enough to conclude that a clear association exists between the use of Herceptin during pregnancy and the occurrence of oligohydramnios; however, the data do suggest a possible association that deserves monitoring. Additional data are needed to more clearly define and understand this possible relationship. If additional data further support an association between Herceptin use during pregnancy and oligohydramnios, then an attempt should be made to answer the following questions:

1. During which periods of gestation is Herceptin exposure associated with an increased risk of oligohydramnios?

2. Does the risk vary with the Herceptin dose and frequency of administration?

3. Does additional IV hydration either at the time of chemotherapy or in between courses of therapy alter the frequency or severity of oligohydramnios?

4. With reference to the time of Herceptin administration, when does the AFI decline and when does it recover?

Based on a woman's individual disease state and course of progression and on risk/benefit counseling between physician and patient, some women may continue Herceptin when oligohydramnios occurs and some may stop. Some women who continue therapy may be delivered depending on the gestational age of the fetus and other factors, and some may continue their pregnancy with fetal monitoring and ultrasound examinations. In order to optimize the clinical outcomes for pregnant women with breast cancer and their babies, women using Herceptin during pregnancy should be monitored for oligohydramnios. If and when oligohydramnios occurs, risk/benefit counseling should occur and fetal testing should begin.

While oligohydramnios is not a classically teratogenic effect, the oligohydramnios may be caused by an untoward effect of Herceptin on nephron growth and function.

RECOMMENDATIONS

5. The pregnancy category for Herceptin (trastuzumab) should be changed to a "D" based on the available human data that suggest a possible teratogenic effect leading to oligohydramnios.

6. The pregnancy portion of the Herceptin label should include information about the known cases of oligohydramnios that occurred with use of Herceptin during pregnancy.

7. The label should recommend that pregnant women using Herceptin undergo screening for oligohydramnios with obstetrical ultrasound examination at regular intervals.

8. If oligohydramnios occurs, the obstetrician should begin fetal testing appropriate for the gestational age of the fetus and consistent with the standards of care for the community. This testing should continue on a regular basis until one of two conditions is met:

a. Herceptin therapy is discontinued and oligohydramnios resolves
b. Delivery.

7. In cases where the physician and patient decide to continue Herceptin therapy for maternal reasons despite the presence of oligohydramnios, additional intravenous hydration should be considered. With other forms of chemotherapy during pregnancy, transient oligohydramnios has been observed, and extra hydration sometimes mitigates this effect.

8. Include contact information for the Cancer and Childbirth Registry and encourage enrollment of pregnant patients using Herceptin.

9. Please see Appendix B for suggested draft language for the pregnancy and nursing mothers portions of the label.

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Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
(b) (6) Table 1 Case1	32	(b) (6) (pre-conception) to (b) (6) (26 weeks gestation)	None	Recurrent breast cancer at 14 weeks gestation. Started on Herceptin 480 mg IV Q 3 weeks. US at about 26 weeks showed oligohydramnios with normal fetal growth. Hospitalized for bedrest and corticosteroids. Herceptin stopped the next day. Amniotic fluid increased. Weekly Herceptin resumed. Received one dose Herceptin 480 mg IV at 28 weeks gestation. Delivered one week later. Gestational age information is not completely consistent in MedWatch report.	By best information, preterm male infant delivered by cesarean section for breech position and oligohydramnios at 29 weeks gestation. Weight=1455g; Apgars 2/3/5. To NICU for respiratory distress and chronic lung disease. Ventilated for 2 weeks. Hospitalized for 3 months for prematurity.
(b) (6) Table 1 Case2	38	Before pregnancy. Stopped for gestational weeks 7-14. Resumed gestational weeks 14-32.	Zoladex	Patient treated for metastatic breast CA with Taxotere and Hercptin until (b) (6) when pregnancy diagnosed. Borderline decreased amniotic fluid at 28 weeks. Oligohydramnios diagnosed at 32 weeks. Fetal monitoring in hospital. Herceptin stopped. Mother had gestational diabetes and hypertension.	Spontaneous labor and normal vaginal delivery at 36.2 weeks. Male infant, 6 lbs, 10 oz., Apgars 8/9. Down's Syndrome. Discharged on 4th day of life.
(b) (6) Table 1 Case 3	28	Herceptin 6 mg/kg Q 3 weeks from (b) (6) (b) (6) (time of conception/implantation) until 20 weeks gestation	None	Patient diagnosed with poorly differentiated carcinoma (grade III) with perinodal involvement and HER-2/neu positivity. Treated with XRT and 3 cycles doxorubicin and cyclophosphamide and 3 cycles paclotaxel. Started Herceptin near conception. Pregnancy diagnosed at 23 weeks with anhydramnios. Herceptin stopped. Amniotic fluid started to reaccumulate at 25 weeks and was normal at 32 weeks gestation. This case was published.	Induction of labor and normal vaginal delivery of a living female infant at 37.5 weeks gestation (2960 g, Apgars 8/9) Baby had normal renal function and no evidence of pulmonary hypoplasia. Normal placenta. Baby had normal growth at six months of age. Watson et al (2005). See references.

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
(b) (6) Table 1 Case 4	29	Two years of Herceptin therapy prior to pregnancy. Herceptin discontinued after dose at about 24 weeks gestation	None	Pregnancy diagnosed and confirmed by US at 17 weeks gestation. Herceptin given at 15 weeks and probably discontinued after treatment at 24 weeks gestation. Borderline low amniotic fluid at 25 weeks gestation progressed to oligohydramnios.	Normal preterm female infant delivered by cesarean section at 34 weeks gestation.
(b) (6) Table 1 Case 10	30	Herceptin prior to and throughout pregnancy	Possibly vinorelbine	Twin pregnancy with oligohydramnios diagnosed at 24 weeks gestation. According to the report, there was "evidence that the lungs were not developing properly" and were considered incompatible with life. Mother had a therapeutic abortion.	Therapeutic abortion after 24 weeks gestation.

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
(b) (6) Table 1 Case 8	26	Herceptin started at 27 weeks gestation	Vinorelbine	Patient diagnosed and treated for Grade III infiltrating ductal carcinoma with positive nodes. She completed treatment with Herceptin, paclitaxel, 5-FU, epirubicin, and cyclophosphamide through a clinical trial. Fourteen months after diagnosis, she presented with right upper quadrant pain and a 27 week pregnancy. Multiple imaging studies including ultrasound were performed. She had multiple hepatic metastases and increased LFTs. Patient was treated with Herceptin (4mg/kg load and 2 mg/kg per week) and vinorelbine (weekly x 3, then 1 week rest). She was seen weekly by a high risk obstetrician and oncologist. After starting treatment, oligohydramnios was noted. This was thought secondary to fluid shifts or systemic therapy. Extra IV hydration given with each chemotherapy treatment. Weekly fetal monitoring. AFIs remained low. Decreased fetal movement at 34 5/7 weeks with occasional, mild fetal heart decelerations.	Induction of labor at 34 5/7 weeks with normal vaginal delivery of a healthy male infant (5 lbs, 11 oz; Apgars 9/9/10). Normal and healthy at six months of age. Fanale et al (2005). See references.
(b) (6) Table 1 Case 9	36	Herceptin throughout pregnancy	None	Patient previously diagnosed with breast cancer. Being treated with Herceptin 441 mg Q 3 weeks. Pregnancy confirmed and dated by 26 week ultrasound. Anhydramnios diagnosed. Patient counseled and chose to continue pregnancy.	Female infant delivered by cesarean section at about 36 weeks gestation (2690 g, Apgars 8/8). Baby had lower limb deformities and died of pulmonary hypoplasia at 6 hours of life.

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
(b) (6) Table 1 Case 7	38	Herceptin at 26 and 29 weeks gestation	Paclitaxel	Seven years prior to pregnancy, the patient was diagnosed with Stage I breast cancer. She was treated with six cycles of cyclophosphamide, methotrexate, and 5-FU followed by XRT and 5 years of tamoxifen. At 17 weeks gestation, the patient developed paresthesia and hypoesthesia of the left arm and cervical neck pain. On MRI, there was metastatic infiltration and collapse of the second cervical vertebrae with spinal compression and metastases in the fourth thoracic vertebrae and femur. Between 26 and 32 weeks gestation, the patient received two treatments of Herceptin and paclitaxel. On US, the fetal abdominal circumference stopped increasing and the amniotic fluid volume decreased nearly to anhydramnios. Corticosteroids given for fetal lung maturation.	Delivery of living infant by cesarean section for anhydramnios, fetal growth restriction, and suspected fetal renal failure. Normal placenta. Admitted to NICU with signs of bacterial sepsis and decreased renal function. Renal function normalized by day of life 28, and the baby was discharged home. Normal development at 12 weeks of age. Bader et al (2007). See references.

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
J Clin Onc 01/10/06 Table 1 Case 11	30	3.5 weeks and 3 days prior to conception	None	Patient diagnosed with multifocal grade 2 invasive ductal adenocarcinoma of the right breast with two of five nodes positive. Estrogen and progesterone receptor negative. Her-2/neu positive. Had been trying to conceive. Treated with four cycles of epirubicin followed by four cycles of cyclophosphamide, methotrexate, and 5-FU over six months. Due to incomplete excision and strong family history of breast CA, had a bilateral mastectomy followed by radiotherapy to the right chest wall. Enrolled in Herceptin Adjuvant trial (HERA) and randomized to trastuzumab treatment every three weeks. Had a positive pregnancy test before third treatment cycle. Conceived three days after second dose. Withdrew from trial.	Spontaneous vaginal delivery of a healthy female infant at full term. No complications. Waterston and Graham (2006). See references.

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
Reprod Tox 06/07 Table 1 Case 5	32	Throughout pregnancy until 24 weeks gestation	None	Patient diagnosed with Her-2/neu positive breast cancer during her first pregnancy. She underwent radical mastectomy and therapeutic abortion. Treated with paclitaxel and carboplatin. Six months after completing chemotherapy, diagnosed with lung metastases. Treated with paclitaxel, carboplatin, and trastuzumab. Eighteen months later had a single brain metastasis treated with surgery and radiation. After one year of ongoing treatment with trastuzumab alone and no recurrence, the patient presented with a five week viable pregnancy. Treatment was continued and the pregnancy progressed normally until trans-thoracic echocardiography revealed an asymptomatic mild low ejection fraction at 18 weeks. Fetal growth and anatomical survey were normal. Repeat maternal echo at 24 weeks was unchanged but trstuzumab was discontinued. Fetal US at 25 weeks gestation showed normal growth, AFI, and BPP.	Cesarean delivery (for breech presentation) of a healthy female infant at 37 weeks gestation. Normal placental pathology without metastases. Shrim et al (20007). See references.

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

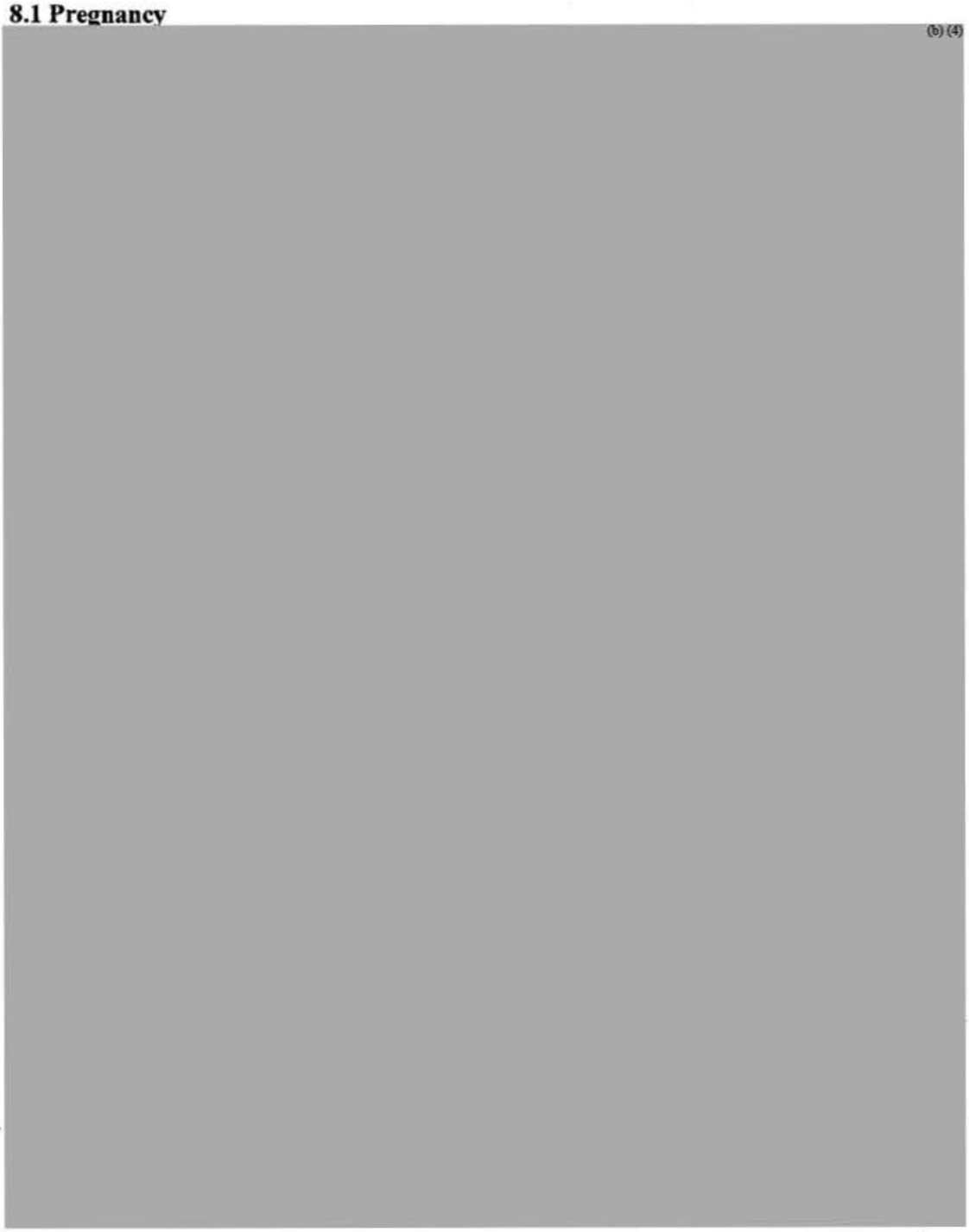
Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
Obstet Gynecol 08/07	28	23, 26, and 27 weeks gestation	Docetaxel	(Australia) Patient was diagnosed with left infiltrating ductal carcinoma, grade 2, stage T2N2M0 in [redacted] (b) (6) She had a radical mastectomy and lymphadenectomy with 18 of 18 nodes positive. The tumor was E/P receptor negative and human epidermal growth factor 2 (Her-2/neu) positive. She was treated with chemotherapy and radiotherapy. At 20 weeks gestation, MRI revealed brachial plexus and pulmonary metastases. She was treated with three cycles of docetaxel and trastuzumab at 23, 26, and 27 weeks gestation. A fetal ultrasound was done at 30 weeks for clinical suspicion of fetal growth restriction. The ultrasound showed fetal growth measurements at <5th percentile consistent with IUGR and anhydramnios. Chemotherapy was held until after delivery. Two doses of betamethasone were given for fetal lung maturation in case delivery was needed. At 33 weeks, amniotic fluid was reaccumulating. Due to the patient's advanced disease state, she was delivered at 36 weeks.	Cesarean delivery for breech presentation at 362/7 weeks due to maternal disease state. Small amount of clear amniotic fluid at delivery. Living male infant, 2230 g, Apgars 7/9. Normal neonatal urine output. No complications. Sekar and Stone (2007). See references.

Appendix B: Proposed Changes to Current Pregnancy Labeling Language

Suggested deletions are indicated with strikeouts, and suggested insertions are indicated with an underline.

8.1 Pregnancy

(b) (4)



8.3 Nursing Mothers

Appendix F Applicant's Original Herceptin Label for BO16348 (HERA)

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

Appendix G Final Herceptin Label for BO16348 (HERA)

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies, NIH Bldg 29B, HFD-123
29B Lincoln Drive, Bethesda, MD 20892-4555

Date: January 10, 2008

From: Wendy C. Weinberg, Ph.D., Product Reviewer, DMA

To: File STN103792 (License 1048)

Through: Patrick Swann, Ph.D., Deputy Director, DMA

Subject: BLA 103792/5175; Product review and categorical exclusion

Sponsor: Genentech, Inc.

Received: December 22, 2006
PDUFA date: January 21, 2007

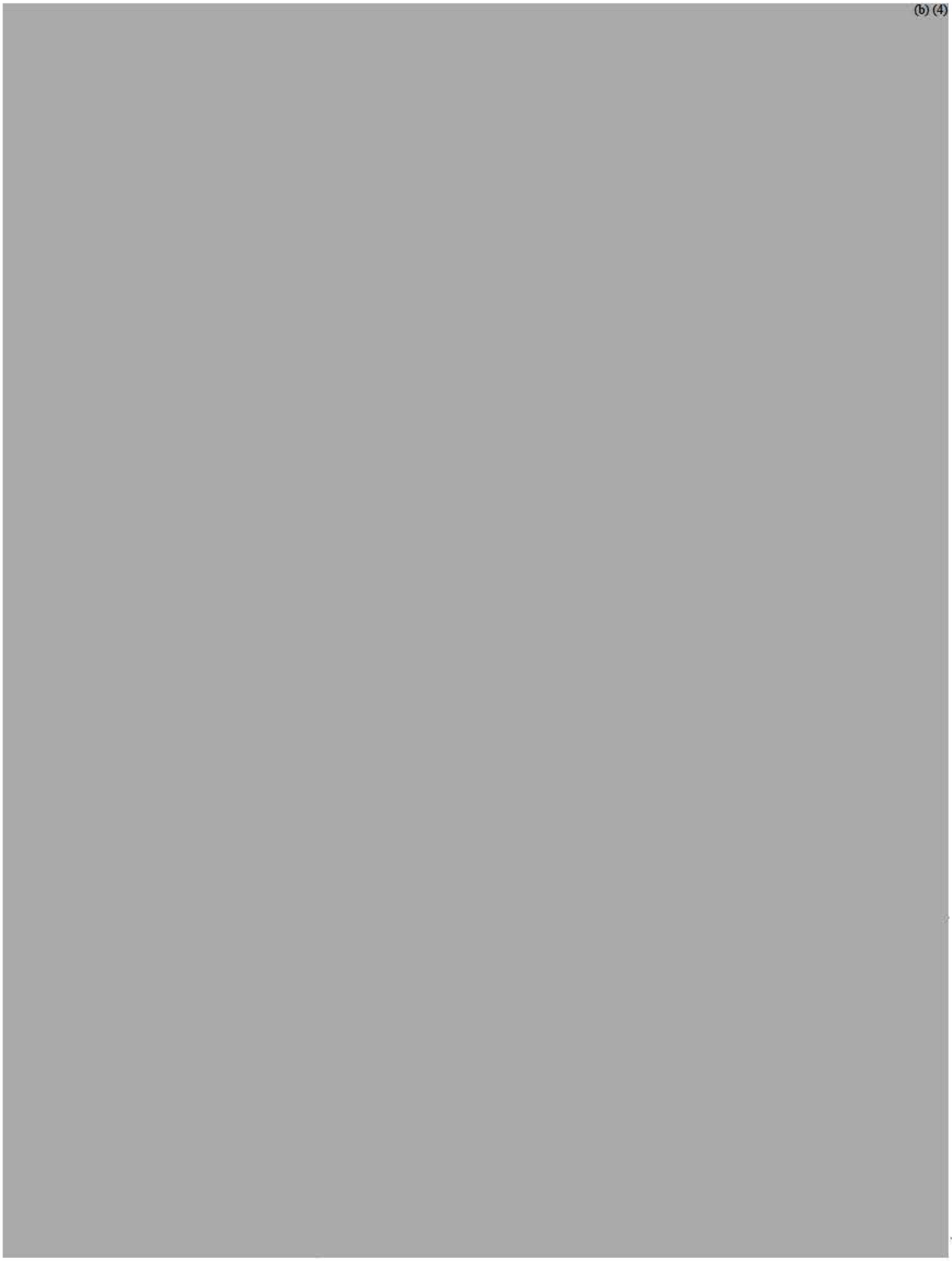
Contact: Erin E. Jones, (b) (6)

Recommendation:
Approval. Based on analysis of the comparability data provided, The Penzberg manufactured material used in the HERA trial presented in this supplement appears to be sufficiently comparable to FDA licensed material to support FDA approval to expand the clinical indication for Herceptin.

Summary:
This is an efficacy supplement to the Herceptin BLA to expand the indication of Herceptin (b) (4) to include an every 3 week dosing schedule, based on the HERA study. Proposed initial dose of 8mg/kg followed by 6 mg/kg once every 3 weeks for 52 weeks; all doses to be administered as 90 minute IV infusion.

The HERA study in this application utilized EU approved Herceptin manufactured at Penzberg by Roche. This review covers the following information submitted during the review process of this supplement: CMC review of the process and biochemical characteristics of EU approved Trastuzumab Drug Substance manufactured by Roche in their Penzberg facility using the v1.0 process compared to Trastuzumab manufactured by Genentech under their FDA license using the v1.0 and v1.1 processes; acceptability of

endotoxin levels of FDA approved Herceptin at the intended dose for this application, and Genentech's Claim of categorical exclusion.



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(b) (4)

II. Environmental Analysis:

Qualification for a categorical exclusion from the Environmental Assessment requirement is claimed in Item 20, section 1.12.14, as specified in 21 CFR Section 25.15(d), under 21 CFR 25.31(c). This section applies to action on an NDA, abbreviated application, application for marketing approval of a biological product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. It is stated that, to the applicant's knowledge, no extraordinary circumstances exist. There is no information indicating that additional environmental information is warranted.

Conclusion: ***The categorical exclusion claim is appropriate.***

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

PHARMACOLOGY REVIEW(S)

MEMORANDUM

TO: The file
THROUGH: Patricia Keegan, M.D., Director, Division of Biologic Oncology Products, Office of Oncology Drug Products, CDER
FROM: Anne M. Pilaro, Ph.D., Acting Supervisory Toxicologist, Pharmacology/Toxicology Branch, Division of Biologic Oncology Products, OODP, CDER
STN BLA #: 103792/5175
SPONSOR: GENENTECH, INC.
PRODUCT: humanized, monoclonal antibody trastuzumab (Herceptin®), directed against the Her2/*neu* receptor, for the treatment of Stage III or IV breast cancer
AMENDMENT TYPE: efficacy supplement, **labeling conversion to PLR format**
DATE: January 10, 2008

SYNOPSIS:

As part of the efficacy supplement STN BLA #103792/5175, the sponsor is converting the labeling to Physician's Labeling Rule (PLR) format. Changes in the *WARNINGS and PRECAUTIONS* (Section 5.6, *Embryo-fetal Toxicity [Pregnancy Category D]*), *USE IN SPECIFIC POPULATIONS* (Section 8.1, *Pregnancy* [*Teratogenic Effects: Pregnancy Category D]* and Section 8.3, *Nursing Mothers*), and *NONCLINICAL TOXICOLOGY* (Section 13.1; *Carcinogenesis, Mutagenesis, Impairment of Fertility,* and 13.2, *Animal Toxicology and/or Pharmacology*) required verification of the supporting nonclinical data. The data were included in the original labeling; however, there was insufficient information available to support the conversion to PLR format. Specifically, the types of studies conducted, the doses of trastuzumab tested and resulting exposure margins compared to human dosing, and the fetal outcomes, as well as any data regarding evaluation of male fertility parameters were required to support the labeling in PLR format.

The sponsor was requested to provide the supporting data for these sections of the label, and responded by submitting .pdf copies of three nonclinical, reproductive and/or developmental toxicology studies with trastuzumab, conducted in cynomolgus monkeys. These studies were initially reviewed in the nonclinical review for the original BLA (STN #103792/0000), and will not be subject to a complete review here. However, evaluation of the study reports confirms that they do contain the supporting data required for the labeling in PLR format. The three studies are summarized in context of the sections of the PLR labeling that they support, below.

Section 5.6 - *WARNINGS and PRECAUTIONS, Pregnancy Category D* and Section 8.1, *Teratogenic Effects*

Study #95-039-1450. GN1450. Intravenous embryo-fetal development study in the cynomolgus monkey.

Twelve presumed pregnant, cynomolgus monkeys per dose group were treated by i/v injection with trastuzumab during the critical period of organogenesis (gestational day [GD] 20 through GD50). The doses tested in this study were vehicle control (GN1450 vehicle, composition not specified), 1, 5, and 25 mg/kg trastuzumab, administered GD20, GD21, GD22, GD23, GD27, GD30, GD34, GD37, GD41, GD44, GD47, and GD50. Dams were followed for clinical and laboratory signs of toxicity, toxicokinetic profiles, and immunogenicity. On GD100, offspring were delivered by Caesarian section and evaluated for skeletal and soft tissue malformations, as well as serum and amniotic fluid trastuzumab and anti-trastuzumab antibody levels.

In general, trastuzumab treatment was well-tolerated by the pregnant animals, and no evidence of maternal toxicity was noted. Early mortalities were present in a total of 5 dams during the study period, and occurred in all dose groups, including the control. In animals #3037and #4210 (1 mg/kg/dose group), and #208 (25 mg/kg/dose group), the deaths occurred 2, 10, and 35 days, respectively following spontaneous abortion by these dams. Early deaths for animals #3115 (vehicle control) and #3257 (1 mg/kg/dose group) were not associated with spontaneous abortion. In all cases, there were no apparent clinical signs of toxicity prior to death. However, on necropsy histologic evidence of bacterial infection was present in skin lesions and in the intestines, and was identified tentatively as β-hemolytic *Streptococcus*, *Staphylococcus sp.*, and/or *Pasteurella* infections. Given the incidence of early mortalities and presence of infection in animals from all dose groups including the control, these findings appear unrelated to trastuzumab treatment.

Spontaneous abortions occurred in 2/12 control (17%), 5/12 low-dose (42%), 3/12 (25%) monkeys treated with 5 mg/kg/dose trastuzumab, and 4/12 (33%) of dams in the 25 mg/kg/dose group. There were no statistically significant differences between the control and trastuzumab-treated dose groups in the incidence of spontaneous abortions ($p = 0.8973$; *Chi* square). Additionally, the incidence of abortion in this study was within the range of historical controls for this laboratory (88/492 or 18%; from a total of 43 embryofetal toxicity studies, with a range of 0-50% spontaneous abortion).

Live fetuses were recovered from 10 monkeys in the control group, 7 animals treated with 1 mg/kg/dose trastuzumab, 9 dams in the 5 mg/kg/dose group, and 8 dams in the 25 mg/kg/dose group. Mean values for fetal measurements (body, placental, and organ weights, crown:rump lengths) in all trastuzumab-treated dose groups were within normal limits for cynomolgus monkeys. There were no gross skeletal or soft tissue malformations in the offspring from trastuzumab-treated dams at any dose level.

Toxicokinetic evaluation showed that maternal levels of trastuzumab increased rapidly during the first week of dosing (GD20 through GD27), and approached steady-state by the end of this period. During the course of the study, mean values for trastuzumab trough levels showed dose-related, approximately linear increases, and were maintained for the duration of the dosing period in all animals except dam #6292 in the 1 mg/kg/dose group. This animal had pre-existing anti-drug antibody and no detectable serum trastuzumab levels present at any time point on study (see below). The mean values for trastuzumab trough levels are presented in Table 1 below, which was abstracted from the sponsor's final study report.

Table 1. Summary Table of Mean (± S.D.) Trastuzumab Maternal Trough Serum Levels and Elimination Half-Life in Pregnant Cynomolgus Monkeys Dosed from GD20 through GD50

Parameter	Group 1 Control (n = 9 - 12)	Group 2 1 mg/kg (n = 6 - 10)[a]	Group 3 5 mg/kg (n = 10 - 12)	Group 4 25 mg/kg (n = 8 - 10)[a]
Trough Concentrations (mcg/mL)[c]				
Maximum	0.000[d]	48.1 (9.22)	349 (87.0)	1697 (474)
Minimum	0.000	27.8 (5.14)	205 (35.8)	938 (268)
Average	0.000	35.6 (6.04)	259 (50.4)	1281 (341)
Half-life (days)[e]	–[f]	7.09 (0.86)	7.72 (1.07)	10.1 (1.51)

a. Concentrations from group 2 animal no. 6292 (all 'ns') were excluded from this table due to antibody reaction.

b. Day 48 and 55 concentrations from group 4 animal no. 5452 were excluded from this table due to apparent misdosing. Half-life could not be calculated for this animal due to early removal from the study.

c. Troughs concentrations reported here were from samples collected during the dosing phase of the study over Days 27 through 48.

d. All concentrations for group 1 were 'ns' (less than the lowest standard on the standard curve, ie. less than 0.078 mcg/mL) and were therefore assigned a value of zero by convention. No standard deviation was calculated for this reason. Concentrations from animals no. 2914 and 5570 were excluded from this table due to apparent misdosing.

e. Half-life was calculated over Days 55 through 100 by linear regression on the natural log of concentrations vs. time.

f. No half-life was calculated for group 1 since all concentrations were 'ns'.

Placental transfer of trastuzumab, with subsequent fetal exposure was also detected in this study. Table 2 below, from the sponsor's final study report shows that at time of Caesarean section on GD100, trastuzumab was present at detectable levels in serum from fetuses in all dose groups, and in amniotic fluid from offspring of dams treated with 5 or 25 mg/kg/dose. The concentration of trastuzumab in fetal samples increased with increasing dose of antibody, and ranged from 10% to approximately 19% of maternal serum levels present in the fetal serum, and approximately 3 to 4% of maternal serum levels present in the amniotic fluid of fetuses in the mid- and high-dose groups. These results are summarized in Table 2, below.

Table 2. Summary of Mean (± S.D.) Trastuzumab Maternal and Fetal Serum and Amniotic Fluid Concentrations, and Concentration Ratios from Pregnant Cynomolgus Monkeys at GD100

Parameter	Group 1 Control (n = 0 - 9)	Group 2 1 mg/kg (n = 2 - 5)[b]	Group 3 5 mg/kg (n = 9)	Group 4 25 mg/kg (n = 8)[b]
Concentrations (mcg/mL):				
Maternal Serum	0.000[c]	0.325 (0.255)	3.70 (1.22)	59.9 (41.3)
Fetal Serum	0.000	0.049 (0.077)	0.679 (0.210)	14.8 (23.2)
Amniotic Fluid	0.000	0.000 [d]	0.155 (0.082)	1.50 (0.851)
Concentration Ratios:				
Fetal / Maternal Serum	--[e]	0.100 (0.137)	0.188 (0.044)	0.171 (0.176)
Amniotic Fluid / Maternal Serum	--	0.000	0.039 (0.019)	0.028 (0.009)
Amniotic Fluid / Fetal Serum	--	0.000	0.214 (0.113)	0.291 (0.214)

a Concentrations from group 2 animal no. 6292 (all 'ns') were excluded from this table due to antibody reaction.

b Day 100 samples could not be obtained from all animals in each group because some animals were previously removed from study due to spontaneous abortion or death.

c All concentrations for group 1 were 'ns' (less than the lowest standard on the standard curve, ie. less than 0.078 mcg/mL) and were therefore assigned a value of zero by convention. No standard deviation was calculated for this reason. Concentrations from animals no. 2914 and 6070 were excluded from this table due to apparent misdosing.

d No standard deviation was calculated since all concentrations were 'ns'.

e No ratios could be calculated since both concentrations were 'ns'.

There were no detectable anti-drug antibody responses in any of the trastuzumab-treated dams or fetuses delivered at GD100, with the exception of one pair. Monkey #6292 and its fetus #6292f had positive titers for anti-trastuzumab antibody in both the ELISA assay for total binding antibody, and the BT-474 neutralization bioassay. Antibody titer values in the dam at GD20 and GD50 were 3.2 and 3.4 absorbance units (AU), respectively, and at GD100 were approximately equivalent in the dam and offspring, with titers of 2.7 and 2.4 AU, respectively. Since anti-product antibodies were initially present in the dam on GD20 prior to treatment with trastuzumab, these results likely represent a pre-existing, cross-reactivity and are not related to a response to trastuzumab.

Comment: The labeling reports oligohydramnios, or decreased amniotic fluid in pregnant women receiving Herceptin® treatment during the second and third trimester. This finding was not observed in either of the cynomolgus monkey developmental toxicology studies (see additional study summary, below). However, since human data are available, Herceptin® is labeled Pregnancy Category D.

Comment: The sponsor reports in the labeling that there are no maternal or fetal toxicities associated with Herceptin® treatment at up to 25-times the human exposure. On a direct mg/kg basis, the dose of trastuzumab tested in the animal studies was only 12.5-fold greater than the recommended weekly human dose of 2 mg/kg. However, in the present developmental toxicity study and in the fertility study, trastuzumab was administered twice weekly. Therefore, the language in the labeling claim regarding the exposure margin is supported by the nonclinical dosing.

In conclusion, the results of this study support the reported findings in Section 5.6, *Pregnancy Category*

D and Section 8.1, *Teratogenic Effects* of the revised, PLR formatted label for trastuzumab (Herceptin®).

Section 8.2 – *USE IN SPECIAL POPULATIONS, Nursing Mothers* and Section 13.2, *NONCLINICAL TOXICOLOGY, Animal Toxicology and/or Pharmacology*
Study #95-238-1450. Late gestational toxicity, placental transfer, and secretion in milk study with GN1450 in the cynomolgus monkey.

Two groups (n = 8/group) of pregnant, cynomolgus monkeys were treated by i/v injection with trastuzumab during the latter part of gestation, from approximately GD120 through either GD150 (Group 1), or through post-partum day (PPD) 28 (Group 2). All animals received 25 mg/kg/dose of trastuzumab by i/v injection daily from GD120 through GD123, then once weekly for the remainder of the dosing periods. Dams were followed for clinical and laboratory signs of toxicity, toxicokinetic profiles, and immunogenicity. For Group 1 animals, pregnancies were terminated by Caesarean section on GD150, while Group 2 females were allowed to deliver naturally and nurse the offspring until PPD29, at which time the animals were returned to the colony.

Maternal blood was sampled once pre-study, and then weekly prior to dosing for measurement of serum trastuzumab levels. For evaluation of serum anti-trastuzumab antibody levels, maternal blood was sampled once pre-treatment for all animals. Amniotic fluid, maternal blood and fetal umbilical vein blood were obtained at GD150 at the time of Caesarean section for Group 1 animals. Maternal and infant blood, and maternal breast milk samples were obtained from animals in Group 2 on PPD28.

Trastuzumab treatment was well-tolerated by the pregnant animals, with no evidence of maternal toxicity. Body weights, body weight gains, clinical chemistry and urinalysis profiles for the treated dams were within normal limits. There were three unsuccessful deliveries/stillbirths during the study. Animal #1791 in Group 2 went into labor on GD163, had difficulty delivering the fetus, and was euthanized for humane reasons. A second Group 2 monkey (animal #3376) did not deliver successfully; the fetus was removed by Caesarean section on GD176, however, the dam survived. One Group 1 monkey (animal #5383) had a stillbirth at GD131.

Live fetuses were removed by Caesarean section from 7/8 animals in Group 1 at GD150, and evaluated morphologically for evidence of toxicity. No trastuzumab-related changes in fetal body measurements, fetal body or organ weights, or placental weights were detected. There were no treatment-related external, visceral or skeletal anomalies and no fetal malformations observed in the offspring in this group. Visceral findings, including hemorrhage in the cardiac area of the stomach or at the stomach wall were present in 5/7 offspring, and likely represent a post-mortem artifact. Minor skeletal variations, including ossification of the vertebra(e), sternebra(e), and/or carpal and tarsal bones were observed in 6/7 offspring in this group. These findings are considered to be normal developmental variations, and not related to trastuzumab treatment.

In Group 2, live infants were successfully delivered to 6/8 dams. There was no observable effect of trastuzumab treatment on infant body weights, as compared to historical control data from the study laboratory. Monkey #9536 from Group 2 had no detectable lactation and therefore could not breast-feed its offspring; this infant was fostered to another lactating female from the stock colony. From PPD11 through PPD28, alopecia at the base of the tail and back of the head was reported for this infant. There were no other clinical signs of toxicity reported for the infants in this group.

Using an ELISA assay, no anti-trastuzumab antibodies were detected in the dams at any time point on study, or in the fetuses at GD150 or the infants at PPD28. However, the sponsor states in the final study report that the interpretation of the negative findings in this study may be limited, since the presence of detectable trastuzumab in the blood samples may interfere with detection of the anti-drug antibody.

Maternal exposures were comparable between both groups of pregnant dams treated with 25 mg/kg/dose trastuzumab. A slight (approximately 40-60%) accumulation in serum trastuzumab levels was observed between the initial value on GD127, and the final values on GD150 (Group 1) and GD169 (Group 2). Following delivery, trastuzumab levels were still present in serum from nursing dams up until PPD28, at approximately similar levels to those observed during gestation (data not shown). The mean values for each group (± S.D.) are presented in Table 3 below, which was abstracted from the final study report.

Table 3. Summary of Mean (± S.D.) Maternal Serum Trastuzumab Levels in Pregnant Cynomolgus Monkeys Following Dosing with 25 mg/kg/dose from GD120 through Delivery

Day of Gestation	Group 1 Cesarean Section (n = 7 - 8) [a]	Group 2 Live Birth (n = 1 - 8)
Predose	0.00 [b]	0.00
120	0.00	0.00
127	1035 (201)	1065 (206)
134	1019 (355)	1220 (265)
141	938 (250)	1439 (348)
148	1746 (1029)	1327 (261)
150±1	1487 (839)	–[c]
155	–[c]	1513 (399)
162	–[c]	1589 (473)
163	–[c]	1572 [d]
169	–[c]	1409 (42.0)
176	–[c]	906 [d]

a Each group contained eight animals, but for some time points samples were available from less than all eight animals.

b For predose and Day 120 samples all concentrations were 'lts' (less than the lowest standard on the standard curve, ie. less than 0.078 mcg/mL); they were therefore assigned a value of zero by convention and no standard deviation was calculated.

c No sample scheduled to be drawn at this time point for this group.

d Only one animal sampled at this time point; therefore no standard deviation was calculated.

Placental transfer of trastuzumab, with subsequent fetal exposure was also detected in this study. Table 4 below, from the sponsor's final study report shows that at time of Caesarean section on GD150, trastuzumab was present at detectable levels in both serum and amniotic fluid from of dams treated with 25 mg/kg/dose. The levels of trastuzumab in fetal blood and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum at GD150, and the amniotic fluid trastuzumab levels were approximately 82% of that present in fetal serum. These results are summarized in Table 4, below.

Transplacental transfer of trastuzumab from dams treated with 25 mg/kg/dose was also evident in infants delivered at term. Mean values for neonatal serum trastuzumab levels were approximately 19% of those present in the dams at time of delivery. Low levels of trastuzumab were also detectable in maternal milk in 5 of the 6 lactating dams, with a mean value of approximately 0.3% of the maternal serum levels and <1% of the neonatal serum levels. These results are presented in Table 4, from the sponsor's final study report.

Table 4. Mean Maternal, Fetal, and Neonatal Serum Levels, and Fetal Amniotic Fluid, and Maternal Milk Levels of Trastuzumab Following Dosing of Cynomolgus Monkeys from GD120 Through GD150 (Group 1) or PPD28 (Group 2)

Parameter	Group 1 Cesarean Section Day 150 ± 1 (n = 7) [a]	Group 2 Live Birth Day 28 Post-Partum (n = 4 - 5) [a]
Concentrations (mcg/mL):		
Maternal Serum [b]	1487 (839)	1544 (862)
Fetal Serum [c]	411 (74.8)	– [e]
Amniotic Fluid [c]	305 (191)	– [e]
Maternal Milk [d]	– [e]	2.73 (1.12)
Neonate Serum [d]	– [e]	376 (213)
Concentration Ratios:		
Fetal / Maternal Serum	0.325 (0.110)	– [e]
Amniotic Fluid / Maternal Serum	0.249 (0.196)	– [e]
Amniotic Fluid / Fetal Serum	0.818 (0.571)	– [e]
Maternal Milk / Maternal Serum	– [e]	0.00280 (0.00269)
Neonate Serum / Maternal Serum	– [e]	0.191 (0.0695)
Maternal Milk / Neonate Serum	– [e]	0.00898 (0.00295)
Neonate Serum / Maternal Milk	– [e]	122 (42.3)

a Each group contained eight animals, but for some time points samples were available from less than all eight animals. For Group 1 animal no. 5383 did not produce a viable fetus; for Group 2 animals no. 1791 and 3376 did not produce a live birth. For Group 2 maternal milk concentration for animal no. 9536 was excluded, and neonate serum concentrations from the neonates of animals no. 6039 and 9536 were excluded. See exclusion listing 3-1 for details.

b Maternal serum reported here was collected on Day 150 ± 1 of gestation for Group 1 and on Day 28 post-partum for Group 2.

c Fetal serum and Amniotic fluid were collected on Day 150 ± 1 of gestation for Group 1; no fetus sampling scheduled for Group 2.

d Maternal milk and neonate serum were collected on Day 28 post-partum for Group 2; no live births scheduled for Group 1 and therefore no maternal milk or neonate serum were collected.

e No sample(s) scheduled to be collected for this group.

In summary, weekly i/v injections of trastuzumab to pregnant cynomolgus monkeys during late gestation through parturition and/or lactation did not result in detectable maternal, fetal, or neonatal toxicity. Transplacental transfer of trastuzumab was observed, with the levels in fetal serum approximately equal to one-third the levels present in maternal blood. Low, but detectable levels of trastuzumab were also present in milk from lactating dams, although the amount transferred to the offspring through milk could not be determined.

In conclusion, the results of this study support the reported findings in Section 8.1, *Teratogenic Effects* and Section 8.2, *Nursing Mothers* of the revised, PLR formatted label for trastuzumab (Herceptin®).

Section 13.1 – *NONCLINICAL TOXICOLOGY, Impairment of Fertility*

Study #95-038-1450. GN1450. Intravenous menstrual cycle study (fertility evaluation) in the

female cynomolgus monkey.

The effects of trastuzumab treatment on female sex hormone levels and menstrual cycle duration were evaluated in cynomolgus monkeys. Six animals per group were treated for 3 menstrual cycles with vehicle control (GN1450 vehicle, composition not specified), or 1, 5, or 25 mg/kg/dose trastuzumab i/v, starting on Days 1-4 of treatment cycle 1, then twice weekly for the remainder of the treatment period. Three observation cycles were monitored for each animal prior to initiating treatment, and animals were also monitored for one recovery cycle following completion of treatment. Serum samples for measurement of progesterone, 17-β estradiol, and luteinizing hormone were obtained on Days 1, 4, 7, 10, 11, 12, 13, 14, 15, 18, 21, 24, and 27 of cycles 3, 4, 5, 6 and 7. Samples for toxicokinetic evaluation of serum trastuzumab levels were obtained once pre-treatment, monthly during the treatment cycles, and once during the second week of the recovery period.

There were no effects of trastuzumab treatment on clinical signs of toxicity, body weight, food consumption, clinical chemistry or urinalysis profiles. Trastuzumab treatment had no remarkable effects on the length of menstrual cycles, or the levels of, or timing to peak levels of the three female sex hormones measured. Toxicokinetic evaluation confirmed that exposure to trastuzumab was maintained over the duration of the three treatment cycles, and declined between the Day 64 (treatment cycle 6) and Day 98 (recovery cycle 7 samples. Mean trastuzumab serum concentrations for animals in the 1, 5, and 25 mg/kg/dose groups were 38, 205, and 1137 mcg/ml, respectively on sampling Day 4 (of Cycle 4). A slight increase in mean serum levels to 61, 360, and 1985 mcg/ml was observed for the three respective dose groups on Day 64, which then declined to 28, 308, and 1106 mcg/ml for the 1, 5, and 25 mg/kg/dose groups, respectively, at the end of the recovery cycle on Day 98. There was no anti-trastuzumab antibody detected by ELISA in any of the treated monkeys at any time point on study.

In conclusion, the results of this study demonstrate no adverse effects of trastuzumab treatment on parameters associated with female fertility, including menstrual cycle duration and sex hormone levels, at weekly doses of up to 25-fold greater than the human recommended dose of 2 mg/kg/week. These data support the labeling claims made by the sponsor in Section 13.2 of the PLR-formatted label, "Impairment of Fertility."

Comment: For PLR labeling, data should be included from evaluation of both male and female fertility parameters. The sponsor was requested to provide information regarding measurement of male fertility (*i.e.*, sperm counts, viability, motility, testicular and epididymal histopathology). In a follow-up electronic mail message on January 11, 2008, the sponsor confirmed that male fertility parameters following trastuzumab treatment have not been evaluated. The licensed indication for trastuzumab is advanced breast cancer which is a disease predominantly of women, although occasional cases are reported in men. The lack of data regarding the effects of trastuzumab on male fertility will be addressed in Section 13.2 of the label. Please see "Suggested Language for Labeling," below.

SUGGESTED LANGUAGE FOR LABELING:

All labeling revisions to Sections 5.6, *Embryo-fetal Toxicity (Pregnancy Category D)*, 8.1, *Pregnancy (Teratogenic Effects: Pregnancy Category D)*, and 8.3, *Nursing Mothers* have been completed and accepted by the sponsor. The following language is suggested for incorporation into Section 13.2, *Impairment of Fertility*, regarding the effects of trastuzumab treatment on parameters associated with female fertility, and the lack of data to address the effects of trastuzumab on male fertility.

Current language in label:

A fertility study (b) (4) conducted in female cynomolgus monkeys at doses up to (b) (4) times the weekly recommended dose of 2 mg/kg Herceptin and has revealed no evidence of impaired fertility.

Suggested revisions to current language:

A fertility study conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg trastuzumab revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels. Studies to evaluate the effects of trastuzumab on male fertility have not been conducted.

Addendum:

The above suggested language was conveyed to Genentech on January 14, 2008 and accepted for incorporation into the PLR label on January 15, 2008. No further actions are required from pharmacology/toxicology to support the approval of this supplement.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

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

Medical Division: Biologic Oncology Drug Products (HFD-107)
Biometrics Division: Division V, Office of Biostatistics (HFD-711)

STATISTICAL KEY WORDS:	**Log-rank statistic; Cox's regression model**
BLA NUMBER:	**sBLA 103792/5175**
DRUG NAME:	**Herceptin® (Trastuzumab)**
INDICATION:	**HER2-positive Breast Cancer**
SPONSOR:	**Genentech, Inc.**
STATISTICAL REVIEWER:	**Yuan-Li Shen, Dr. P.H. (HFD-711)**
STATISTICAL TEAM LEADER:	**Mark Rothmann, Ph.D. (HFD-711)**
DIVISION OF BIOMETRICS V:	
DIRECTOR:	**Aloka Chakravarty, Ph.D. (HFD-711)**
CLINICAL REVIEWERS:	**Katherine Fedenko, M.S. (HFD-107)**
CLINICAL TEAM LEADER:	**Joe Gootenberg (HFD-107),**
PROJECT MANAGER:	**Monica Hughes (HFD-107)**

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File directory:
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STATISTICAL REVIEW AND EVALUATION

1 Executive Summary of Statistical Findings

The sponsor, Genentech, Inc., is seeking supplemental labeling claims of Herceptin® (b) (4)

(b) (4)

This review provides a summary of the clinical efficacy and safety results, statistical issues and an overview of the studies submitted in this application.

1.1 Recommendations and Conclusions

Based on study BO16348, the interim analysis results from two of the three treatment arms demonstrate that 1-year Herceptin arm had a significantly longer time to disease free survival as compared with the observation arm (hazard ratio of 0.54 for 1-year Herceptin arm versus observation arm, p-value<0.0001). The beneficial treatment effect of 1-year Herceptin is consistent across various subgroup, such as age, race, nodal status and HER2 assay results.

Since the 2-year Herceptin data are not submitted, the protocol pre-specified comparisons can not be completed. The comparison of 2-year Herceptin to observation arm must be performed in order to determine whether there is any remaining alpha to test secondary endpoints. In the current submission, any further evaluation of secondary efficacy endpoints can not be interpreted.

The cardiac safety results demonstrated that the 1-year Herceptin arm had higher incidences of cardiac events based on the sponsor's specified primary and secondary cardiac event endpoints. The 1-year Herceptin arm also had higher incidence rate of the worst post-baseline LVEF value <50% and ≥10% LVEF reduction from baseline. However, since the interpretation of the primary and secondary cardiac endpoints is not clear and the lack of pre-specified analysis of the LVEF assessment, further studies are recommended to evaluate the effect of Herceptin on Cardiac endpoints.

1.2 Brief Overview of Clinical Studies

Genentech submitted an international, multicenter, randomized, open-label, controlled clinical trial (study BO16348) to evaluate the 1-year Herceptin as a single agent for adjuvant treatment of HER-2 overexpressing breast cancer. Patients in the 1-year Herceptin arm received Herceptin every 3 weeks by i.v. infusion over an approximate 90-minute infusion period for all doses.

The study was submitted to support the following proposed claim for Herceptin :

(b) (4)

Study BO16348 was conducted outside of the US by F. Hoffmann-La Roche Ltd and the Breast International Group (B.I.G). Over 70% of the patients in this trial were from Europe, Nordic, Canada, South Africa, Australia and New Zealand.

A stratified randomization scheme was used based on the nodal status, adjuvant chemotherapy regimen, receptor status/endocrine therapy, age and region.

The primary endpoint of this study is disease-free survival and the secondary efficacy endpoints include overall survival, recurrence-free survival and distant disease-free survival. The primary comparison was between each of the 1-year Herceptin arm versus the observation arm using an unstratified log-rank test.

1.3 Statistical Issues and Findings

The primary efficacy result based on disease-free survival from study BO16348 shows statistical significance in favor of 1-year Herceptin arm. The hazard ratio of 1-year Herceptin arm versus observation arm is 0.54 (95% C.I.=[0.44, 0.67]) with p-value <0.0001 based on a log-rank statistic.

The beneficial treatment effect of the 1-year Herceptin arm is consistently demonstrated

in various subgroups such as age, race and nodal status, etc.

The cardiac safety results demonstrated higher incidences of cardiac events in the 1-year Herceptin arm (0.6% vs. 0.1% for the primary cardiac endpoint; 3.0% vs. 0.5% for the secondary cardiac endpoint). In addition, the 1-year Herceptin arm had consistently higher incidence of worst post-baseline LVEF value <50% (24.6% vs. 13.8%) and ≥10% LVEF reduction from baseline (9.0% vs. 3.2%).

There are some statistical issues related to the analysis:

- Based on the original statistical plan, the primary comparisons are between the observation arm versus 1-year Herceptin and the observation arm versus 2-year Herceptin. The comparison of 2-year Herceptin to observation arm must be performed in order to determine whether there is any remaining alpha to test secondary endpoints. Since the 2-year Herceptin data are not available, the protocol specified comparisons can not be completed. Therefore, further evaluation of secondary efficacy endpoints may not be meaningful.
- Since the sponsor's primary and secondary cardiac endpoints are based on composite measures which are not well documented, the interpretation of the results is not clear. The information obtained from LVEF assessment may be more informative. However since the definition of the change from baseline or post-baseline value in LVEF is not pre-specified and the choice of cut-off points is not well justified, further study with longer follow-up with respect to the effect of Herceptin on cardiac events and LVEF function is recommended.

2 Introduction

This section provides an overview of the submitted trials.

2.1 Overview

This subsection provides a background of the design of the submitted trial, the data analyzed and the source, and any major statistical issues.

2.1.1 Background

Genentech submitted the results from a multicenter, randomized, open-label, controlled clinical trial for Herceptin (b) (4) A stratified randomization scheme was used for this study.

The primary efficacy endpoint of this trial is disease-free survival and the secondary efficacy endpoints include overall survival, recurrence-free survival and distant disease-free survival. The primary comparisons for disease-free survival is between each of the 1-year Herceptin arm versus observation arm.

This trial was sponsored by the Breast International Group and F. Hoffmann-La Roche, Ltd., Genentech, Inc. provided additional financial support.

In November, 2006, the agency approved Herceptin, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel, for the adjuvant treatment of HER2-positive node-positive breast cancer. Adjuvant therapy is given to women with early-stage (localized) breast cancer who have had initial treatment surgery with or without radiation therapy. The approval was based on data from an interim joint analysis of more than 3,700 patients enrolled in two Phase III clinical trials. These results showed that the addition of Herceptin to standard adjuvant therapy (i.e. doxorubicin and cyclophsphamide followed by paclitaxel plus Herceptin : AC→T+H) significantly reduced the risk of disease recurrence (a hazard ratio of 0.48 with 95% C.I.=[0.39, 0.59]) as compared with standard adjuvant therapy arm alone (i.e. doxorubicin and cyclophsphamide followed by paclitaxel alone) in women with HER2-positive breast cancer.

2.1.2 Major Statistical Issues

The major statistical issues are summarized below:

- Based on the original statistical plan, the primary comparisons are between the observation arm versus 1-year Herceptin and the observation arm versus 2-year Herceptin. Since the 2-year Herceptin data is not available, the protocol specified comparisons can not be performed and the remaining alpha can not be determine for the secondary endpoints. Therefore, further evaluation of secondary efficacy endpoints may not be meaningful.
- Since the sponsor's primary and secondary endpoints are based on composite measures which are not well documented, the interpretation of the results is not clear. The information obtained from LVEF assessment may be more informative. However since the definition of the change from baseline or post-baseline value in LVEF is not pre-specified and the choice of cut-off points is not well justified, further study with longer follow-up with respect to the effect of Herceptin on cardiac events and LVEF function is recommended.

2.2 Data Sources

Data used for review is from the electronic submission received on 12/12/06. The network path is in :

\\Cbsap58\m\EDRSubmissions\2006 BLA\DCC60002776\blamain\crt\datasets\BO16348.

3 Statistical Evaluation

The efficacy and safety analysis results will be presented in this section for protocols BO16348.

3.1 Evaluation of Efficacy

3.1.1 Introduction

This was an open-label, three-arm, multicenter study. Upon completion of definitive surgery and systemic adjuvant chemotherapy, patients were randomized on a 1:1:1 basis to

- No Herceptin (observation),
- One year of Herceptin treatment arm, and
- Two years of Herceptin treatment arms.

In this data submission, only data from the observation arm and 1-year Herceptin arm were submitted. For all discussions in this review, the Herceptin arm was referring to the 1-year Herceptin arm.

Patients were stratified prior to randomization based on a number of prognostic and other factors that could impact the patients' outcome (see the following table).

Table 1 Stratification Factors Used in the HERA Trial

1. Nodal status :
   (1) Any nodal status, neo-adjuvant chemotherapy (nodal status unknown prior to chemotherapy)
   (2) No positive nodes, no neoadjuvant chemotherapy
   (3) 1-3 nodes positive, no neoadjuvant chemotherapy
   (4) >4 nodes positive, no neoadjuvant chemotherapy
2. Adjuvant chemotherapy regimen:
   (1) no anthracyclines or taxanes
   (2) anthracyclines but no taxanes
   (3) anthracyclines + taxanes
3. Receptor status and endocrine therapy [a b c]:
   (1) Negative
   (2) Positive and no endocrine therapy
   (3) Positive and endocrine therapy
4. Age:
   (1) < 35 years
   (2) 35 - 49 years
   (3) 50 - 59 years
   (4) ≥60 years
5. Region
   (1) Europe, Nordic Countries, Canada, South Africa, Australia, New Zealand
   (2) Asia Pacific and Japan
   (3) Eastern Europe
   (4) Central and South America

[a] Patients with synchronous bilateral breast primaries: Stratification was based on the highest stage tumor
[b] Hormone receptor status was based on local lab for both estrogen and progesterone receptors, or estrogen receptors alone for centers that did not routinely measure progesterone receptors. Actual values obtained from assays were used to define cohorts for exploratory analyses.
[c] Endocrine therapy included tamoxifen, anastrozole (Arimidex) and ovarian ablation. Chemotherapy induced amenorrhea was not considered endocrine therapy.

A minimization procedure according to Pocock and Simon (Biometrics, 1985) was used to allocate patients to the treatment arms in order to secure a balance between the treatments for stratification factors. Randomization was performed by an automated Interactive Voice Response System (IVRS).

Eligible patients must be 18 years or older, have Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, non-metastatic operable primary invasive adenocarcinoma of the breast (histologically confirmed, adequately excised), axillary node positive or negative and tumor size ≥ T1c according to TNM, known hormone receptor status (ER/PgR or ER alone), received at least four cycles of an approved (neo-)

adjuvant chemotherapy regimen, baseline LVEF $\geq$ 55% measured by echocardiography or MUGA scan, completion of (neo-)adjuvant chemotherapy or radiotherapy and HER2-overexpressing(determined by IHC 3+ or FISH positive) on the primary tumor as well as other inclusion/exclusion criteria.

Patients were randomized up to a maximum of 7 weeks following day 1 of the last chemotherapy cycle or a maximum of 6 weeks from the end of radiotherapy or definitive surgery, whichever occurred first. Whenever possible, the first dose of Herceptin was given within a maximum of 2 weeks after randomization.

This trial was conducted in 478 centers across 39 countries, all of them are outside of U.S.. Over 70% of patients population came from Europe, Nordic, Canada, South Africa, Australia and New Zealand.

Patients in the 1-year Herceptin arm received Herceptin every 3 weeks by i.v. infusion. The initial infusion was given at a loading dose of 8 mg/kg and subsequently infusion were given at a dose of 6 mg/kg. Herceptin was administered over an approximate 90-minute infusion period for all doses.

The primary objective of this study is

- To compare disease-free survival (DFS) in patients with HER2 over-expressing breast cancer who have completed acceptable adjuvant chemotherapy and radiotherapy, if applicable, and who have been randomized to Herceptin for one year versus no Herceptin.
- To compare disease-free survival (DFS) in patients with HER2 over-expressing breast cancer who have completed acceptable adjuvant chemotherapy and radiotherapy if applicable, and who have been randomized to Herceptin for two years versus no Herceptin.

The secondary objectives of this study are

- To compare overall survival (OS) in patients randomized to no Herceptin versus one year of Herceptin, and in patients randomized to no Herceptin versus two years of Herceptin.
- To compare recurrence-free survival (RFS) in patients randomized to no Herceptin versus one year of Herceptin, and in patients randomized to no Herceptin versus two years of Herceptin.
- To compare distant disease-free survival (DDFS) in patients randomized to no Herceptin versus one year of Herceptin, and in patients randomized to no Herceptin versus two years of Herceptin.
- To evaluate safety and tolerability of Herceptin.
- To compare the incidence of cardiac dysfunction in patients treated and not treated with Herceptin.

Efficacy assessments schedule

It is advised that patients to be seen at approximately every 3 months for the first 2 years, every 3-6 months for years 3-5 and every 6-12 months beyond five years after the end of primary therapy. In this study, patients were seen for evaluation at weeks 13, 25, 37, 52, 64, 79, 91, 103 (treatment period), at week 56 and 107 (for safety follow-up after completion/discontinuation of treatment period), every three months for the first 2 year, and every six months thereafter up to year 5 post randomization, then yearly up to year 10 (follow-up visit).

Radiological examinations occurred at baseline, weeks 52, 64, 79, 91 (103 for 2-year Herceptin), and yearly up to 5 year. In the case of a solitary bone lesion, a radiological examination was to be repeated in three months.

In addition, all patients were followed for survival once a year after completion or discontinuation of the study treatment period for any reason (e.g. disease recurrence, toxicity, experiencing a cardiac event leading to discontinuation of study treatment etc) unless the patient withdrew consent to participate in the study. Survival data will be collected until 10 years after randomization of the last patient into the study.

Cardiac safety assessments and Schedule

Due to the concern of cardiac dysfunction in patients received Herceptin in combination with anthracyclines in the chemotherapy plus Herceptin studies, cardiac safety was monitored in all patients through out the trial.

Cardiac monitoring(including ECG, LVEF and signs/symptoms, etc) was conducted every 3 months in the first 6 months, then at 1 year, every 6 months during the first 3 years and year 5.

Patients' LVEF (Left Ventricular Ejection Fraction) status was monitored either by echocardiogram and/or MUGA scan during baseline visit, before the next scheduled dose of Herceptin and the follow-up visits. throughout the trials. The same method was encouraged to be used for all LVEF assessments for a patient. According to the protocol, among the first 900 patients enrolled, those with echocardiogram (or MUGA scan) monitoring of LVEF function had to have all echocardiograms (or radiology reports) sent to Core Lab for independent review within 4 weeks of the examination.

The primary responsibility of the Core Lab was to provide blinded review the quality of echocardiography videotapes obtained at baseline, after 3, 6 months after start of Herceptin treatment or observation for the 900 patients. In general results of the review of cardiac monitoring video tapes would override echocardiography measurements done at the study site.

The numbers of patients randomized, treated and pre-mature withdrawals were summarized in the following table:

Table 2 Summary of the Number of Patients

Study	Duration	Population	Observation	Herceptin 1-year
BO16348	11/30/01-ongoing (first patient in: 12/7/01; last patient in : 3/11/05)	Randomized	1693	1693
		Not Treated		19 (1.1%) [a]
		Receive Herceptin	4 (<1%) [b]	1674 (98.9%)
		Safety population [c]	1708	1678
	Clinical cut-off date : 3/29/05 (database closure on 10/07/05)	Pre-mature withdrawals	267 (267/1708=16%)	218 (218/1678=13%)

[a] This group did not receive Herceptin and will be counted as safety population in observation arm.

[b] This is from observation arm and will be counted as safety population in Herceptin 1-year arm.

[c] Defined as all randomized patients who received Herceptin prior to recurrence or not.

Reviewer's comment :

- *While the sponsor indicated that 19 patients in the 1-year Herceptin arm did not receive Herceptin, this reviewer found 21 patients in the 1- year Herceptin arm did not have Herceptin exposure data. The sponsor explained the discrepancy in the Feb. 13, 2007 response as that the two patients (patients (b) (6) and (b) (6)), although did not have at least one record of Herceptin exposure, had a potential to receive Herceptin since they have not yet experienced disease recurrence. These two patients were therefore included in the 1-year Herceptin arm of the safety analysis population.*

At the time of the interim analysis, three protocol amendments had been made to the original protocol (version A, dated 6/5/01). The statistical analysis related amendments are summarized as follows:

Protocol version B (dated 12/3/01)

- Define the primary cardiac endpoints/symptomatic congestive heart failure.
- Schedule of assessments and procedures – include time windows.

Protocol version C (dated 11/25/02)

- Allow inclusion of patients with positive surgical margins based on specific conditions. Since this subgroup of patients may have different prognosis and outcome, the steering committee (SC) decided to require free positive surgical margins in patients to be randomized.
- Change HER2 testing strategy – require central reconfirmation of local HER2 status.
- Adjustment of number of events required for efficacy interim and primary analysis (see description of the interim analysis later in this section).

Protocol version D (dated 11/13/03)

- Increase sample size (see sample size calculation section later).
- Allow concomitant hormonal therapy with Anastrozole (Arimidex).
- Clarification of target population – exclude patients taken anti-tumor agents acting on certain member of HER family of receptors (e.g. Iressa) ; Also, the definition of non-metastatic disease was revised based on a new version of the TNM(tumor-node-metastasis) nomenclature.
- Revision of acceptable chemotherapy regimens.

One interim efficacy analysis was planned to compare Disease Free Survival (DFS) between the 1-year Herceptin arm versus the observation arm and 2-year Herceptin versus the observation arm. The O'Brien-Fleming procedure implemented by Lan and DeMets method was used for the interim analysis. This interim analysis was planned to be performed after half of the calculated 951 events had been observed (i.e. 475 events). The interim analysis was performed by an independent statistician and the results were presented to IDMC (Independent Data Monitoring Committee).

The protocol specified that two comparisons would be performed between each of the

Herceptin arm versus the observation arm. A step-down adjustment procedure of the Bonferroni method (proposed by Holm) would be used for the analyses. Based on this procedure, the significance levels for the most significant pair-wise comparison were 0.001 for the interim analysis and 0.0247 for the final analysis. If the significance was reached, the significance levels for the second pair-wise comparison were to be 0.002 for the interim analysis and 0.0494 for the final analysis. This procedure assured that the overall study-wise significance level was controlled at 0.050 level.

Three interim analyses for cardiac endpoints were also planned : after the first 300, 600 and 900 patients had been enrolled and treated for 6 months. If an absolute difference of more than 4% in the incidence of primary cardiac endpoints was observed between the 1-year Herceptin arm versus the observation arm, the IDMC was to consider recommending stopping or modifying the trial.

Reviewer's comments:

- *On March 29th, 2005, 475 events had been recorded on the clinical database (clinical cut-off). The interim analysis was performed on April 25th, 2005. The results showed significant results in favor of Herceptin treated arm and the IDMC recommended to the HERA Steering Committee the disclosure of data from 1- year Herceptin arm and the observation arm. This current review is based on the database that was used for the interim analysis.*
- *There is no interim analysis planned for overall survival.*

The sponsor provided Roche statistical analysis plan (dated 1/17/06, version 7; for filing in Europe after significant efficacy interim analysis) for the submission. Since the history of the statistical analysis plan (SAP) is not clear and the most current SAP available was finalized after the database unblinded, this review used the methods presented in he protocol (version D, dated 11/13/03). However, it is noted that sponsor's analyses basically follow Roche's SAP and the basic approaches written in the Roche's SAP and the protocol were very similar.

3.1.2 Efficacy Endpoints

Primary Efficacy variable

The primary efficacy variable, Disease Free Survival (DFS), was defined as the time between randomization and the date of first event. An DFS event was defined as any loco-regional or distant recurrence of breast cancer, the development of secondary primary cancer other than basal or squamous carcinoma of the skin and carcinoma *in situ* of the cervix, or death from any cause without documentation of one of these events. LCIS (Lobular carcinoma *in situ*) was not considered as an event. Diagnosis of a second primary cancer had to be confirmed histologically whenever possible.

Patients without an event will be censored at the last follow-up date.

Reviewer's comment :
It is noted that the sponsor's calculation was based on Roche's SAP (dated on 1/17/06) in which the censoring date is defined as the last date of 'last radiological exam', 'last LVEF assessment', 'date of randomization', 'last contact' or 'last survival follow-up'.

Secondary efficacy variables

The protocol specified the following variables as the secondary efficacy endpoints:

- Overall Survival : Defined as the time from randomization to death due to any cause. Patients who were still alive at the time of analysis were censored at date of the last follow-up (defined as the last date of 'last radiological exam', 'last LVEF assessment', 'date of randomization', 'last contact', 'last survival follow-up' or 'last post study treatment' in Roche's SAP).
- Recurrence Free Survival (RFS) : Defined as the time from randomization to the first local, regional and/or distant tumor recurrence. Patients without an event were censored at date of the last follow-up (defined as the first date of second primary cancer, contralateral breast cancer or death without evidence of disease recurrence, or the last date of 'last radiological exam', 'last LVEF assessment', 'date of randomization', 'last contact', or 'last survival follow-up' in Roche's SAP).

- Distant Disease-free Survival (DDFS) : Defined as the time between randomization and the date of the first distant tumor recurrence, second primary cancer, or contralateral breast cancer, whichever occurred first. Patients who had died without evidence of disease, the censoring time is the date of death. Patients without events, were censored at the date of last follow-up (defined as 'last radiological exam', 'last LVEF assessment', 'date of randomization', 'last contact' or 'last survival follow up' in Roche's SAP).

Other Efficacy Variables

The statistical analysis plan also considered other secondary efficacy variables : Time to Recurrence (TTR), Time to distant Recurrence (TTDR), Disease Free Survival from definitive surgery (DFSS) and Overall Survival from Definitive Surgery (OSS).

Since these variables were not pre-specified in the protocol, no further discussion will be provided.

Reviewer's comments:

- *The sponsor did not pre-specify any testing procedure for the secondary endpoints in order to obtain a secondary claim.*

3.1.3 Safety Endpoints

Primary Cardiac Endpoint

The event occurred at any time after randomization, but prior to the start of any new therapy includes:

- Symptomatic congestive heart failure of NYHA (New York Heart Association) class III or IV (confirmed by a cardiologist) and a drop in LVEF of at least 10 EF points (%) from baseline and to below 50%.
- Cardiac death defined as either :
  - Definite cardiac death: due to CHF (Congestive Heart Failure) cardiac infarction or documented primary arrhythmia;

- Probable cardiac death: sudden unexpected death within 24 hours of a definite or
- Probable cardiac event (syncope, cardiac arrest, chest pain, infarction, arrhythmia, etc.) without documented etiology.

All primary cardiac endpoints, as defined above, were to be reported as serious adverse events (SAEs) irrespective of treatment allocation.

Secondary Cardiac Endpoint

A secondary cardiac endpoint could occur any time after randomization, but prior to the start of any new therapy for recurrent disease, and was defined as:

- A significant asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) drop in LVEF identified by MUGA scan or echocardiogram, unless the following LVEF assessment indicated a return to levels which did not meet the definition of a significant LVEF drop. NYHA class II CHF had to be confirmed by a cardiologist. A significant LVEF drop is defined as a drop in LVEF of at least 10 EF points from baseline and to below 50%.

A repeat assessment had to be performed approximately 3 weeks after the first significant LVEF drop. If the repeat assessment of NYHA class II CHF by a cardiologist was not available, the Cardiac Advisory Board (CAB) would review the case to determine the secondary cardiac event.

In Roche's SAP (version 7, dated 1/17/06), a computation specification and algorithm for the secondary cardiac endpoint were provided. It indicated that two sources were used for identify potential secondary cardiac endpoint : LVEF records on CRF pages and the results from the CAB review.

3.1.4 Sample Size Consideration

There were two changes in the sample size section in this study :

In Amendment C -- the sponsor used statistical package EaSt to compute the sample size, stopping boundary and target number of events for the primary and interim efficacy analyses. This resulted in a slight change to the required number of events, i.e. from a total of 930 events to a total of 951 events (for the first pair-wise comparison : from 639 to 634). Also, the required number of events for the interim analysis change from a total of 465 events to 475 events. Originally, the number of events required was calculated based on the method proposed by Collett (Chapman & Hall, 1994).

In Amendment D – The sponsor changed the assumption for the 5-year DFS rate for control group from 60% to 65% due to the concern of more patients with lymph node (LN) negative disease were being entered and fewer patients with 1-3 positive LNs. Based on this change, the total 4482 patients (1494 in each three arms) were planned to be randomized over 3 year instead of 3192 patients (1064 in each three arms) randomized over 4 years in earlier plan. It is noted that the number of events for the interim and final analyses was not changed (475 and 951 events for interim and final analyses, respectively).

Since the original design has two pair-wise comparisons, the alpha level was adjusted following a step-down adjustment procedure of the Bonferroni method as proposed by o Holm (1979, Scan. Journal of Statistic. See Efficacy Analysis Method section for details). The sample size is calculated based on the most significant of the two comparisons (at an alpha level of $\alpha/2=0.025$) and the following assumptions:

- The 5-year DFS rate on the observation arm is **65%**;
- A 23% reduction in the risk of an event for DFS is considered a clinically meaningful benefit. This corresponds to a risk ratio of 0.77 and a 5-year DFS rate for the Herceptin of 71.8%;
- Recruitment was 1 case in 2001, 173 from January to June 2002, 519 from July 2002 to December 2002, 1021 from January 2003 to June 2003, and assumed to be 170 per month after June 2003. Total enrolment of 4482 patients should be completed in approximately 3 years. The accrual rate in EaSt was adjusted (annualized) to account for the slow start. Calculations used an annualized recruitment rate of 1992 patients per year over 2.25 years;
- The follow-up period after accrual terminated was to be 2 years;

- 5% drop-out rate.

With these assumptions, **1494** patients per treatment arm were required to achieve an 80% power to detect a hazard ratio of 0.77 at a two-sided significance level ≤ 0.025. This calculation is based on a log-rank test, assuming that 634 events are seen for the most significant of the two pair-wise comparisons and one interim analysis and one final analysis are planned. This leads to a target sample size of **4482** patients and a target number of 951 events in the study.

Reviewer's comments:

- *The sponsor indicated that the actual number of patients recruited (n=5090 for all three arms) exceeded the planned enrollment (n=4482) by approximately 600 patients). In the submitted data including only 2 arms, the actual recruited data (n=3386) exceeded the planned enrollment (n=2988) by 398. The sponsor explained that this was primarily the result of a long potential lag time between screening and randomization (Note: randomization took place up to a maximum of 7 weeks from Day 1 of the last chemotherapy cycle, or 6 weeks from the end of radiotherapy or definitive surgery, whichever was last).*

3.1.5 Efficacy Analysis Method

Full analysis set (FAS) defined as all randomized patients irrespective of Herceptin treatment actually received and eligibility, will be used for the primary analysis. The safety population, consists of all randomized patients based on whether they received Herceptin prior to recurrence or not, will be used for the safety analysis. The safety population will group patients to the arm in which the patients actually received their treatment, regardless of how they were randomized.

The protocol specified that two comparisons would be performed between each of the Herceptin arm versus observation arm. A step-down adjustment procedure of the Bonferroni method as proposed by Holm based on the unstratified log-rank test would be used for the analyses. In the Holm's procedure, the testing is conducted in a decreasing order of significance. The smallest of the p-value is tested at a level of $\alpha/2$. If the corresponding hypothesis is rejected, the second p-value is tested at a level of α, otherwise both the null hypotheses that there is no treatment difference in hazard rates

between treatment arms are accepted. The overall significance level was controlled at α level.

For this review purpose, the primary analysis will be based on the comparison between the Herceptin 1-year arm versus observation arm. The Kaplan-Meier curves would be displayed and the two year DFS rates and the 95% confidence limits (CL) for these are given for each treatment group. The hazard ratios and its 95% CL would be displayed as well.

Similar analyses strategy like those for the primary efficacy endpoint analysis were used for the analysis of the secondary efficacy endpoints, such as overall survival, recurrence free survival (RFS) and distant disease free survival (DDFS).

3.1.6 Safety Analysis Method

Based on Roche's statistical analysis plan (dated 1/17/06), the incidence of primary cardiac event will be summarized along with the 95% confidence interval based on Pearson-Clopper's method (Biometrika, 1934). The difference in incidence will be presented and the Hauck-Anderson approach (The American Statistician, 1986) will be used to calculate the 95% confidence interval for the difference.

Similar analysis strategy will be used for the secondary cardiac endpoint.

For exploratory analysis, time-to-event analyses (similar to the analysis for the primary efficacy endpoint) based on primary, secondary cardiac endpoint or combined primary and secondary cardiac endpoint were performed.

3.1.7 Sponsor's Results and Statistical Reviewer's Findings/Comments

The sponsor's submitted data is based on the database closed on 10/07/05 with 3/29/05 as the clinical cut-off date.

A total of 13% and 16% of patients had premature withdrawals from the study for 1-year Herceptin and observation arm, respectively. Within these early withdrawals, 6% and less than 1% of patients in the 1-year Herceptin and observation arm, respectively,

prematurely withdrew from the study due to safety concern.

Table 3 Sponsor's Summary of Premature Withdrawals by Reason (Safety population) (study bo16348)

	Observation (n=1708)	Herceptin 1-year (n=1678)
Safety	4 (<1%)	100 (6%)
Adverse Event	1	97
Death	3	3
Non safety	263 (15%)	118 (7%)
Insufficient therapeutic response	148 (9%)	69 (4%)
Violation of selection criteria at entry	6	5
Other protocol violation	1	0
Refuse treatment	100 (6%)	40 (2%)
Failure to return	6	1
Other	2	3
Total	267 (16%)	218 (13%)

In the original submission, there is no summary of protocol deviations. In response to the agency's request (teleconference on 1/31/07), the sponsor provides a summary of protocol deviation from baseline eligibility criteria (see sponsor's response from the 2/13/07 submission). Most of the deviations appear to be compatible between treatment arms and include less than 1% of the population except that

- 2.4% and 1.7% of patients did not complete more than 4 cycles of chemotherapy, for observation and 1-year Herceptin arm, respectively.
- 1.4% and 1.3% of patients had the LVEF assessment done prior to completion of chemotherapy, for observation and 1-year Herceptin arm, respectively.
- 6.4% and 6.7% of patients whose baseline chest imaging not completed within 6 months prior to randomization, for observation and 1-year Herceptin arm, respectively.

- 4.0% and 5.0% of patients whose screening mammogram not completed within 1 year prior to randomization, for observation and 1-year Herceptin arm, respectively.

The sponsor also provides a summary of on-study protocol deviation (dated 5/8/07), some notable deviations include :

- The percentage of patients who had missing LVEF assessments at one or more scheduled visits are higher in the observation arm (4.2% versus 2.3% for the observation arm and 1-year Herceptin arm, respectively).
- The percentage of patients who did not have a safety follow-up is higher in observation arm (16.4% versus 7.0% for the observation arm and 1-year Herceptin arm, respectively).
- The percentages of patients who received concomitant chemotherapy after randomization and before documented disease recurrence are compatible between treatment arms (2% and 1.7% in the observation and 1-year Herceptin arm, respectively).

3.1.7.1 Baseline Characteristics

A summary of patient characteristics based on the stratification characters provided by the sponsor are shown in the following table. It indicates that only few patients received neo-adjuvant (about 10 to 11%) chemotherapy, about 68% of the patients in both arms received anthracyclines (but no Taxanes), approximately 50% of patients with receptor positive or negative in both treatment groups, the majority of patients are between 35 to 49 years old, and most patients were from Europe, Nodic countries, Canada, South Africa, Australia and New Zealand region.

Table 4 Sponsor's Summary of Population Characteristics by Stratification Factors at Baseline (Study bo16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Nodal Status		
Any Nodal Status, neo-adj chemotherapy	176 (10.4%)	190 (11.2%)
No Positive Nodes, no neo-adj chemotherapy	555 (32.8%)	543 (32.1%)
1-3 Nodes Positive, no neo-adj chemotherapy	490 (28.9%)	483 (28.5%)
>=4 Nodes Positive, no neo-adj chemotherapy	471 (27.8%)	477 (28.2%)
missing values	1 (0.1%)	0 (0.0%)
Adjuvant Chemotherapy Regimen[1]		
No Anthracyclines or Taxanes	99 (5.8%)	97 (5.7%)
Anthracyclines but no Taxanes	1154 (68.2%)	1150 (67.9%)
Anthracyclines + Taxanes	438 (25.9%)	443 (26.2%)
Receptor Status and Endocrine Therapy		
Negative	841 (49.7%)	838 (49.5%)
Positive and no Endocrine Therapy	34 (2.0%)	53 (3.1%)
Positive and Endocrine Therapy	818 (48.3%)	802 (47.4%)
Unknown	0 (0.0%)	0 (0.0%)
Age group		
< 35 years	126 (7.4%)	126 (7.4%)
35 - 49 years	749 (44.2%)	751 (44.4%)
50 -59 years	546 (32.3%)	546 (32.3%)
>= 60 years	272 (16.1%)	270 (15.9%)
Missing and invalid values	0 (0.0%)	0 (0.0%)
Region		
Europe, Nordic Countries, Canada, South Africa, Australia, New Zealand	1222 (72.2%)	1208 (71.4%)
Asia Pacific and Japan	202 (11.9%)	202 (11.9%)
Eastern Europe	175 (10.3%)	189 (11.2%)
Central and South America	94 (5.6%)	94 (5.6%)

[1] Patients may have received other, non-predefined therapies

Reviewer's comment:

- *It is noted that among patients who had node-negative disease, more than 90% had tumor that were at least 1.0 cm in diameter and 45% of these patients had at least 2.0 cm in diameter of tumor size.*

The following table summarizes the demographic data at baseline. The distribution of these demographic data appears to be balanced between treatment arms. The results shown that 83-84% of the patients are Caucasian, the mean age is 49 years old, the average weight is 67-68 kg and the average height is 162 cm. Also, the majority of the women (86-87%) are non-smokers. Approximately, 44% and 42% of patients had postmenopausal status for the observation and 1-year Herceptin arm, respectively.

Table 5 Sponsor's Summary of Demographic and Characteristics at Baseline (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Sex		
Male	-	-
Female	1693 (100%)	1693 (100%)
n	1693	1693
Race		
Caucasian	1411 (83%)	1414 (84%)
Black	5 (<1%)	9 (<1%)
Oriental	213 (13%)	213 (13%)
Other	64 (4%)	57 (3%)
n	1693	1693
Age in years		
Mean (SEM)	49.2 (0.24)	49.0 (0.24)
SD	10.08	10.05
Median (Min-Max)	49.0 (23-77)	49.0 (21-80)
n	1693	1693
Weight in kg		
Mean (SEM)	67.43 (0.318)	67.98 (0.320)
SD	13.009	13.142
Median (Min-Max)	65.00 (40-137.5)	66.00 (36-149.0)
n	1675	1686
Height in cm		
Mean (SEM)	162.0 (0.17)	162.0 (0.17)
SD	7.16	7.17
Median (Min-Max)	162.0 (136-196)	162.0 (129-185)
n	1689	1688
Female reproductive status		
Postmenopausal	745 (44%)	718 (42%)
Surgically Steril.	215 (13%)	206 (12%)
With Cont. Prot.	723 (43%)	763 (45%)
Without Cont. Prot.	8 (<1%)	6 (<1%)
n	1691	1693
Does subject consume tobacco?		
No	1470 (87%)	1450 (86%)
Yes	223 (13%)	243 (14%)
n	1693	1693

A summary of early breast cancer history is presented in the following table. The distribution of these early breast cancer history appear to be compatible between treatment groups. The median duration of breast cancer is 8 months. The majority of the patients presented with one-sided breast cancer while less than 1% of patients presented with bilateral breast cancer. The median pathologic tumor size and clinical

tumor size are 22 mm and 40 mm, respectively and are the same for both treatment arms. Some patients were diagnosed with more than one cancer subtype, but the majority of patients (94-95%) had ductal breast cancer subtype. The majority of patients had G3 (poorly/undifferentiated) histological grade (about 60% in both treatment arms).

Table 6 Sponsor's Early Breast Cancer History at Baseline (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Duration of Disease at Randomization (months)		
n	1693	1693
Median (Min-Max)	8 (3 – 20)	8 (3 – 20)
Location of Tumor		
n	1693	1693
Right	789 (46.6%)	843 (49.8%)
Margins free	769 (45.4%)	825 (48.7%)
Margins not free	18 (1.1%)	18 (1.1%)
Left	893 (52.7%)	843 (49.8%)
Margins free	876 (51.7%)	822 (48.6%)
Margins not free	16 (0.9%)	20 (1.2%)
Bilateral	11 (0.6%)	7 (0.4%)
Both Margins free	10 (0.6%)	7 (0.4%)
Right Margins free only	1 (0.1%)	0 (0.0%)
Left Margins free only	0 (0.0%)	0 (0.0%)
Both Margins not free	0 (0.0%)	0 (0.0%)
Pathologic Tumor Size (mm)[1]		
n	1649	1657
Median (Min - Max)	22 (0 – 220)	22 (0 – 260)
Clinical Tumor Size (mm)[1],[2]		
n	193	214
Median (Min – Max)	40 (0 – 170)	40 (0 – 200)
Breast Cancer Subtype		
n	1692	1693
Ductal	1598 (94.4%)	1600 (94.5%)
Lobular	89 (5.3%)	97 (5.7%)
Medullary	23 (1.4%)	22 (1.3%)
Tubular	12 (0.7%)	13 (0.8%)
Mucinous	16 (0.9%)	13 (0.8%)
Comedo	120 (7.1%)	134 (7.9%)
Inflammatory	2 (0.1%)	3 (0.2%)
Not known	0 (0.0%)	0 (0.0%)
Other	96 (5.7%)	88 (5.2%)
Histological Grade		
n	1685	1682
Gx: Can't be assessed	77 (4.5%)	72 (4.3%)
G1: Well differentiated	38 (2.2%)	37 (2.2%)
G2: Moderately differentiated	557 (32.9%)	550 (32.5%)
G3: Poorly/Undifferentiated	1013 (59.8%)	1023 (60.4%)

[1] Largest diameter if both sides involved

[2] Only for patients who received neo-adjuvant chemotherapy

All patients had their HER2+ status confirmed centrally, except 14 patients had not been confirmed centrally (5 and 9 patients for observation and 1-year Herceptin arm, respectively). IHC or FISH tests were performed locally for initial screening. Patients had 2+ and 3+ IHC scores based on local laboratory results would have the samples sent to the central laboratory to be confirmed by FISH (if IHC2+ locally). The distribution of the HER2 status is balanced between treatment arms. The majority of patients had IHC3+ only status (69% and 65% for observation and 1-year Herceptin arm, respectively).

Table 7 Sponsor's Summary of HER2 Status at Baseline (Study BO16348)

	Observation (n=1693)	**Herceptin 1-year (n=1693)**
Central Results		
IHC 3+ only	1160 (68.5%)	1098 (64.9%)
FISH (+) only	342 (20.2%)	382 (22.6%)
IHC 3+ and FISH (+)	38 (2.2%)	53 (3.1%)
IHC 2+ and FISH (+)	148 (8.7%)	151 (8.9%)
Local Results		
IHC 2+ only	136 (8.0%)	146 (8.6%)
IHC 3+ only	1340 (79.1%)	1312 (77.5%)
FISH (+) only	18 (1.1%)	21 (1.2%)
IHC 3+ and FISH (+)	123 (7.3%)	132 (7.8%)
Other	76 (4.5%)	82 (4.8%)

Reviewer's Comment :

- *The agreement between the central and local HER2 status results is approximately 64%, i.e. 64% of the patients had the same HER2 testing status : IHC3+ only, FISH(+) only, IHC3+ and FISH(+), IHC 2+ and FISH (+)..*

In general, the proportion of patients with positive oestrogen receptor and progesterone receptor are compatible between treatment groups. There were more oestrogen receptor positive patients (45% for each arm) than the progesterone receptor positive patients (32% vs. 36% for observation arm and 1-year Herceptin arm, respectively). Over 50% of the patients in either arms had either positive Oestrogen receptor or progesterone receptor status.

Table 8 Sponsor's Summary of Hormone Receptor Status at Baseline (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Oestrogen receptor status		
n	1693 (100.0%)	1693 (100.0%)
Positive	766 (45.2%)	768 (45.4%)
Negative	927 (54.8%)	924 (54.6%)
Unknown	0 (0.0%)	1 (0.1%)
Progesterone receptor status		
N	1693 (100.0%)	1693 (100.0%)
Positive	542 (32.0%)	610 (36.0%)
Negative	1064 (62.8%)	1013 (59.8%)
Unknown	87 (5.1%)	70 (4.1%)
Oestrogen and Progesterone receptor status[1]		
n	1693 (100.0%)	1693 (100.0%)
ER Positive/PgR Positive	456 (26.9%)	523 (30.9%)
ER Positive/PgR Negative	250 (14.8%)	207 (12.2%)
ER Positive/PgR Unknown	60 (3.5%)	38 (2.2%)
ER Negative/PgR Positive	86 (5.1%)	86 (5.1%)
ER Negative/PgR Negative	814 (48.1%)	806 (47.6%)
ER Negative/PgR Unknown	27 (1.6%)	32 (1.9%)
Other	0 (0.0%)	1 (0.1%)

[1] Patients with ER status unknown are excluded

All patients in this study receive surgery for early breast cancer. The most frequent used procedure is the modified radical mastectomy (48 vs. 49% for observation arm and 1-year Herceptin arm, respectively) and the second most frequent used procedure is the Quadrantectomy/Segmentectomy (30 vs. 31% for observation arm and 1-year Herceptin arm, respectively).

Approximately 95-96% of the patients had resection of axillary lymph nodes.

Table 9 Sponsor's Summary of Surgery for Early Breast Cancer (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Resection of Primary Lesion	1693 (100.0%)	1693 (100.0%)
Lumpectomy	419 (24.7%)	371 (21.9%)
Quadrantectomy/Segmentectomy	503 (29.7%)	528 (31.2%)
Simple Mastectomy (Total)	98 (5.8%)	73 (4.3%)
Modified Radical Mastectomy	806 (47.6%)	821 (48.5%)
Radical Mastectomy (Halsted)	82 (4.8%)	73 (4.3%)
Other	332 (19.6%)	371 (21.9%)
Resection of Axillary Lymph Nodes	1625 (96.0%)	1610 (95.1%)

Patients could record more than one surgical procedure.

Approximately 50% of the patients in each treatment arm received adjuvant endocrine therapy. Tamoxifen alone is the most frequent endocrine therapy for both arms (31% for each arm), followed by Tamoxifen+LHRH (6% for each arm) and Tamoxifen followed by aromatase inhibitor (5% and 4% for observation only and 1-year Herceptin arm, respectively).

Table 10 Sponsor's Summary of Adjuvant Endocrine Therapy for Early Breast Cancer (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Patients with Adjuvant Endocrine Therapy	844 (49.9%)	828 (48.9%)
Tamoxifen alone	516 (30.5%)	521 (30.8%)
AI alone	75 (4.4%)	71 (4.2%)
LHRH alone	18 (1.1%)	13 (0.8%)
Ovarian Ablation alone	11 (0.6%)	7 (0.4%)
Tamoxifen -> AI	83 (4.9%)	63 (3.7%)
Tamoxifen + LHRH	93 (5.5%)	103 (6.1%)
Tamoxifen + Ovarian Ablation	16 (0.9%)	17 (1.0%)
Tamoxifen + LHRH -> AI	15 (0.9%)	10 (0.6%)
Tamoxifen + LHRH + Ovarian Ablation	2 (0.1%)	3 (0.2%)
Tamoxifen + Ovarian Ablation -> AI	3 (0.2%)	4 (0.2%)
Tamoxifen + Ovarian ablation + LHRH -> AI	1 (0.1%)	0 (0.0%)
LHRH -> AI	9 (0.5%)	12 (0.7%)
LHRH + Ovarian Ablation	0 (0.0%)	0 (0.0%)
LHRH + Ovarian Ablation -> AI	1 (0.1%)	2 (0.1%)
AI + Ovarian Ablation	1 (0.1%)	2 (0.1%)

AI: Aromatase Inhibitor; ->: followed by

Reviewer's Comment :

- *This summary includes patients who received hormone therapy for early breast cancer following surgery, chemotherapy and radiotherapy, but prior to the start of the study (2.6% and 2.1% for observation arm and 1-year Herceptin arm, respectively), as well as patients who continue hormone therapy after taking study drug.*

About 49% and 48% of patients in observation arm and 1-year Herceptin arm were receiving concomitant hormone treatment for early breast cancer at baseline. Tamoxifen was the most common used concomitant treatment for early breast cancer (42% of patients in either treatment arm).

Table 11 Sponsor's Summary of Concomitant Breast Cancer Hormone Treatment (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
ALL CLASSES		
Total Pts with at Least one Treatment	822 (49%)	815 (48%)
Total Number of Treatments	1045	1018
ANTI-ESTROGENS		
Total Pts With at Least one Treatment	713 (42%)	710 (42%)
TAMOXIFEN	713 (42%)	710 (42%)
Total Number of Treatments	714	711
AROMATASE INHIBITORS		
Total Pts With at Least one Treatment	186 (11%)	160 (9%)
Total Number of Treatments	195	167
GONADOTROPIN AND ANALOGUES		
Total Pts With at Least one Treatment	134 (8%)	137 (8%)
Total Number of Treatments	136	140

Ninety four percent of patients in either treatment arm received prior anthracycline therapy (see the table for Summary of Population Characteristics by Stratification Factors at Baseline). Majority of the chemotherapy for primary breast cancer is for adjuvant chemotherapy. The median number of cycles among patients treated with Doxorubicin, Epirubicin, Paclitaxel, Docetaxel, Cyclophosphamide, Fluorouracil and Methotraxate are very compatible between treatment arms.

In responding to the agency's request (Nov., 2006), the sponsor provided a summary of chemotherapy regimes in the January 30, 2007 submission. The summaries show that about 68% of patients received Anthracyclines, but no taxanes in each arm, 26% of patients received Antracyclines and taxanes and 6% of patients received no anthracyclines (with or without taxanes).

Table 12 Sponsor's Summary of Prior Chemotherapy Drug Combination Subgroups (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Anthracyclines but no taxanes	1156/1693(68.3%)	1150/1693(67.9%)
A with/without C, no F, no M and no T	187/1693(11.0%)	180/1693(10.6%)
E with/without C, no F, no M and no T	161/1693(9.5%)	166/1693(9.8%)
A with/without C, with F, no M and no T	168/1693(9.9%)	166/1693(9.8%)
E with/without C, with F, no M and no T	511/1693(30.2%)	520/1693(30.7%)
A, C, F and M but no T	44/1693(2.6%)	37/1693(2.2%)
E, C, F and M and no T	69/1693(4.1%)	70/1693(4.1%)
Other anthracycline(s) (A with E, mitoxantrone, or pirarubicin) but no T	16/1693(0.9%)	11/1693(0.6%)
Anthracyclines and taxanes	438/1693(25.9%)	443/1693(26.2%)
A and paclitaxel	126/1693(7.4%)	115/1693(6.8%)
A and docetaxel	73/1693(4.3%)	62/1693(3.7%)
E and paclitaxel	123/1693(7.3%)	141/1693(8.3%)
E and docetaxel	109/1693(6.4%)	113/1693(6.7%)
Others (anthracyclines and taxanes)*	7/1693(0.4%)	12/1693(0.7%)
No anthracycline, with/without taxane	99/1693(5.8%)	100/1693(5.9%)

A=doxorubicin; C=cyclophosphamide; E=epirubicin; F=fluorouracil or floxuridine; M=methotrexate; T=paclitaxel or docetaxel.
* Includes A with E and either paclitaxel or docetaxel, or at least one anthracycline with both docetaxel and paclitaxel.

Reviewer's comments:

- *Per medical reviewer, other anthracycline(s) (A with E, mitoxantrone, or pirarubicin) but no paclitaxel or docetaxel and A with E and either paclitaxel or docetaxel, or at least one anthracycline with both docetaxel and paclitaxel are not considered protocol acceptable regimens. These two categories will be summarized as non-approved chemotherapy regimens in later subgroup analyses.*

Seventy six percent of patients in the observation arm and 78% of patients in the 1-year Herceptin arm received previous radiotherapy related to breast cancer. The percentage of patients who received radiotherapy at right side, left side or both sides are comparable between treatment arms.

Table 13 Sponsor's Summary of Previous Radiotherapy for Primary Breast Cancer (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Previous Radiotherapy	1279 (75.5%)	1312 (77.5%)
Right side	601 (35.5%)	649 (38.3%)
Left side	668 (39.5%)	646 (38.2%)
Both sides	8 (0.5%)	12 (0.7%)
Not Identifiable	2 (0.1%)	5 (0.3%)

3.1.7.2 Primary Efficacy Endpoint Analyses

Based on the sponsor's summary of DFS, the results shows that Herceptin treated arm had significant lower risk of DFS (hazard ratio based on Cox's proportional hazards model=0.54 with 95% C.I.=[0.44, 0.67] and p-value based on unstratified log rank test <0.0001) as compared with observation arm. Due to the low DFS event rate, the median survival time has not reached for two treated arms.

Table 14 Sponsor's Summary of Disease Free Survival (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Number of patients with event	219 (12.9%)	127 (7.5%)
Number of patients without event[a]	1474 (87.1%)	1566 (92.5%)
2 year DFS Rate	78.18%	85.80%
95% CI for 2 year DFS Rate[b]	(75%, 81%)	(83%, 89%)
Range of DFS time (months) [c]	0.00, 36.04	0.00, 36.24
P-Value (Unstratified log-rank test)	<.0001	
Hazard Ratio vs observation	0.54	
95% CI for hazard ratio	(0.44, 0.67)	

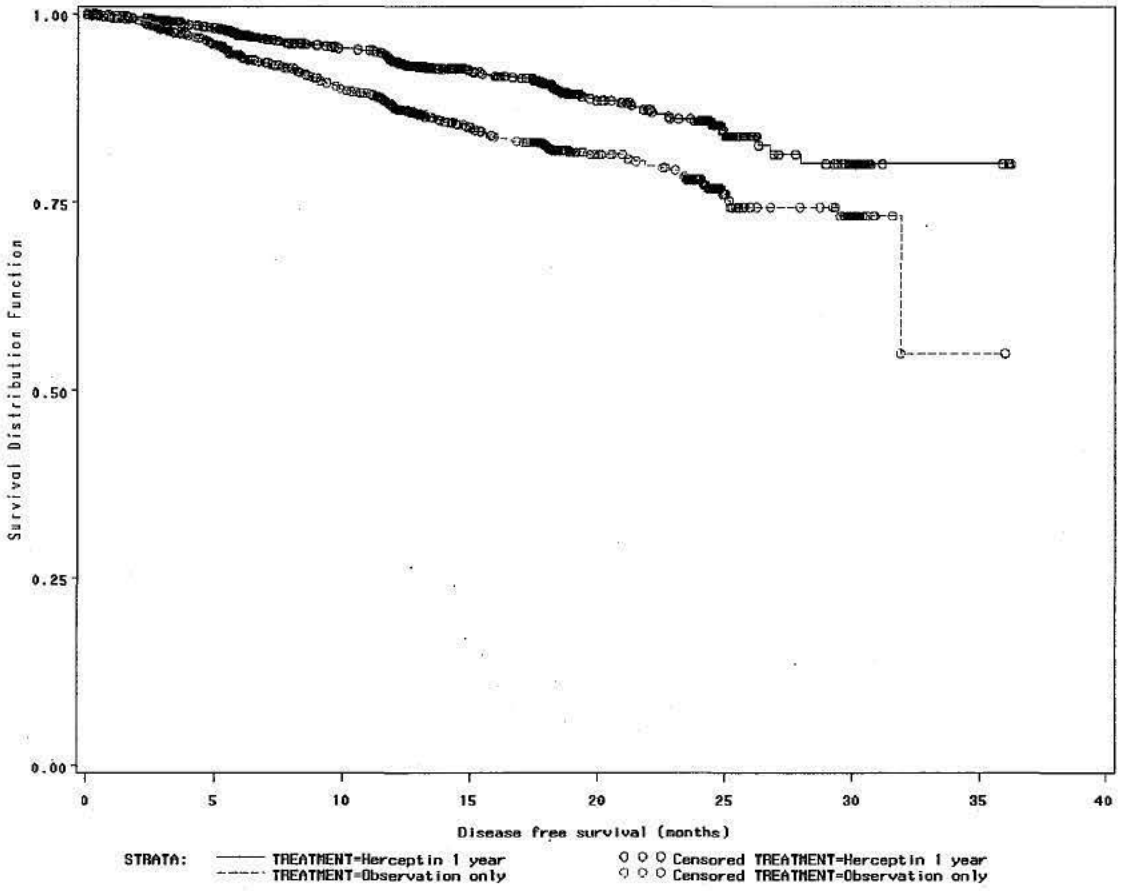
[a] Censored
[b] Kaplan-Meier estimates
[c] Including censored observations

Reviewer's comments:

- *This sponsor compared the duration of follow-up by switching the censoring and event indicator for the time to disease-free survival variable. The results show that the median duration of follow-up is compatible between treatment arms (the median duration of follow-up were 12.4 months and 12.7 months for observation and 1-year Herceptin arm, respectively).*
- *The sponsor's also shows that the results based on the stratified and unstratified log rank test are consistent (both had p-value <0.0001).*
- *It is noted that no new DFS event was found after the clinical data cut-off date (March 29, 2005). 41 patients (24 and 17 for observation and 1-year Herceptin arms, respectively) were censored after 3/29/05, but prior to 10/7/05 (database closure date). When these 41 patients were censored at 3/29/05, the log-rank test result, the hazard ratio estimates and the 95% confidence intervals were not changed.*
- *The frequency and duration of radiological assessment seem compatible between treatment arms. The median number of radiological examination (including CT-scan, X-ray, Bone scan, mammogram) for determination the recurrence of disease is 5 for each arm. The duration between radiological assessment is 101 and 107 days for observation arm and 1-year Herceptin arm, respectively.*

The corresponding Kaplan-Meier estimates for disease-free survival are presented in the following figure:

Figure 1 Kaplan-Meier estimates for Disease-free Survival



The sponsor provided a summary of recurrence of disease, second primary malignancy and contralateral breast cancer in the following table. It is noted that if more than one site of recurrence on the first date of recurrence was identified, recurrence of all sites are counted. The results show that distant recurrence is the most frequent recurrence (5% and 9.2 % for Herceptin and observation arm, respectively) as compared with local (1.1% vs. 2.3% for Herceptin and observation arm, respectively) and regional (0.6% vs. 0.9% for Herceptin and observation arm, respectively). The most frequent occurred sites of distant recurrence for both arms were the liver (1.3% vs. 3.5% first recurrences for Herceptin and observation arm, respectively) and bone (1.8% versus 2.5% first recurrences for Herceptin and observation arm, respectively).

Table 15 Sponsor's Summary of Recurrence of Disease, Second Primary Malignancy and Contralateral Breast cancer (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Local Recurrence	39 (2.3%)	18 (1.1%)
Breast surgical scar	11 (0.6%)	7 (0.4%)
Ipsilateral breast	13 (0.8%)	6 (0.4%)
Ipsilateral anterior chest wall	15 (0.9%)	5 (0.3%)
Regional Recurrence	15 (0.9%)	11 (0.6%)
Ipsilateral axillary	7 (0.4%)	7 (0.4%)
Infraclavicular	8 (0.5%)	3 (0.2%)
Internal mammary	0 (0.0%)	1 (0.1%)
Distant Recurrence	155 (9.2%)	85 (5.0%)
Skin or lymph nodes (other than above)	15 (0.9%)	4 (0.2%)
Bone solitary	11 (0.6%)	8 (0.5%)
Bone multiple	30 (1.8%)	19 (1.1%)
Bone marrow	2 (0.1%)	1 (0.1%)
Solitary lung nodule	0 (0.0%)	0 (0.0%)
Multiple lung nodules	22 (1.3%)	12 (0.7%)
Solitary liver nodule	7 (0.4%)	4 (0.2%)
Multiple liver nodules	53 (3.1%)	19 (1.1%)
Central nervous system	16 (0.9%)	21 (1.2%)
Other distant sites	19 (1.1%)	9 (0.5%)
Contralateral breast cancer	9 (0.5%)	8 (0.5%)
Second non breast malignancy	6 (0.4%)	3 (0.2%)

If there was more than one site of recurrence on the first date of recurrence all sites are counted.

Reviewer's comments:

- *According to the protocol (dated 11/13/03), contralateral breast cancer is not part of the definition of disease free survival and a questionable inclusion of the secondary non-breast malignancy (i.e. may be a separated event from earlier diagnosis). When these two type of events were censored, this reviewer obtained a hazard ratio of 0.53 (95% C.I. = [0.43, 0.67]). This computation censored 7 and 6 patients with contralateral breast cancer at the first DFS event and 6 and 3 patients with secondary breast malignancy, for observation and 1-year Herceptin arm, respectively.*

3.1.7.3 Secondary Efficacy Endpoint Analyses

The sponsor also presented results for overall survival (although there is no plan for an OS interim analysis). The results based on log-rank test does not show statistical

difference in overall survival (p=0.24). The hazard ratio of 1-year Herceptin versus observation arm is 0.75 with 95% C.I.=[0.47, 1.21].

Table 16 Sponsor's Summary of Overall Survival (Study BO16348)

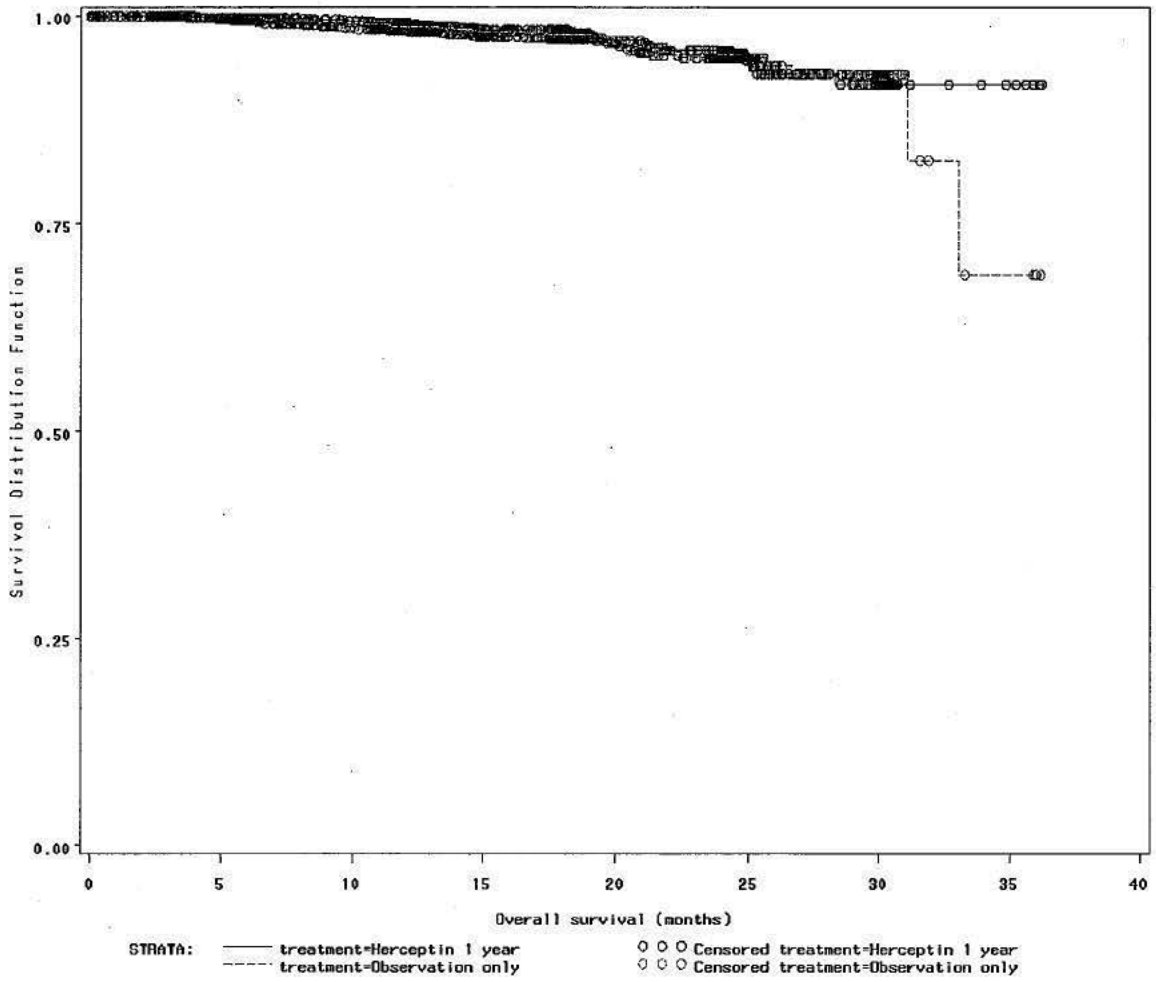
	Observation (n=1693)	Herceptin 1-year (n=1693)
Number of patients with event	40 (2.4%)	31 (1.8%)
Number of patients without event	1653 (97.6%)	1662 (98.2%)
P-Value vs observation (log-rank test)	0.2379	
Hazard Ratio vs observation	0.75	
95% CI for hazard ratio	(0.47, 1.21)	

Reviewer's comments:

- *It is noted that one death (patient (b) (6)) was found after the March 29, 2005 data cut-off date, but prior to database closure on Oct. 7, 2005.*
- *The sponsor indicates that the most common reason for death was for disease progression of the underlying breast cancer (38 and 26 due to progressive disease for observation and 1-year Herceptin arm, respectively).*

The corresponding Kaplan-Meier curve for overall survival is presented in Figure 2:

Figure 2 Kaplan-Meier estimates for Overall Survival



Another secondary efficacy endpoint stated in the protocol is the recurrence-free survival (RFS) which is defined as the time from randomization to the first local, regional or distant tumor recurrence. Since the majority of DFS event are distant tumor recurrence, the comparison of the RFS results should be similar to the comparison of DFS. The results of RFS comparison show nominally statistically significant advantage in favor of Hercelptin arm (HR=0.51, 95% C.I.= [0.40, 0.64]).

Table 17 Sponsor's Summary of Recurrence-Free Survival (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Number of patients with event	208 (12.3%)	113 (6.7%)
P-Value vs observation (log-rank test)	<.0001	
Hazard Ratio vs observation	0.51	
95% CI for hazard ratio	(0.40, 0.64)	

The third secondary efficacy endpoint stated in the protocol is the distant disease-free survival (DDFS) which is defined as the time from randomization to the first distant tumor recurrence, second primary cancer, or contralateral breast cancer, whichever occurred first. Local and regional recurrences are ignored in the calculation of the DDFS. Similarly, since majority of DFS event is from distant tumor recurrence, the comparison of the DDFS results should be similar to that from comparison of DFS. The results of the DDFS comparison also show nominally statistically significant advantage in favor of 1-year Herceptin arm (HR=0.50, 95% C.I.= [0.39, 0.64]).

Table 18 Sponsor's Summary of Distant Disease-Free Survival (Study BO16348)

	Observation (n=1693)	Herceptin 1-year (n=1693)
Number of patients with event	184 (10.9%)	99 (5.8%)
P-Value vs observation (log-rank test)	<.0001	
Hazard Ratio vs observation	0.50	
95% CI for hazard ratio	(0.39, 0.64)	

3.1.7.4 Herceptin Exposure and Results of Cardiac Event and LVEF Assessment

Based on the Herceptin dosing CRF page, 1672 patients had the Herceptin dosing data. The median duration of Herceptin treatment is 51 weeks and the median number of infusions is 18 times. A total of 633 patients had at least one dosing delays. A total of 90 patients had at least one dose "adjustment" performed during the study.

Table 19 Summary of Extent of Exposure to Herceptin before Recurrence (Safety Population) (Study BO16348)

	Herceptin 1-year (n=1678)
Treatment Duration (weeks)	
n	1672
Median	51
Range	1 -60
Number of Infusions	
n	1672
Median	18
Range	1 -20
Number of Dose Delays (total)	
n	633
Median	1
Range	1 -10
Number of Dose Adjustments	
n	90
Median	1
Range	1 -17

Reviewer's comments:

- *Among all safety population in the 1-year Herceptin arm (n=1678, patients who received at least one dose of study medication), 4 patients are actually from oberservation arm (i.e. so no Herceptin dosing data) and 2 patients from 1-year Herceptin arm did not have Herceptin dosing information. Therefore, only 1672 patients were summarized in this table.*
- *Following recurrence, all patients could be treated with Herceptin. According to the sponsor, there were 50 patients from 1-year Herceptin arm received Herceptin following recurrence and 82 patients from abservation arm received Herceptin following recurrence.*

The sponsor observed a higher incidence of the primary cardiac event in the 1-year Herceptin arm (0.6% and 0.1% of in Herceptin and observation arm, respectively). The difference in incidences is 0.54% with 95% C.I. between 0.12% and 0.95%.

Table 20 Sponsor's Summary of Primary Cardiac Endpoint (Safety Population) (Study BO16348)

	Observation (n=1708)	Herceptin 1-year (n=1678)
Incidence of Primary Cardiac Endpoint	1 (0.1%)	10 (0.6%)
Exact 95% CI for Incidence [a]	(0.00%, 0.33%)	(0.29%, 1.09%)
Difference in Incidence	0.537 %	
95% CI for the difference [b]	(0.12% , 0.95%)	

[a] Exact 95% Confidence Interval for one sample binomial using Pearson-Clopper method

[b] Approximate 95% Confidence Interval for difference of two rates using Hauck-Anderson correction

Reviewer's comment :

- *The one patient in the observation arm who had the primary cardiac events was due to cardiac death.*
- *The sponsor indicates that of the 10 1-year Herceptin patients with a primary cardiac endpoint, 8 were asymptomatic at the last scheduled assessment on the database (as per 12/15/05 data). Six of the 10 patients had a recovery of the LVEF to at least 55% at a median of 121 days (ranged from 36-409 days)from the initial LVEF drop.*

The sponsor also observed a higher incidence of the secondary cardiac events in the 1-year Herceptin arm (3% and 0.5% of in the 1-year Herceptin and observation arm, respectively). The difference in incidences is 3% with 95% C.I. between 1.6% and 3.4%.

Table 21 Sponsor's Summary of Secondary Cardiac Endpoint (Safety Population) (Study BO16348)

	Observation (n=1708)	Herceptin 1-year (n=1678)
Incidence of Secondary Cardiac Endpoint	9 (0.5%)	51 (3.0%)
Exact 95% CI for Incidence[a]	(0.24%, 1.00%)	(2.27%, 3.98%)

[a] Exact 95% Confidence Interval for one sample binomial using Pearson-Clopper method

Reviewer's comment :

- *The sponsor indicates that of the 51 Herceptin patients with a secondary cardiac*

endpoint, 45(88%) were aymptomatic at the last scheduled assessment on the database (as per 12/15/05 data). Thirty-five of the 51 patients (69%) had a recovery of the LVEF to at least 55% at a median of 189 days (ranged from 13-831 days) from the initial LVEF drop.

- *The sponsor provided a summary of the primary and secondary endpoints by NYHA class. The results show that 1-year Herceptin arm had higher incidence of cardiac events across all NYHA classes. The percentages of patients with NYHA class II-IV event, the cardiac dysfunction or cardiac death are 1.8% and 0.2% for the 1-year Herceptin and observation arm, respectively.*
- *The sponsor also performed time to first primary or secondary cardiac event analysis based on Cox's proportional hazards model. The Cox's model includes treatment, age (≤5 vs. >50 years old), race (Caucasian vs. non-Caucasian), prior or current use of cardiovascular disease medication at baseline, prior or current hypertension at baseline and investigator-assessed LVEF status at screening (<60% vs. ≥60%) in the model. The results show that LVEF status at screening is a significant predictor for time to the first primary or secondary cardiac event. When screening LVEF status was the only covariate in the model, the hazard ratio for treatment is 5.88 (95% C.I.=[3.01,11.47] which indicates the 1-year Herceptin arm had much higher risk of developing primary or secondary cardiac event when the screening LVEF status was taken into account.*
- *The primary and secondary cardiac events defined by the sponsor are composite measures and are not a well documented measures in the field. The interpretation based on these two endpoints is not clear.*

Since it is not clear about the interpretability of the primary and secondary cardiac endpoints. These endpoints are composite measures which combined a subjective assessment (NYHA class) and an objective assessment (LVEF assessment). It would be more informative if an objective assessment, such as LVEF, is used to evaluate the event rate and chronological changes.

The following table summarized the change from baseline to worst LVEF values. The results show that the 1-year Herceptin arm had higher incidence of 10 unit (%) or more reduction in LVEF value from baseline (25% and 14% for 1-year Herceptin and

observation arm, respectively). The 1-year Herceptin arm also had higher incidence of less than 50% post-baseline LVEF value (9% and 3% for 1-year Herceptin and observation arm, respectively) and higher incidence of significant LVEF drop (7.4% and 2.3% for 1-year Herceptin and observation arm, respectively)

Table 22 Sponsor's Summary of Change from Baseline to Worst LVEF Value (Safety Population) (Study BO16348)

	Observation (n=1708)	Herceptin 1-year (n=1678)
Overall n (worst value)	1545	1600
Decrease ≥ 10%	213 (13.8%)	394 (24.6%)
LVEF < 50%	49 (3.2%)	144 (9.0%)
LVEF < 50% and decrease ≥ 10% (significant LVEF drop)	35 (2.3%)	118 (7.4%)

Reviewer's comment:

- *There are many approaches of computing the change from baseline of LVEF value. The sponsor used the last LVEF assessment prior to randomization as the baseline LVEF value and the WORST post-baseline LVEF value as the post-baseline LVEF value for this computation.*
- *It is noted that the choice of cut-off points for LVEF<50% and ≥ 10% LVEF drop was not pre-specified and not well-justified.*
- *To evaluate the temporal trend of the worst post-baseline LVEF values, the reviewer calculated the incidence of the worst post-baseline LVEF <50% and ≥10% LVEF drop by study visit and the results are presented in the following tables. Since the study is still on-going, only less than half of the patients had visits beyond week 52. Based on by-visit results up to week 52, the 1-year Herceptin arm shows consistently higher incidences of LVEF <50% throughout the 12 months period.*
- *The reviewer performed a time-to-the-first-significant-LVEF-drop analysis and observed that the 1-year Herceptin arm has 3 times higher risk of significant LVEF drop event when compared with the observation arm (HR=3.3, 95% C.I.=[2.3, 4.8]).*

Table 23 Reviewer's Summary of Incidences of Worst Post-baseline LVEF Value < 50% and ≥ 10% LVEF Drop by Visit (Safety Population) (Study BO16348)

	Observation (n=1708)	Herceptin 1-year (n=1678)
LVEF Value < 50%		
Week 13	19/1494 (1.27%)	63/1572 (4.01%)
Week 25	20/1375 (1.45%)	76/1458 (5.21%)
Week 52	18/928 (1.94%)	56/1056 (5.30%)
Week 79/Month 18	6/541 (1.11%)	27/608 (4.44%)
Week 103/Month 24	6/246 (2.44%)	5/266 (1.88%)
FU Month 30	3/67 (4.48%)	1/64 (1.56%)
≥ 10% LVEF drop		
Week 13	94/1494(6.29%)	179/1572(11.39%)
Week 25	110/1375(8.00%)	216/1458(14.82%)
Week 52	66/928(7.11%)	177/1056(16.76%)
Week 79/Month 18	47/541(8.69%)	72/608(11.84%)
Week 103/Month 24	19/246(7.72%)	28/266(10.53%)
FU Month 30	5/67(7.46%)	3/64(4.69%)

3.1.8 Sponsor's Conclusions and Reviewer's Conclusions/Comments

The sponsor concluded that

- Herceptin given every three weeks for one year following (neo-) adjuvant chemotherapy and radiotherapy (if applicable) significantly prolong DFS, RFS and DDFS for women with HER2 positive early breast cancer.
- The observed effect of Herceptin is independent of patients' baseline characteristics (node positive or negative, hormone receptor status, age) and previous (neo-) adjuvant therapy.
- Herceptin significantly reduces the risk of distant metastases which is considered

an incurable condition.

- Herceptin therapy is associated with a low incidence of NYHA class III or IV congestive heart failure (0.6%).
- No new or unexpected safety findings were identified with adjuvant Herceptin therapy.
- Cardiac dysfunction is manageable and reversible, affecting up to 7.4% of patients, for half of whom the clinical significance of a single LVEF drop is not clinically well understood.

In summary, the sponsor concluded that these data support the use of 1-year Herceptin as adjuvant treatment for patients with HER2 positive early breast cancer, who have completed (neo)adjuvant systemic chemotherapy, definitive surgery and radiotherapy (if applicable) . In cardiac safety, the sponsor indicated that the majority of primary and secondary cardiac endpoints occurred during the first 6 months post-randomization. Further follow-up is required to define the long term risk of cardiac dysfunction associated with 1-year of Herceptin treatment.

This reviewer concluded that

- The 1-year Herceptin treated arm appears to have significant lower risk of DFS (hazard ratio based on Cox's proportional hazards model=0.54 with 95% C.I.=[0.44, 0.67] and p-value based on unstratified log-rank test <0.0001) as compared with the observation arm.
- The treatment benefit based on DFS appears to be consistent across various subgroups, e.g. age, race, nodal status, HER2 status, chemotherapy regimens, etc. However, some subgroup results should be interpreted with caution due small sample sizes.
- Based on original statistical plan, the primary comparisons are between the observation arm versus 1-year Herceptin and the observation arm versus 2-year Herceptin. The comparison of 2-year Herceptin to observation arm must be performed in order to determine whether there is any remaining alpha to test secondary endpoint. Since the 2-year Herceptin data are not available, the protocol specified comparisons can not be performed. Therefore, further evaluation of secondary endpoints may not be meaningful.

In cardiac safety analysis, the reviewer concluded that

- the 1-year Herceptin arm shows higher incidence rates in both primary cardiac endpoint (0.6% versus 0.1 % for 1-year Herceptin and observation arm, respectively) and secondary cardiac endpoint (3% versus 0.5 % for 1-year Herceptin and observation arm, respectively).
- The result shows that 1-year Herceptin arm had higher incidence of the worst post-baseline LVEF < 50% (9% vs. 3.2% for 1-year Herceptin and observation arm, respectively) and reduction by ≥ 10 unit. However since the cut-off point used to define lower LVEF value and reduction from baseline is not pre-specified and not well justified, further study with longer follow-up with respect to the effect of Herceptin on cardiac events and LVEF function is recommended.
- The sponsor's claim that "Cardiac dysfunction is manageable and reversible" can not be confirmed based on limited number of cardiac events.

4 Findings in Special/Subgroup Populations

This section provides summary statistics (hazard ratio, median survival time, count of patients) based on selected subgroups for overall survival.

4.1 Gender

Only female patients were included in the study.

4.2 Race

Sub-group analyses based on race subgroup for DFS were performed by this reviewer and sponsor. The 1-year Herceptin arm consistently showed lower risk than the observation arm across racial subgroups.

Table 24 Reviewer's Summary of Disease Free Survival by Race (Study BO16348)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio (Herceptin vs. observation arm)
Race	Caucasian	2825	<0.0001	0.56(0.44,0.71)
	Non-Caucasian	561	0.00600	0.43(0.24,0.78)

The sponsor also provided subgroup analysis results for primary and secondary cardiac endpoints by racial subgroup. The incidence of primary and secondary cardiac endpoints are higher in the 1-year Herceptin arm than that in the observation arm across all racial subgroups. However, due to insufficient number of cardiac events, the difference in incidence of cardiac events should be interpreted with caution.

Table 25 Sponsor's Summary of Incidence of Primary and Secondary Cardiac Endpoint by Race Subgroup (Study BO16348)

	Observation (n=1708)	Herceptin 1-year (n=1678)
Primary cardiac endpoint	1/1708 (0.1%)	10/1678 (0.6%)
Non-Caucasian	0/ 283 (0.0%)	1/ 278 (0.4%)
Caucasian	1/1425 (0.1%)	9/1400 (0.6%)
Secondary cardiac endpoint	9/1708 (0.5%)	51/1678 (3.0%)
Non-Caucasian	1/ 283 (0.4%)	10/ 278 (3.6%)
Caucasian	8/1425 (0.6%)	41/1400 (2.9%)

The reviewer performed the subgroup analysis for incidence of $\geq$ 10% LVEF drop from baseline and worst post-baseline LVEF < 50% by racial group. The incidences of $\geq$ 10% drop in LVEF value and worst post-baseline less than 50% are also consistently higher in the 1-year Herceptin arm than that in the observation arm in all racial subgroups.

Table 26 Reviewer's Summary of Incidence of ≥ 10% LVEF Drop and Worst Post-baseline LVEF < 50% by Race (Study BO16348)

	Observation (n=1708)	Herceptin 1-year (n=1678)
LVEF decrease ≥ 10%	211/1708 (12.4%)	395/1678(23.5%)
Non–Caucasian	42/283(14.8%)	68/278(24.5%)
Caucasian	169/1425(11.9%)	327/1400(23.4%)
Worst post-baseline LVEF <50%	45/1708(2.6%)	148/167(8.8%)
Non–Caucasian	7/283(2.5%)	25/278(9.0%)
Caucasian	38/1425(2.7%)	123/1400(8.8%)

Reviewer's note:
The reviewer's results of the incidences of LVEF drop ≥ 10% and Worst post-baseline LVEF <50% are slightly different from the sponsor's results (see 3.1.7.4 Herceptin Exposure and Results of Cardiac Event and LVEF assessment) because the results were based on independently derived variables (i.e. baseline LVEF, post-baseline LVEF values) which may use slightly different computation algorithm during the analysis data creation.

4.3 Age

Sub-group analyses based on age subgroup (<65, ≥ 65 years old) for DFS were performed by this reviewer. The 1-year Herceptin arm showed a lower risk in disease free survival as compared with the observation arm in all patients. However, the magnitude of the risk reduction seems to be larger in patients younger than 65 years old than that in patients 65 years or older.

Table 27 Reviewer's Summary of Disease Free Survival by Age Subgroup (Study BO16348)

Endpoint	Level	# of Patients	P-value[a]	Hazard Ratio (Herceptin vs. observation arm)
Age	<65	3152	0.00000	0.52(0.41,0.66)
	>=65	234	0.48000	0.78(0.39,1.55)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

The sponsor also provided subgroup analysis results for primary and secondary cardiac endpoints by age subgroup. In patients younger than 65 years old, the 1-year Herceptin group had higher incidences in both primary and secondary cardiac endpoint. In patients over than 65 years old, the difference in incidence of cardiac events is less clear. Due to the insufficient number of events, the results should be interpreted with caution.

Table 28 Sponsor's Summary of Incidence of Primary and Secondary Cardiac Endpoint by Age Subgroup (Study BO16348)

	Observation # event/total (%)	Herceptin 1-year # event/total (%)
Primary cardiac endpoint	1/1708 (0.1%)	10/1678 (0.6%)
Age < 65 years	0/1594 (0.0%)	10/1558 (0.6%)
Age >= 65 years	1/ 114 (0.9%)	0/ 120 (0.0%)
Secondary cardiac endpoint	9/1708 (0.5%)	51/1678 (3.0%)
Age < 65 years	7/1594 (0.4%)	48/1558 (3.1%)
Age >= 65 years	2/ 114 (1.8%)	3/ 120 (2.5%)

The reviewer performed the subgroup analysis for the incidences of $\geq$ 10% LVEF drop from baseline and worst post-baseline LVEF < 50% by age group. The incidences of $\geq$ 10% drop in LVEF value and worst post-baseline less than 50% are consistently higher in the 1-year Herceptin arm than that in the observation arm in all age subgroups.

Table 29 Reviewer's Summary of Incidence of ≥ 10% LVEF Drop and Worst Post-baseline LVEF < 50% by Age Subgroup (Study BO16348)

	Observation # event/total (%)	Herceptin 1-year # event/total (%)
LVEF decrease ≥ 10%	211/1708 (12.4%)	395/1678 (23.5%)
Age < 65 years	200/1594(12.5%)	378/1558(24.3%)
Age >= 65 years	11/114(9.6%)	17/120(14.2%)
Worst post-baseline LVEF <50%	45/1708 (2.6%)	148/1678 (8.8%)
Age < 65 years	40/1594(2.5%)	137/1558(8.8%)
Age >= 65 years	5/114(4.4%)	11/120(9.2%)

4.4 Other Special/Subgroup Populations

Additional subgroup analyses based on several baseline prognostic factors were performed by this reviewer (see Appendix) for the disease-free survival. The 1-year Herceptin arm had consistently lower risk in disease free survival, except in several cases where the numbers of patients are small and the trend is less clear. In this section, the subgroup analysis based on chemotherapy regimen, nodal status and HER2 status will be discussed.

The results demonstrated that the 1-year Herceptin arm had consistently lower risk in disease-free survival in patients whose nodal status was unknown but received neoadjuvant therapy, and patients who had positive or negative nodal status. Within the 1098 nodes negative patients, 1055 of them are considered as high risk patient population (ER and/or PgR positive and at least of the following features: pathologic tumor size > 2cm, Grades 2-3 or age<35 years old; ER and PgR negative). In the high risk subgroup, the Herceptin also had lower risk as compared with the observation arm (HR=0.54, 95% C.I.= [0.32, 0.94]).

The results of disease-free survival across the HER2 assay subgroup also show consistent results in favor of the 1-year Herceptin arm. The results of IHC 2+ and FISH

positive and IHC 3+ and FISH positive subgroups should be interpreted with caution due to the small sample sizes.

The beneficial treatment effect of Herceptin based on disease-free survival also demonstrated in patients who received approved prior chemotherapy. The magnitude of the treatment effect appears to be larger in patients who received the anthracyclines, but no taxanes as compared with that in the anthracyclines and taxanes subgroup. Due to the small size in patients who received non-approved chemotherapy regimens, the treatment benefit of Herceptin is less clear. However, the hazard ratio estimate seems to indicate a positive trend in favor of Herceptin.

Table 30 Reviewer's Summary of Disease-free Survival by Baseline Prognostic Factors (Study BO16348)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio (Herceptin vs. observation arm)
Nodal Status	Any nodal status, neoadjuvant therapy	366	0.01800	0.54(0.33,0.90)
	Nodes negative, (no neoadjuvant therapy)	1098	0.00900	0.49(0.29,0.84)
	High Risk[b]	1055	0.029	0.54(0.32, 0.94)
	Nodes positive, no neoadjuvant therapy	1921	<0.0001	0.53(0.41,0.70)
HER2 Assay	IHC 2+ & FISH (+)	299	0.20900	0.53(0.20,1.42)
	IHC 3+ & FISH (+)	91	0.44600	0.56(0.12,2.50)
	IHC 3+ & FISH unknown	2258	<0.0001	0.53(0.41,0.69)
	IHC unknown & FISH (+)	724	0.02300	0.59(0.38,0.93)
Chemotherapy regimen	Approved chem regimen	3141	<0.0001	0.53(0.42,0.67)
	Anthracyclines, but no taxanes	2279	<0.0001	0.43(0.32,0.57)
	Anthracyclines and taxanes	862	0.18800	0.78(0.53,1.13)
	Not approve chem reg	245	0.29600	0.66(0.30,1.44)

[a] P-value based on Wald statistic from unstratified Cox's proportional hazards model.

[b] ER and/or PgR positive and at least of the following features: pathologic tumor size > 2cm, Grades 2-3 or age<35 years old; ER and PgR negative

5 Summary and Conclusions

Genentech submitted study BO16348, a multicenter, randomized, open-label, controlled

clinical trial for Herceptin as an adjuvant treatment for patients with HER2-overexpressing, node negative (≥ T1c) or node positive operable breast cancer following completion of surgery, anthracycline-containing chemotherapy and/or radiotherapy.

In study BO16348, patients were randomized to observation, 1-year and 2-year Herceptin arm. In this submission, only observation and 1-year Herceptin arm was submitted. Patients in the 1-year Herceptin arm received Herceptin every 3 weeks by i.v. infusion. The randomization was stratified by nodal status, adjuvant chemotherapy regimens, receptor status/endocrine therapy, age and region.

The protocol specified that one interim analysis will be performed when a total of 476 DFS events (for three arms) were obtained. The interim analysis was conducted on 4/25/05 with data cutoff date on 3/29/05. The data submission is based on the data used for the first interim analysis. A total of 3386 patients were randomized to observation and 1-year Herceptin arm (1693 for each arm).

In study BO16348, the primary efficacy endpoint was disease-free survival. The overall survival, recurrence-free survival and distant disease-free survival were the protocol specified secondary endpoints.

5.1 Summary of Collective Evidence

The efficacy results demonstrated that the 1-year Herceptin arm had a statistical significant treatment effect based on the disease free survival for adjuvant breast cancer ($p<0.0001$ based on log-rank test; hazard ratio=0.54, 95% C.I.=[0.44, 0.67]) (see section 3.1.7.2 Primary Efficacy Endpoint Analyses). The beneficial treatment effect of the 1-year Herceptin arm is consistently demonstrated in various subgroups, such as age, race and nodal status, etc. (see Section 4 Findings in Special/Subgroup Populations). The results further confirm the beneficial effect of Herceptin shown from the joint analysis of two previous trials (Hazard ratio of 0.48, 95% C.I.=[0.39, 0.59], comparing patients who received doxorubicin and cyclophsphamide followed by paclitaxel alone : AC→T or paclitaxel plus Herceptin : AC→T+H; see the Herceptin label for further details).

In cardiac event assessment, the 1-year Herceptin arm shows higher incidences of the

primary and secondary cardiac endpoints (0.6% vs. 0.1% for the primary cardiac endpoint; 3.0% vs. 0.5% based on the secondary cardiac endpoint). The results based on LVEF assessments also show that the 1-year Herceptin arm had higher incidences of 10% or more drop in LVEF value (24.6% vs. 13.8%) and higher incidence of the worst post-baseline LVEF <50% (9.0% vs. 3.2%) (For these cardiac event results and LVEF assessment, please see section 3.1.7.4 Herceptin Exposure and Results of Cardiac Event and LVEF Assessment). The incidences of post baseline LVEF <50% appears to be similar in magnitude from combined analysis results from the previous two studies (8.8% and 4.1% for AC→T+H and AC→T, respectively).

5.2 Summary of Statistical Issues

The major statistical/data issues are summarized as follows:

- According to the protocol, the primary comparisons are between observation arm versus 1-year Herceptin and observation arm versus 2-year Herceptin. The comparison of 2-year Herceptin to observation arm must be performed in order to determine whether there is any remaining alpha to test secondary endpoints. Since the 2-year Herceptin data are not available, the step-down procedure based on Holm's approach can not be completed for the two comparisons based on DFS. Therefore, further evaluation of secondary endpoints will not be meaningful.
- Since the sponsor's primary and secondary endpoints are based on composite measures and are not well documented, the interpretation of the results is not clear. The information obtained from LVEF assessment may be more informative. However since the definition of the change from baseline or post-baseline value in LVEF is not pre-specified and the choice of cut-off points is not well justified, further study with longer follow-up with respect to the effect of Herceptin on cardiac events and LVEF function is recommended.

5.3 Conclusions and Recommendations

Based on this current study, the results demonstrated beneficial treatment effect of the 1-year Herceptin arm on disease free survival for adjuvant breast cancer ($p<0.0001$ based

on log-rank test; hazard ratio=0.54, 95% C.I.=[0.44, 0.67]). This beneficial treatment effect of 1-year Herceptin on disease free survival appears to be consistent across various subgroups, such as age, racial and nodal status, etc.

Since the 2-year Herceptin data are not submitted, the protocol pre-specified comparisons can not be completed. The comparison of 2-year Herceptin to observation arm must be performed in order to determine whether there is any remaining alpha to test secondary endpoints. In current submission, any further evaluation of secondary efficacy endpoints will not be meaningful.

Since the interpretation of the sponsor's primary and secondary cardiac events is not clear and the definition and cut-off points for LVEF evaluation are not pre-specified, the results of the magnitude and duration of the effect of the 1-year Herceptin on cardiac events and LVEF function should be interpreted with caution. Further studies of the impact of Herceptin on cardiac adverse event is warranted.

6 Appendix

6.1 Additional Subgroup Analysis for Disease-Free Survival

Table 31 Reviewer's Summary of Disease-Free Survival by Baseline Prognostic Factors (Study BO16348)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio (Herceptin vs. observation arm)
ECOG status	0	3092	<0.0001	0.52(0.41,0.66)
	1 or 2	292	0.37900	0.73(0.37,1.46)
Menopause status	Post-menopausal	1530	0.00100	0.57(0.41,0.79)
	Ppre-menopausal	487	0.04400	0.59(0.35,0.99)
	Uncertain	1367	<0.0001	0.49(0.34,0.70)
Previous surgery status	Prior Breast Conservation	1423	<0.0001	0.45(0.31,0.66)
	Prior Mastectomy	1962	<0.0001	0.60(0.46,0.78)
Histological grade	G1	75	0.82700	1.17(0.29,4.73)
	G2	1107	<0.0001	0.35(0.22,0.55)
	G3	2036	0.00100	0.64(0.49,0.83)
	Cat not be assessed	149	0.05800	0.29(0.08,1.04)
Radiotherapy	NO	795	0.02100	0.52(0.30,0.91)
	YES	2591	<0.0001	0.53(0.42,0.68)
Oestorgen /Progesterone	Neg/Neg	1620	<0.0001	0.51(0.38,0.68)
	Neg/Pos	172	0.25700	0.54(0.19,1.57)

receptor status	Neg/Unknown	59	0.02400	0.07(0.01,0.71)
	Pos/Neg	457	0.39000	0.76(0.41,1.42)
	Pos/Pos	979	0.04000	0.60(0.37,0.98)
	Pos/Unknown	98	0.25800	0.40(0.08,1.94)
Recepto status and endocrine therapy	Negative	1679	<0.0001	0.49(0.37,0.65)
	Positive and Endocrine Therapy	1620	0.00900	0.62(0.43,0.88)
	Positive and no Endocrine Therapy	87	0.33000	0.54(0.15,1.88)
Tobacco use	NO	2920	<0.0001	0.54(0.43,0.69)
	YES	466	0.04500	0.55(0.30,0.99)
Pathologic tumor size	<=10 mm	198	0.78600	0.81(0.18,3.63)
	>10, < 20mm	1147	0.00700	0.57(0.37,0.86)
	>20, <=50mm	1479	<0.0001	0.47(0.34,0.66)
	>50 mm	171	0.55500	0.77(0.33,1.82)

7 SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer: **Date:** September 24, 2007

Dr. Yuan-Li Shen
Mathematical Statistician Yuan-Li Shen 9-24-07

Concurrence:

Mark Rothmann 9-24-07
Dr. Mark Rothmann
Statistical Team Leader

Alaka Chakravarty 9/24/07
Dr. Aloka Chakravarty
Director, Division of Biometrics V

CC:

HFD-107/ Gootenberg, Keegan, Fedenko, Hughes
HFD-711/Chakravarty, Rothmann, Shen
HFD-700/Nevius, Patrician

This review consists of 60 pages
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

BLA; STN:	103792/5175
Submission Date:	1/10/2008
PDUFA Due Date:	Original: 9/22/07; New Date: 1/22/08
Drug Name:	Herceptin (Trastuzumab)
Sponsor:	Genentech, Inc.
Reviewer:	Angela Yuxin Men, M.D., Ph.D.

In this submission, Genentech [redacted (b) (4)] Meanwhile, Genentech provided additional information on the pharmacokinetic (PK) simulation [redacted (b) (4)]

[redacted (b) (4)] This model was based on PK parameters that better match HERA PK than the population PK parameter estimates.

The simulation results show that after a 7-day or 14-day dose delay, restart of 6 mg/kg of Herceptin undershoots trough concentrations and it takes 2-4 cycles of standard treatment to catch the trough concentrations. An 8 mg/kg reload matches trough concentrations by taking up to 2-cycle treatment. However, this reload of 8 mg/kg Herceptin results in approximately 30% higher in peak concentration compared to the observed peak concentration in HERA study, which raises a safety concern. [redacted (b) (4)] If Herceptin dosing is delayed by more than one week (> 28 days from the last actual dose), Herceptin will be still administered at doses of 6 mg/kg once every three weeks without loading dose of 8 mg/kg.

Signatures:

1/17/08

Angela Yuxin Men, M.D., Ph.D.
Clinical Pharmacology Reviewer, Biologic Product Team
Division of Clinical Pharmacology V

1/17/08

Hong Zhao, Ph.D.
Team Leader, Biologic Product Team
Division of Clinical Pharmacology V

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA; STN	**103792/5175**
Submission Date(s)	**12/22/2006, 1/30/2007, 2/13/2007, 9/17/2007**
PDUFA Due Date	**Original: 9/22/07; New Date: 1/22/08**
Brand Name	**Herceptin®**
Generic Name	**Trastuzumab**
Reviewer	**Angela Yuxin Men, M.D., Ph.D.**
Team Leader	**Hong Zhao, Ph.D.**
OCP Division	**DCP 5**
OND Division	**OODP/DBOP**
Sponsor	**Genentech, Inc.**
Submission Type	**Supplement BLA**
Formulation; Strength(s)	**Solution for IV infusion 440 mg/vial**
Proposed Indication	**As a single agent for adjuvant therapy of breast cancer**
Proposed Dosage and Administration	**8 mg/kg loading dose following by 6mg/kg administered every 3 weeks as 90-minute IV infusion**

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Herceptin (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Herceptin was approved by FDA on September 25, 1998 for use as a single agent for patients with HER2-overexpressing metastatic breast cancer (MBC) who have received one or more chemotherapy regimens for their metastatic disease and also in combination with paclitaxel for patients with HER2-overexpressing MBC who have not received chemotherapy for their metastatic disease. On 16 November 2006, the Agency approved Herceptin as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer. In this submission, the Sponsor is seeking an extended indication of Herceptin, as a single agent, for adjuvant therapy of breast cancer given as an 8-mg/kg loading dose followed by 6-mg/kg administered every 3 weeks as 90-minute IV infusions. This submission contains data from a pharmacokinetic (PK) sub-study within the HERA trial (Study BIG01-01/BO16348) in women with HER2-positive early breast cancer following surgery and completion of established adjuvant chemotherapy.

The PK of Herceptin for dose regimen of a 4-mg/kg loading dose followed by a 2-mg/kg maintenance dose given weekly remained unchanged.

1.1. Recommendation

The clinical pharmacology and biopharmaceutics information included in this submission is acceptable provided that a satisfactory agreement is reached between the applicant and the Agency regarding the proposed language to be included in the package insert.

1.2. Phase 4 Study Commitments

There is no phase 4 commitment.

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics:

As a single agent, for adjuvant therapy of breast cancer, the mean half-life of Herceptin of 16.2 days (range = 11.0 to 22.8 days) was observed after a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg every three weeks. Between weeks 6 and 37, Herceptin steady-state concentrations were achieved, with mean trough and peak concentrations of 63 mcg/mL and 216 mcg/mL, respectively.

Drug Interaction:

The pharmacokinetics of paclitaxel was not altered by Herceptin when this combination therapy was administered to patients with HER2 positive metastatic breast cancer in a drug interaction study.

Relationship between circulating extracellular domain of the HER2 receptor (HER2-ECD shed antigen) and PK or PD (pharmacokinetics or pharmacodynamics) of Herceptin

Given the limited sample size studied and inconsistent results, no conclusions could be drawn with respect to the relationship between circulating extracellular domain of the HER2 receptor and Herceptin serum trough concentration or clinical responses of Herceptin using data from Studies BO15935 and WO16229.

Date: 11/28/07

Angela Yuxin Men, M.D., Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5
Office of Clinical Pharmacology

Date: 11/28/07

Hong Zhao, Ph.D.
Team Leader
Division of Clinical Pharmacology 5
Office of Clinical Pharmacology

2. QUESTION-BASED REVIEW

(Reviewer's Note: this section includes only updates on the pharmacokinetics and drug-interaction sections. Please refer to the original review for details. All Tables and Figures are obtained from the sBLA submission, otherwise it will be mentioned.)

2.1. General Attributes

No updates.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Three studies, which include PK information, are listed in the Table 1.

Table 1. Clinical Studies Including PK Information

Study	Design	Subjects	N	Dose
BO16348 (HERA)	Phase 3, open-label, Randomized, multi-center	Women with HER2(+), early-stage, node+ or high-risk node- breast cancer	3386 (PK-44)	8 mg/kg loading dose followed by 6mg/kg q3w
WO16229	Phase 2, open-label, single-arm	Women with metastatic breast cancer with HER2 overexpression/amplification (IHC3+ and/or FISH+)	105	8 mg/kg loading dose followed by 6mg/kg q3w
BO15935	Phase 1/2 open-label,	Women with metastatic breast cancer with HER2 overexpression/amplification (IHC2+ or 3+ or FISH+)	32	8 mg/kg loading dose on Day1 followed by 6mg/kg q3w with/without paclitaxel

The HERA study is an ongoing, randomized, three-arm, open-label, multicenter study comparing 1 or 2 years of treatment with Herceptin versus observation. For the HERA PK substudy, data have been analyzed for 44 patients randomized to the 1-year treatment arm only. Blood samples for Herceptin serum concentration analysis were collected pre-dose and extensively from 1.5 hours to 21 days post-dose during Cycles 1 and 13. During Cycle 18, the final administration of Herceptin for patients in the 1-year treatment arm, samples were collected pre-dose and extensively from 1.5 hours to 42 days post-dose. In addition, a pre-dose sample was drawn on Day 1 of Cycle 3.

Study WO 16229 is an open-label, single-arm study of efficacy and safety. Trough concentrations of Herceptin were collected. The first loading dose of Herceptin was 8 mg/kg, followed 3 weeks later by 6 mg/kg and given thereafter every 3 weeks.

Study BO15935 is an open label PK study. A loading dose of 8mg/kg of Herceptin was given i.v. on Day 1 and thereafter a dose of 6mg/kg was administered i.v. every three weeks. For the first cycle, paclitaxel was given 24 h before Herceptin administration. Thereafter, Herceptin was administered together with paclitaxel (175mg/m^2) every three weeks for seven cycles (Cycles 2-8). Herceptin was then continued every three weeks until progression of disease or until the patient left the study. Patients continuing Herceptin beyond Cycle 16 entered an extension protocol. The PK parameters were compared between cycles 4 and 12 for Herceptin and between cycles 1 and 4 for paclitaxel.

2.2.2 What are the pharmacokinetics parameters?

Of the 44 patients in the 1-year treatment arm of the HERA PK substudy, Herceptin serum concentration data were available from 37 patients at Cycle 1, from 12 patients at Cycle 13, and from 8 patients at Cycle 18 who provided extensive samples. The mean serum concentration–time profiles for these patients at these cycles are shown in Figure 1. PK parameters are shown in Table 2.

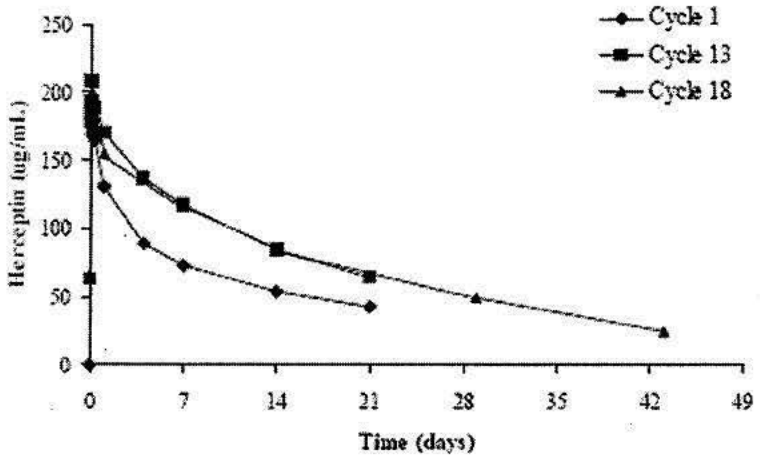

Figure 1. Mean Herceptin Concentration Profiles (HERA Trial)

Table 2. PK Parameters of Herceptin (HERA Trial)

Cycle	n	C_{max} (µg/mL)	T_{max} (hr)	AUC [a] (mg•day/L)	$t_{½}$ (days)	CL [b] (L/day)
1	34–37 [c]	198±38.2	2.9±1.9 [d]	1494±317	14.4±3.5	0.232±0.054
13	10–12 [c]	216±21.7	3.5±1.5 [e]	2255±370	16.0±2.8	0.169±0.040
18	8	210±12.3	3.0±2.2	2206±388	16.4±4.0	0.181±0.038

The mean half-life of Herceptin of 16.2 days (range = 11.0 to 22.8 days) was observed after a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg every three weeks. Up to 42 days of blood sample collection make the terminal $t_{1/2}$ was underestimated. Between weeks 6 and 37, Herceptin steady-state concentrations were observed, with mean trough and peak

concentrations of 63 μg/mL and 216 μg/mL, respectively. With the same dosing regimen, the trough and peak concentrations of Herceptin obtained from HERA trial were comparable to data from two other studies in HER2-positive MBC in which Herceptin was administered, either as monotherapy (Study WO16229) or in combination with paclitaxel (Study BO15935) (Table 3).

Table 3. Herceptin Trough Concentrations (μg/mL) prior to Cycles 2, 3, 13, 14 and 18 in the HERA, WO16229, and BO15935 Studies (Mean±SD)

Study	Cycle 2 (3 weeks)	Cycle 3 (6 weeks)	Cycle 13 (36 weeks)	Cycle 14 (39 weeks)	Cycle 18 (51 weeks)
HERA	42.9±31.2 (n=34)	48.2±14.5 (n=31)	63.2±13.7 (n=12)	64.6±12.3[a] (n=10)	66.5±22.0 (n=8)
WO16229	27.3±14 (n=92)	32.8±19 (n=81)	57.8±19 (n=13)	50.9±17 (n=12)	63.9±20 (n=6)
BO15935	28.2±12.8 (n=29)	41.1±15.1 (n=25)	72.3±33.2 (n=13)	NA	NA

2.3. Intrinsic Factors

2.3.1. What intrinsic factors influence dose-exposure and/or dose-response and what is the impact of any differences in exposure or response?

2.3.1.1. Relationship between circulating extracellular domain of the HER2 receptor (HER2-ECD shed antigen) and C_{trough} of Herceptin

ECD levels were quantified using the HER2/neu enzyme-linked immunosorbent assay (ELISA). Patients were considered to have an elevated baseline HER2-ECD shed antigen level if their baseline value was higher than the 75th percentile from each study (115 ng/mL for Study BO15935; 100 ng/mL for Study WO16229).

In Study WO16229, Herceptin was given as a single agent, 25 out of 102 patients had an increased ECD level at baseline. Figure 2 shows the C_{trough} of Herceptin for patients with higher and normal ECD levels during the treatment period. In general, C_{trough} of Herceptin in patients with higher ECD is lower than those in patients with normal ECD levels.

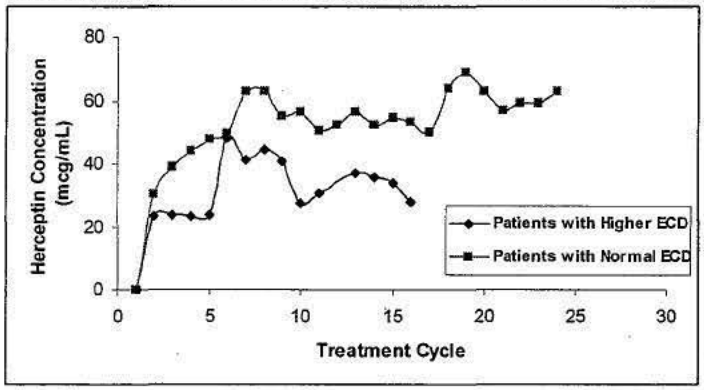

Figure 2. Trough Concentration of Herceptin for Patients with Higher or Normal ECD Levels (Study WO16229) – Reviewer's Plot

In Study BO15935, 7 out of 30 patients had higher ECD levels at baseline. The analyses showed that the majority of these 7 patients achieved target serum Herceptin concentrations of 20 µg/mL by Week 7 (Day 1 of Cycle 3) and by Week 10 (Day 1 of Cycle 4) (Table 4). In Study WO16229, among those patients with higher ECD levels at baseline, the analyses showed that approximately one-third of these patients achieved target serum Herceptin concentrations of 20 µg/mL by Week 7 (Day 1 of Cycle 3) and by Week 10 (Day 1 of Cycle 4) (Table 4).

Table 4. Number of Patients with Higher Baseline Shed Antigen Levels Whose C_{trough} of Herceptin ≥20 µg/mL

Week	BO15935 n=7	WO16229 n=25
7	5 (71%)	9 (36%)
10	6 (86%)	8 (32%)

Given the limited sample size and inconsistent results obtained from Study BO15935 and Study WO16229, no conclusion could be drawn with respect to the relationship between circulating extracellular domain of the HER2 receptor (HER2-ECD shed antigen) and Herceptin serum trough concentration for the once-every-three-week dose regimen.

2.3.1.2. Relationship between HER2-ECD shed antigen and responses of Herceptin

Study WO16229 was a multicenter, open-label, single-arm Phase II study of the safety and efficacy of Herceptin administered once every 3 weeks (Q3W) as a monotherapy in patients with HER2-overexpressing metastatic breast cancer. Correlation of baseline ECD levels with best responses revealed no clear relationship between baseline ECD levels and the best responses achieved (Figure 3). However, patients who had progressive disease showed much higher ECD level at Cycle 4 (Figure 4).

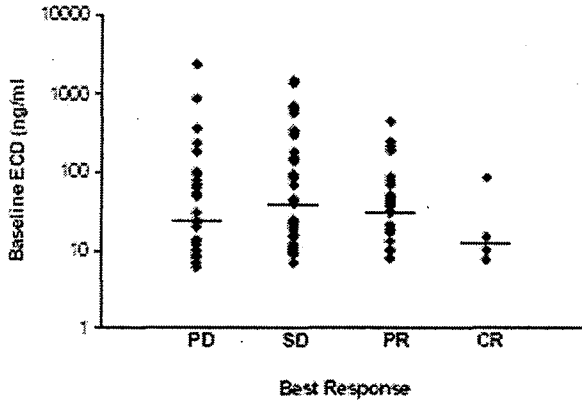

Figure 3. Correlation Between Best Response and Baseline ECD Concentrations

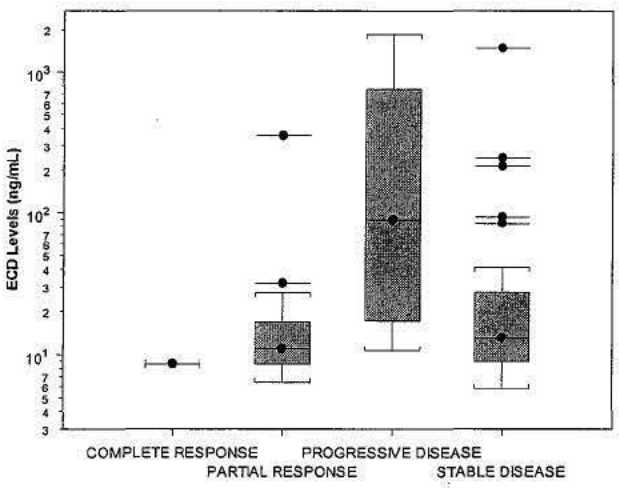

Figure 4. Correlation Between Response and ECD Concentrations at Cycle 4 (Study Wo16229) – Reviewer's Plot

2.4. Extrinsic Factors

2.4.1. Drug-drug interactions

Effect of Herceptin on Paclitaxel Pharmacokinetics

Study BO15935 was a Phase I/II study to determine the safety, tolerability and PK of Herceptin and paclitaxel administered every 3 weeks (Q3W) in women with HER2+ metastatic breast cancer. A total of 32 patients were enrolled. For the first cycle, Herceptin was given on Day 1; paclitaxel (175 mg/m^2) was given 24 hours before Herceptin administration. Thereafter, Herceptin was administered together with paclitaxel every 3 weeks for seven cycles (Cycles 2-8). Subsequently, Herceptin treatment as monotherapy was continued until disease progression or patient withdrawal from the study. Pharmacokinetic samples were taken for trough concentration (pre-dose) on Day 1 of each treatment cycle for Cycles 1–13.

Paclitaxel concentrations versus time profiles with and without Herceptin are shown in Figure 5. Using PK parameters of paclitaxel in Cycle 1 as reference, the comparison of PK of paclitaxel with and without co-administration of Herceptin is shown in Table 5.

Table 5. Comparison of PK of Paclitaxel With and Without Co-administration of Herceptin

PK parameters	Cycle 1 (ref.) n=30	Cycle 4 n=25	GMR	90% CI
AUC_{last} (ng*h/mL)	5060 (39)	4310 (38)	0.86	73.6-99.8
C_{max} (ng/mL)	16620 (33)	14044 (31)	0.85	72.0-101.0

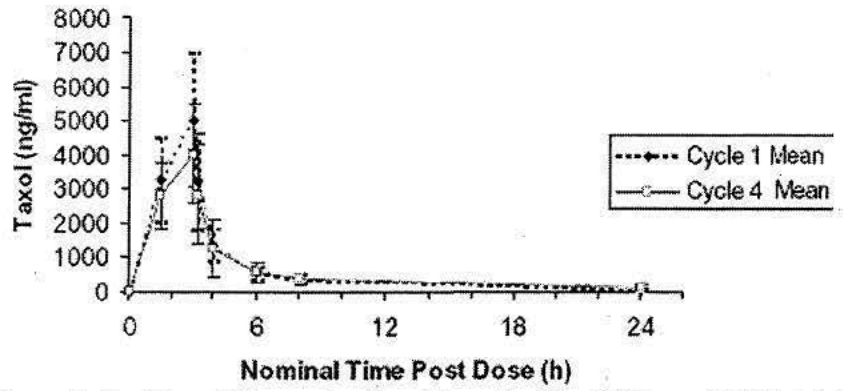

Figure 5. Paclitaxel Concentration-Time Profiles With and Without Co-administration of Herceptin

On average, paclitaxel C_{max} and systemic exposure was 15% lower when administered in combination with Herceptin compared to that administered alone. Since efficacy has been demonstrated in the combination therapy, these observed PK difference is not considered clinically significant.

Effect of Paclitaxel on Herceptin Pharmacokinetics

Mean PK profiles of Herceptin at cycles 4 (with paclitaxel), 10 and 12 (without paclitaxel) are presented in Figure 6. Estimates of PK parameters are shown in Table 6.
Note: Only three patients had samples taken at cycle 10.

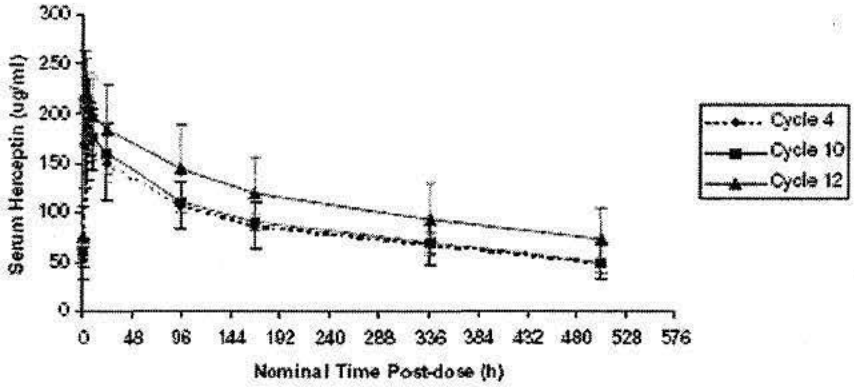

Figure 6. Mean (SD) Herceptin concentration profiles obtained at cycles 4, 10 and 12

Table 6. Mean PK Parameters of Herceptin at Cycles 4, 10 and 12

Parameter	Cycle		
mean (CV%)	4 (n=25)	10 (n=3)	12 (n=15)
C_{min} (µg/mL)	50.1 (36)	66.0 (39)	72.3 (46)
C_{max} (µg/mL)	196 (14)	203 (7)	237 (12)
Tmax (h after start of infusion)	4.4 (56)	1.7 (22)	2.7 (45)
AUC_{last} (µg.h/mL)	42040 (25)	45037 (10)	55529 (35)
$t_{1/2}$ (h)	457 (41)	649 (22)	439 (44)
Cl (mL/h)	9.8 (23)	8.8 (24)	8.2 (57)

Average trough concentrations of Herceptin increased 45% from 50.1 μg/mL at cycle 4 to 72.3 μg/mL at cycle 12 (Table 6). It is not clear this increase is due to the repeated dose accumulation or co-administration of paclitaxel. The design of this Study BO15935 does not allow for a within study evaluation of the effect of paclitaxel on Herceptin PK. Thus, it is not appropriate to determine the effect of paclitaxel on Herceptin by comparing PK parameters between Cycle 4 and Cycle 12.

2.5. General Biopharmaceutics

No updates.

2.6. Analytical

The Sponsor did not provide analytical reports in this submission.

3. DETAILED LABELING RECOMMENDATIONS

Proposed Labeling:

7. DRUG INTERACTIONS

(b) (4)

FDA suggested labeling:

(b) (4)

In drug interaction studies, the pharmacokinetics of docetaxel and paclitaxel were not altered when each was administered in combination with Herceptin (b) (4)

Proposed Labeling:

12.3 Pharmcokinetics

(b) (4)

FDA suggested labeling:

In a study of women receiving adjuvant therapy for breast cancer, a mean half-life of trastuzumab of 16 days (range: 11-23 days) was observed after an initial dose of 8 mg/kg followed by a dose of 6 mg/kg every three weeks. Between weeks 6 and 37, trastuzumab serum concentrations reached a steady-state with mean trough and peak concentrations of 63 mcg/mL and 216 mcg/mL, respectively.

Proposed Labeling:

(b) (4)

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 18, 2008

From: Monica Hughes, M.S., Lead, Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: BL 103792/5175

FDA proposed revised labeling is attached. In section 14.1, we are proposing to delete the word "pathological" from "pathological tumor size (b) (4) cm", keeping " tumor size (b) (4) cm". We are proposing to retain our language proposed on January 17, 2008. Data from the efficacy population revealed an n=1098 was node-negative disease. Of the 1098 node-negative women, an n=512 met the following criteria: node-negative and ER/PR positive and one of the following: pathological tumor greater than 2 cm, Grade 2-3 or age less than 35. Of the 1098 node-negative women, an n=543 was node-negative and ER/PR negative. Based on this data, our January 17, 2008, proposal is reflected in the attached label.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 17, 2008

From: Monica Hughes, M.S., Lead, Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: BL STN 103792/5175

Please find attached FDA's counter-proposed revisions to the Herceptin PLR labeling submitted for review under BL STN 103792/5175 in response to your second January 16, 2008, submission.

1. Please note, we have made additional revisions to sections 5.1, 6.1, table 3, and 14.1.

2. We are attaching a final PMC agreement for your review. We have added the additional information you forwarded to us regarding the QT study. Please note, this additional information will not appear in the final action letter, but for record keeping purposes we would like Genentech to include it in the final formal PMC agreement submission to the file, for future reference.

Final PMC agreements related to STN BL 103792/5175:

1. To provide a final clinical study report (CSR) of the safety and efficacy of 2-years of Trastuzumab treatment in Study BO16348 (HERA)in order to provide a final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility. The final study report will include the primary datasets and programs for generation of analyses; analyses will include, but not be limited to the analyses described in the statistical analysis plan. The final CSR will be submitted by December 31, 2013. If the results from the 2-year Trastuzumab arm are released by the IDMC at the interim analysis, then the final CSR will be submitted by December 31, 2009.

2. To provide updated safety information of the observation and 1-year Trastuzumab arms in Study BO16348 (HERA). Interim cardiac safety updates (narratives of new primary or secondary cardiac events) will be provided on an annual basis beginning in December 2008 and continuing until the time of the final CSR, which will be submitted by December 31, 2013. If the results from the 2-year Trastuzumab arm are released by the IDMC at the interim analysis, then the CSR will be submitted by December 31, 2009.

3. To submit a protocol for review for a prospectively and actively enrolled pregnancy registry that will collect information assessing pregnancy complications and birth outcomes in women with breast cancer exposed to a Herceptin-containing regimen prior to conception or during pregnancy. Notice of a pregnancy registry and the telephone contact number will be included in the package insert. A proposal, including a prospective protocol for FDA review will be submitted to FDA by June 30, 2008. The registry will become active by December 31, 2008, and interim reports of all data collected will be submitted on an annual basis to FDA through December 31, 2019.

4. To conduct a QT protocol according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in a minimum of 50 subjects receiving trastuzumab. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by March 31, 2009, and will be completed by March 31, 2013. A final study report will be submitted by September 30, 2013. A supplement with revised labeling, if applicable, will be submitted by March 31, 2014.

Additional information regarding PMC 4:

Genentech will incorporate ECG evaluations into a proposed drug-drug interaction study to be performed between Herceptin and Carboplatin as a PMC for the BCIRG.006 sBLA. Although the study design is preliminary, it is proposed that HER2-positive patients with metastatic cancer receive TCH on a q3-weekly schedule. On Day 1 of Cycle 1, patients would receive carboplatin

(AUC=6) and docetaxel (75 mg/m^2), and serial blood sampling for carboplatin PK will be taken for 24 hours following Carboplatin administration. On Day 2 of Cycle 1, Herceptin (8 mg/kg) will be administered. Herceptin (6 mg/kg), Carboplatin (AUC=6) and Docetaxel (75 mg/m2) will be given on Day 1 of each subsequent cycle. On Cycles 2, and 3 Day 1, serial blood draws for carboplatin and Herceptin PK will be taken for 24 hours following Carboplatin administration. The impact of Herceptin on Carboplatin PK between Cycle 1 (no Herceptin) and Cycle 2 (with Herceptin) will be evaluated for drug-drug interaction.

To address the PMC for QT evaluation in the HERA sBLA, Genentech will incorporate triplicate ECG evaluations, read by a central vendor and including cardiologist adjudication, into a minimum of (b)(4) patients in this DDI study. Triplicate ECGs will be performed at Baseline, Cycles 1 and 3. With 40 patients, the probability of observing 2 or more significant QT prolongations is 0.19 if the true underlying rate is 2%, and is 0.70 if the true underlying rate is 6%. A clinical significant QTc prolongation is defined as an absolute value ≥ 530 msec or a change from baseline ≥ 60 msec.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 16, 2008

From: Monica Hughes, M.S., Lead, Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: BL STN 103792/5175

Please find attached FDA's counter-proposed revisions to the Herceptin PLR labeling submitted for review under BL STN 103792/5175 in response to your January 16, 2008, submission.

1. The highlights section now meets the ½ page requirement.

2. With respect to references throughout the FPI, we revised the label for consistency [see **name of section, (section #)].**

3. Please ensure numbering of all tables is correct in the label along with any references to those tables in the text of the label.

4. Please note, cardiac arrythmias was dervived from a HLGT (higher level grouping term) that maps down to multiple perferred terms of different arrythmias. We put a foot note in the table to reflect this.

5. We do not agree with the revised numbers in section 6.1 and have revised them based on the following:

   Adjuvant Breast Cancer Studies

   The data below reflect exposure to Herceptin across three randomized, open-label studies, Studies 1, 2, and 3, with (n= 3355) or without (n= 3308) trastuzumab in the adjuvant treatment of breast cancer.

   total =study1+study2+study3

   Note : 3355=920 +757 +1678

   3308=876 +724 +1708

6. With respect to the PMCs, we agree with revisions made to PMCs 1, 2, and 3. However, we do not agree with your proposal to evaluate (b) (4) patients. We are proposing that you evaluate 50 patients.

PMC's

1. To provide a final clinical study report (CSR) of the safety and efficacy of 2-years of Trastuzumab treatment in Study BO16348 (HERA)in order to provide a final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility. The final study report will include the primary datasets and programs for generation of analyses; analyses will include, but not be limited to the analyses described in the statistical analysis plan. The final CSR will be submitted by December 31, 2013. If the results from the 2-year Trastuzumab arm are released by the IDMC at the interim analysis, then the final CSR will be submitted by December 31, 2009.

2. To provide updated safety information of the observation and 1-year Trastuzumab arms in Study BO16348 (HERA). Interim cardiac safety updates (narratives of new primary or secondary cardiac events) will be provided on an annual basis beginning in December 2008 and continuing until the time of the final CSR, which will be submitted by December 31, 2013. If the results from the 2-year Trastuzumab arm are released by the IDMC at the interim analysis, then the CSR will be submitted by December 31, 2009.

3. To submit a protocol for review for a prospectively and actively enrolled pregnancy registry that will collect information assessing pregnancy complications and birth outcomes in women with breast cancer exposed to a Herceptin-containing regimen prior to conception or during pregnancy. Notice of a pregnancy registry and the telephone contact number will be included in the package insert. A proposal, including a prospective protocol for FDA review will be submitted to FDA by June 30, 2008. The registry will become active by December 31, 2008, and interim reports of all data collected will be submitted on an annual basis to FDA through December 31, 2019.

4. To conduct a QT protocol according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in a minimum of (b)(4) 50 subjects receiving trastuzumab. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by March 31, 2009, and will be completed by March 31, 2013. A final study report will be submitted by September 30, 2013. A supplement with revised labeling, if applicable, will be submitted by March 31, 2014.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 15, 2008

From: Monica Hughes, M.S., Regulatory Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: BL STN 103792/5175

Please find attached FDA's counter-proposed revisions to the Herceptin PLR labeling submitted for review under BL STN 103792/5175 in response to your January 10, 2008, submission.

We have highlighted comments and request for clarification/additional information in the attached label. In addition to those comments, we have the following comments:

1. Please further revise the highlights section to ensure it meets the ½ page requirement.

2. For consistency throughout the label, please label all references to other sections as follows: [see **name of section, (section #)].**

3. Some tables/figures may have been deleted, please ensure numbering of all tables is correct in the label along with any references to those tables in the text of the label.

In addition, we have attached our counter-proposals for revised PMCs.

We will speak with you at 1:00 PM EST today, during our standing teleconference time, to address any questions you may have.

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Division of Drug Marketing, Advertising, and Communications

Internal Consult

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

To: Monica Hughes, Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D. 1/11/08
Division of Drug Marketing, Advertising and Communications, CDER

Date: January 11, 2008

Re: **Herceptin (Trastuzumab)**
STN BL 103792/5175
Comments on draft labeling

In response to your consult request via email on January 8, 2007, we have reviewed Genentech's draft labeling (working copy sent by electronic mail on January 10, 2008) for Herceptin and offer the following comments.

Genentech has submitted a supplemental BLA based on the HERA study in which Genentech proposes to expand the adjuvant indication to include: (b) (4) with Herceptin administration once every 3 weeks for 52 weeks: Initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every 3 weeks. Administer all doses of Herceptin as 90 minute IV infusions."

Section	Statement from draft	Comment
HIGHLIGHTS: INDICATIONS AND USAGE	"Herceptin is a (b) (4) (b) (4) (b) (4) indicated for the treatment of HER2 overexpressing breast cancer" (emphasis added)	Are the words (b) (4) appropriate to describe the drug's pharmacologic class? The Label Review Tool dated June 12, 2007 states," If the drug is a member of an established pharmacologic class, the concise statement under this heading must identify the class ... If the drug is not a member of an established pharmacologic class, the statement should be omitted." Is Herceptin a member of an established

		pharmacologic class? If so, we recommend revising the indication statement to include the appropriate class term to avoid a misleading or potentially confusing established pharmacologic class term. Reference is made to the Draft Guidance for Industry and Review Staff: Labeling for Human Prescription Drugs – Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information.
FULL PRESCRIBING INFORMATION: BOXED WARNING: **Infusion Reactions; Pulmonary Toxicity**	"Herceptin administration can result in serious infusion reactions and pulmonary toxicity. (b) (4) (b) (4)." (emphasis added)	(b) (4) (b) (4) (b) (4) DDMAC recommends (b) (4) and revising the statement to wording similar to that of the Warnings sections (5.2 and 5.3) ". . . serious and fatal infusion reactions **have been reported**" or "Herceptin use can result in serious **and fatal** pulmonary toxicity." The Guidance for Industry for the Adverse Reactions Section of Labeling (b) (4)
2. DOSAGE AND ADMINISTRATION **2.2 Dose Modifications**	*"Infusion Reactions [see Boxed Warning, (5.2)]* • **Decrease** the rate of infusion for mild or moderate infusion reactions • Interrupt the infusion in patients with dyspnea or clinically significant hypotension • Discontinue Herceptin for severe or life-threatening infusion reactions." (emphasis added)	The Dose Modification section discusses decreasing, interrupting and discontinuing Herceptin; however the Boxed Warnings, Warnings and Adverse Reactions sections of the label only discuss interruption and discontinuation. Should a discussion regarding a decrease in the rate of infusion also be included in these other sections?
5. WARNINGS AND PRECAUTIONS **5.2 Infusion Reactions** **6. ADVERSE REACTIONS**	"Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. (b) (4) (b) (4) *[see (6.1)]*." **Adjuvant Breast Cancer Studies** "The following non-cardiac adverse	Considering that the label contains a Black Boxed Warning, Warnings and Precautions for infusion reactions, the claims (b) (4) (b) (4) and (b) (4) (b) (4) (b) (4) (b) (4) We recommend deletion of these claims. The Label Review Tool (version June 12, 2007) states that labeling should avoid arbitrary categories of (b) (4) (b) (4)

6.1 Clinical Trials Experience **Adjuvant Breast Cancer Studies** **Metastatic Breast Cancer Studies – Infusion Reactions**	reactions of Grade 2-5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (31% vs. 28%), fatigue (28% vs. 22%), infection (22% vs. 14%), hot flashes (17% vs. 15%), anemia (13% vs. 7%), dyspnea (12% vs. 4%), rash/desquamation (11% vs. 7%), neutropenia (7% vs. 5%), headache (6% vs. 4%), and insomnia (3.7% vs. 1.5%). **The majority of these events were grade 2 in severity.**" "The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (11% vs. 8.4%), myalgia (10% vs. 8%), nail changes (9% vs. 7%), and dyspnea (2.5% vs. 0.1%). **The majority of these events were Grade 2 in severity.**" **Metastatic Breast Cancer Studies** *"Infusion Reactions* "During the first infusion with Herceptin, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. (b) (4) and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in < 1% of patients."	We note that the Adverse Reactions - Adjuvant Breast Cancer Studies section (6.1) uses more specific wording "The majority of these events were **grade 2** in severity." Is this supported by substantial evidence?
Diarrhea	*Diarrhea* An increased incidence of diarrhea, (b) (4) (b) (4) was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer. (emphasis added)	The claim (b) (4) (b) (4) to minimize the risk of diarrhea. We recommend avoiding (b) (4) (b) (4) (b) (4)
Boxed Warning	**"WARNING:** **CARDIOMYOPATHY, INFUSION**	We recommend that the order in which the Warnings are presented throughout the label be changed to reflect the priority given in the Boxed Warning, i.e.,

	REACTIONS, and PULMONARY TOXICITY"	first - cardiomyopathy, second - infusion reactions and third - pulmonary toxicity as this is the priority given these events in the Boxed Warning. For example, "Pulmonary Toxicity" should be listed as item number 3 instead of item number 4. "Exacerbation of Chemotherapy-Induced Neutropenia" should be listed as number 4 instead of item number 3. The rest of the Adverse Reactions section should also maintain this priority.
FULL PRESCRIBING INFORMATION: CONTENTS	**"WARNING – CARDIOMYOPATHY, INFUSION REACTIONS, PULMONARY TOXICITY"** **5 WARNINGS AND PRECAUTIONS** 5.1 Cardiomyopathy 5.2 Infusion Reactions 5.3 Exacerbation of Chemotherapy-Induced Neutropenia 5.4 Pulmonary Toxicity	
FULL PRESCRIBING INFORMATION	**5 WARNINGS AND PRECAUTIONS** **5.1 Cardiomyopathy** **5.2 Infusion Reactions** **5.3 Exacerbation of Chemotherapy-Induced Neutropenia** **5.4 Pulmonary Toxicity** **6 ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the label: • Cardiomyopathy *[see WARNINGS AND PRECAUTIONS (5.1)]* • Infusion reactions *[see WARNINGS AND PRECAUTIONS (5.2)]* • Exacerbation of chemotherapy-induced neutropenia *[see WARNINGS AND PRECAUTIONS (5.3)]* • Pulmonary toxicity *[see WARNINGS AND PRECAUTIONS (5.4)]* [emphasis added]	
5. WARNINGS AND PRECAUTIONS **5.1 Cardiomyopathy** **5.2 Infusion Reactions** **5.4 Pulmonary Toxicity**	"Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death *[see Boxed Warning: Cardiomyopathy]*." "Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. (b) (4) (b) (4) *[see (6.1)]*." [emphasis added] Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial	We recommend also adding a cross-reference to 6.1 for cardiomyopathy and pulmonary toxicity. We recommend also adding a cross-reference to the Boxed Warning for infusion reactions and pulmonary toxicity.

	pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions *[see (5.2)]*. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.	
6. ADVERSE REACTIONS	The following adverse reactions are discussed in greater detail in other sections of the label: • Cardiomyopathy ***[see WARNINGS AND PRECAUTIONS (5.1)]*** • Infusion reactions ***[see WARNINGS AND PRECAUTIONS (5.2)]*** • Exacerbation of chemotherapy-induced neutropenia ***[see WARNINGS AND PRECAUTIONS (5.3)]*** • Pulmonary toxicity ***[see WARNINGS AND PRECAUTIONS (5.4)]***	We recommend also adding a cross-reference to the Boxed Warning.
17. PATIENT COUNSELING INFORMATION		Genentech wants to add the following language to the (b) (4) (b) (4) (b) (4) Should this language also be added to the Patient Counseling Information section?

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 9, 2008

From: Monica Hughes, M.S., Lead, Regulatory Health Project Manager, DBOP/OODP/OND/CDER/FDA

Subject: 103792/5175: FDA proposed revisions to Genentech's proposed PMCs.

FDA forwarded the following proposed PMCs to Genentech for discussion during the January 10, 2008 teleconference.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 9, 2008

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Subject: 103792/5175: FDA proposed revisions to Genentech's proposed PMCs.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

M E M O R A N D U M

Date: December 17, 2007 **Date Consulted:** November 29, 2007

From: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff /K B Feibus MD

Through: Lisa Mathis, MD LLM MD 12/19/07
Associate Director, Pediatric and Maternal Health Staff

To: Division of Biological Oncology Products

Drug: Trastuzumab (Herceptin®)

Subject: Pregnancy registry post-marketing commitment

Materials Reviewed:
Proposed post-marketing commitments for HERA (Study BO16348) sBLA

Consult Question:
Determine if the proposed pregnancy registry is adequate, and if not, assist DBOP in developing comments to send back to Genentec

INTRODUCTION

The Division of Biologic Oncology Products (DBOP) is currently reviewing a supplemental BLA for Herceptin (trastuzumab) that contains a number of proposed post-marketing commitments (PMCs). One of these proposed PMCs is a pregnancy exposure registry. This Maternal Heath Team (MHT) review responds to a DBOP request to assess the adequacy of Genentech's proposed pregnancy registry concept.

BACKGROUND

Herceptin

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the Erb-2/Her2/neu receptor (epithelial growth factor receptor 2 protein). It is indicated as single agent therapy in metastatic, Her2-overexpressing breast cancer and as adjuvant therapy when part of a chemotherapy regimen for Her2-overexpressing, node positive breast cancer. During the summer of 2007, the Division of Biologic Oncology Products (DBOP) consulted the MHT regarding the potential need for changes in labeling based on 18 case reports of oligohydramnios associated with Herceptin use during pregnancy.

MHT reviewed the available data and recommended changes to the pregnancy and nursing mothers sections of labeling. At the time of the MHT consult on Herceptin, there were nine unique reports of oligohydramnios associated with Herceptin use in pregnancy both in the published literature and post-marketing reports in the AERS database. In four, and possibly five, of these cases, the amniotic fluid volume recovered following discontinuation of Herceptin therapy. There was one case with both a positive dechallenge and rechallenge. Pre-clinical data suggest an important role for epidermal growth factor in renal development. Human renal tubular development continues until 36 weeks gestation. Data from studies in organ culture, where an antibody is used to block the epidermal growth factor receptor, suggest that blocking the EGF receptor may interfere with normal nephron development. It seems scientifically plausible, based on the drug's mechanism of action that Herceptin could increase the likelihood of oligohydramnios. Transient oligohydramnios has occasionally been reported following courses of chemotherapy with other agents, but the amniotic fluid volume has generally recovered in a short period of time. Sometimes clinicians use additional intravenous hydration in an attempt to compensate for fluid compartment shifts and blunt this effect following chemotherapy.

Based on the possible association between Herceptin use during pregnancy and oligohydramnios, MHT made the following recommendations:

1. The pregnancy category for Herceptin (trastuzumab) should be changed to a "D" based on the available human data that suggest a possible teratogenic effect leading to oligohydramnios.

2. The pregnancy portion of the Herceptin label should include information about the known cases of oligohydramnios that occurred with use of Herceptin during pregnancy.

3. The label should recommend that pregnant women using Herceptin undergo screening for oligohydramnios with obstetrical ultrasound examination at regular intervals.

4. If oligohydramnios occurs, the obstetrician should begin fetal testing appropriate for the gestational age of the fetus and consistent with the standards of care for the community. This testing should continue on a regular basis until one of two conditions is met:

    a. Herceptin therapy is discontinued and oligohydramnios resolves
    b. Delivery.

5. In cases where the physician and patient decide to continue Herceptin therapy for maternal reasons despite the presence of oligohydramnios, additional intravenous hydration should be considered. With other forms of chemotherapy during pregnancy, transient oligohydramnios has been observed, and extra hydration sometimes mitigates this effect.

6. Include contact information for the Cancer and Childbirth Registry and encourage enrollment of pregnant patients using Herceptin.

The MHT provided the DBOP with draft language for the pregnancy and nursing mothers sections of labeling.

Breast cancer and pregnancy

In the United States, there are more than four million live births annually and another 2.5 million pregnancies that end in either spontaneous or induced abortion. Breast cancer complicates about 1 in 3000 pregnancies. Based on the National Cancer Institute's Surveillance, Epidemiology, and End Results Program Cancer Statistics Review and rates from 2001 – 2003, one out of eight American women will develop breast cancer during their lifetime. One of eight women diagnosed with breast cancer will be between 20 and 44 years of age at the time of diagnosis, and 10% will be pregnant. Among the nonpregnant women with breast cancer ages 20 – 44 years old, some may choose to become pregnant following diagnosis and treatment.

The number of pregnant women with a history of breast cancer or with a new diagnosis of breast cancer is expected to increase as more women delay childbearing until their 30's and 40's. Pregnancy-associated breast cancer is age-related, and women who have their first term pregnancy after age 30 years have a two to three times higher risk of developing breast carcinoma than women who have their first pregnancy before the age of 20 years.

REVIEW OF DATA

In lieu of a prospectively enrolled pregnancy registry, Genentech proposes (b) (4) [redacted] in women with breast cancer exposed to a Herceptin-containing regimen. All pregnant Herceptin-treated women for this study would be identified (b) (4) [redacted]

Genentech provided the following reason for proposing (b) (4) [redacted]

(b) (4)

With this study approach, Genentech states (b) (4)

DISCUSSION/CONCLUSIONS

FDA's Guidance for Industry on Establishing Pregnancy Exposure Registries (http://www.fda.gov/cder/guidance/3626fnl.htm) states that a sponsor should seriously consider establishing a pregnancy exposure registry when *it is likely that the medical product will be used during pregnancy as therapy for a new or chronic condition.* In addition, a drug is considered a good candidate for a pregnancy registry when inadvertent exposures are expected due to a high likelihood of use by women of childbearing age. Breast cancer most often occurs in women beyond their reproductive years; however, as women more often delay childbearing into their 30's and 40's, the number of women diagnosed with breast cancer during pregnancy or who become pregnant following breast cancer treatment has increased. Some pregnant women with a history or breast cancer may conceive while using Herceptin or may experience a breast cancer recurrence where Herceptin is one of the better treatment alternatives. Breast cancer complicates about 1 in 3000 pregnancies. One of eight women diagnosed with breast cancer will be between 20 and 44 years of age at the time of diagnosis, and 10% will be pregnant.

Based on these numbers, there may be only about 1200 pregnant patients with breast cancer per year in the United States, and it is likely that only a portion of them would be treated with Herceptin. While Genentech is concerned about identifying pregnant women with breast cancer who are using Herceptin in and around conception or later in pregnancy, (b) (4)

Pregnancy exposure registries can be designed to achieve a range of objectives from open-ended safety surveillance to testing hypotheses about how Herceptin use during pregnancy affects pregnancy and infant outcomes. Pregnancy registries may include collection of information from healthcare professionals, patients, and medical records, and can be structured as single product registries or as registries that enroll patients with a particular medical condition who may be treated with a number of different pharmaceutical therapies. Examples of multi-drug pregnancy registries include the Anti-retroviral Pregnancy Registry, the National Transplant Pregnancy Registry, and the Antiepileptic Drug Pregnancy Registry.

As suggested in the Guidance for Industry on Establishing Pregnancy Exposure Registries, in certain situations, other study designs, such as case control studies, can provide additional data. (b) (4)

[redacted] (b) (4) In the case of Herceptin, the number of pregnant women exposed to Herceptin or using Herceptin each year will be quite limited.

In order to obtain the most comprehensive and useful information about the safety and efficacy of Herceptin treatment during pregnancy, Genentech should establish a prospectively enrolled pregnancy registry that utilizes active recruitment techniques. This pregnancy exposure registry could be a single drug registry, or Genentech could choose to collaborate with other companies that manufacture breast cancer therapies and establish a breast cancer pregnancy exposure registry that would enroll pregnant patients receiving any and all breast cancer therapies during gestation. Data obtained from the proposed database study could potentially augment the knowledge gained from the pregnancy registry over time but should not be used as an alternative approach to obtaining this important information.

RECOMMENDATIONS

1. Genentech's post-marketing commitments should include development of a prospectively enrolled pregnancy exposure registry. The company should refer to the Guidance for Industry on Establishing Pregnancy Exposure Registries (http://www.fda.gov/cder/guidance/3626fnl.htm).

2. Genentech should be asked to submit a protocol to the Division for review. This protocol should include plans for active recruitment and should define pregnancy and fetal/infant outcomes that the registry will evaluate. The sponsor should consider how to assess first and second trimester pregnancy loss.

3. Genentech should be encouraged to use the proposed automated database study to augment the information obtained from the pregnancy exposure registry.

4. Genentech should be informed that FDA supports collaboration among pharmaceutical companies that manufacture drug and therapeutic biologic products used in the treatment of a particular condition. A pregnancy exposure registry designed to enroll all pregnant breast cancer patients undergoing treatment offers advantages with data analysis over a single product registry. For example, maternal and fetal/infant outcomes could be compared across treatments.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 4, 2007

From: Monica Hughes, M.S., Regulatory Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: BL STN 103792/5175

Please find attached FDA's proposed revisions to the Herceptin PLR labeling submitted for review under BL STN 103792/5175. There are potions of the labeling that are highlighted; these contain requests from FDA to Genentech to be addressed in your labeling response. In addition, FDA has the following comments and requests for Genentech:

1. On page 7 of the attached Herceptin PLR label, please insert the graph included on the following page. Your censoring scheme (censoring disease recurrence date first then the last date of follow-up, radiological exam, LEVF assessment, last contact, last survival follow-up) for the time to the first significant LVEF drop may be informative. Please re-define the censoring date as the last date of

   a. the last follow-up,
   b. the last radiological exam,
   c. last LVEF assessment',
   d. last contact,
   e. last survival follow-up or
   f. disease recurrence date, whichever occurs last, for patients who did not experienced significant LVEF drop,

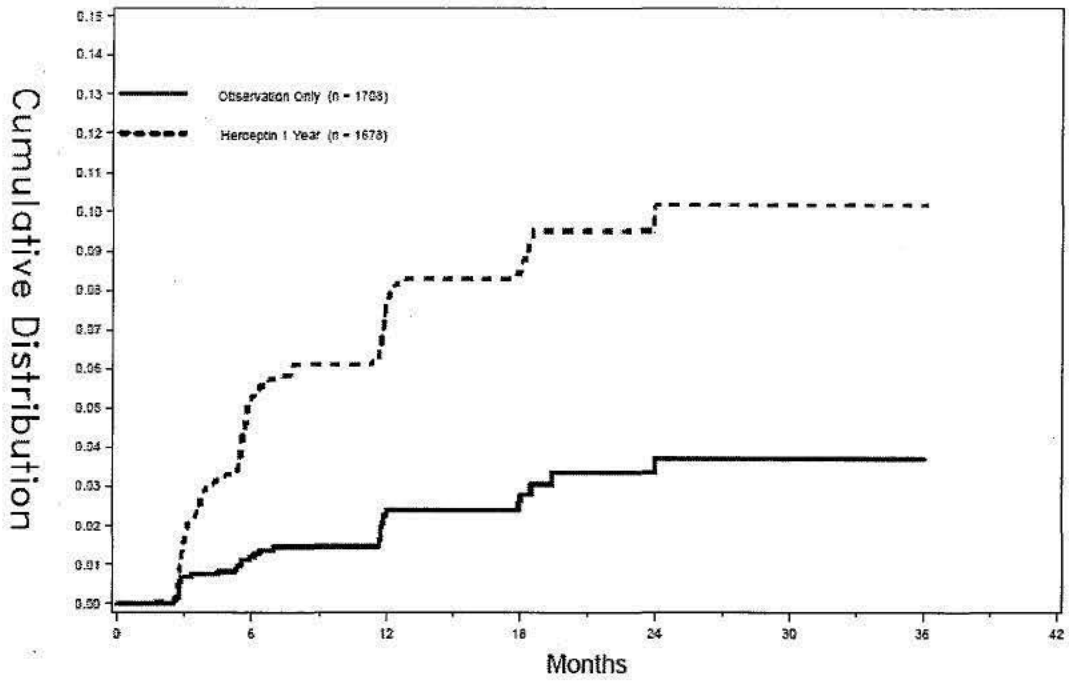
   and provide the results from both the log rank test and the Cox's proportional hazards model.

   Also, please provide a cumulative incidence plot for the time to the first significant LVEF drop using the format shown on the following page.

   We also request that you perform the same analysis and provide the data from Studies 1 and 2 in the same figure, appropriately labeled.

2. Please update the numbering of all the tables and graphs throughout the label, and ensure that all the references within the text of the label match with the respective updated numbering.

3. Please note additional revisions may be necessary following DBOP's receipt of comments from the PLR endpoints group and our colleagues at CDRH who are reviewing the HER2 test kit sections of the label.



Number at risk							
Observation Only	1703	1149	837	600	263	67	31
Herceptin 1 Year	1678	1129	853	536	273	66	29

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

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

M E M O R A N D U M

Date: August 17, 2007 **Date Consulted:** May 29, 2007

From: Karen B. Feibus, M.D. 9/7/07
Medical Team Leader, Pediatric and Maternal Health Staff

Through: Lisa Mathis, MD 9/7/07
Associate Director, Pediatric and Maternal Health Staff

Sandra Kweder, MD
Deputy Director, Office of New Drugs

To: Division of Biological Oncology Products

Drug: Trastuzumab (Herceptin®)

Subject: Case reports of oligohydramnios associated with Herceptin use during pregnancy. Are changes needed in the pregnancy section of labeling?

Materials Reviewed:

- 19 MedWatch reports that reported on eight unique cases of oligohydramnios
- Published literature on oligohydramnios associated with Herceptin use during pregnancy
- Published literature on oligohydramnios associated with pregnancies in patients with cancer or pregnancies in patients with cancer receiving chemotherapy
- Published literature on the role of epidermal growth factor in renal development.

Consult Question:

Should available information on the 18 case reports of oligohydramnios with Herceptin® use during pregnancy lead to changes in labeling of the drug for use during pregnancy?

EXECUTIVE SUMMARY

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the Erb-2/Her2/neu receptor (epithelial growth factor 2 protein). In 1998, FDA approved Herceptin (BLA 103792) alone and in combination with paclitaxel (chemotherapy-nieve patients only) for the treatment of metastatic breast cancer in women with HER2-overexpressing metastatic breast cancer. On November 16, 2006, FDA approved Herceptin as part of an adjuvant treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel in women with HER2-overexpressing, node-positive breast cancer. Up to one in 3000 live births is complicated by breast cancer. [7]

The Division of Biologic Oncology Products (DBOP) consulted the Maternal Health Team (MHT) regarding the potential need for changes in labeling based on 18 case reports of oligohydramnios associated with Herceptin use during pregnancy. The Pregnancy and Lactation Labeling Team (PLT, now the Maternal Health Team) reviewed this issue in September 2004, when there were five known cases of oligohydramnios associated with Herceptin use in pregnancy, and at that time, PLT felt that the data was confounded and not robust enough to include in labeling. The current label mentions the existence of a limited number of post-marketing cases of oligohydramnios and states that no association between oligohydramnios and the use of Herceptin has been established. DBOP would like MHT to revisit this issue in light of additional reported oligohydramnios cases and the drug's relatively new indication as adjuvant therapy for breast cancer. DBOP is concerned about potential increased use of Herceptin among women of reproductive age women with breast cancer.

Currently, there are nine unique reports of oligohydramnios associated with Herceptin use in pregnancy both in the published literature and post-marketing reports in the AERS database. In four, and possibly five, of these cases, the amniotic fluid volume has recovered following discontinuation of Herceptin therapy. There is one case with both a positive dechallenge and rechallenge. Transient oligohydramnios has occasionally been reported following courses of chemotherapy with other agents, but the amniotic fluid volume has generally recovered in a short period of time. Sometimes clinicians have used additional intravenous hydration in an attempt to compensate for fluid compartment shifts and blunt this effect following chemotherapy.

Pre-clinical data suggest an important role for epidermal growth factor in renal development. Human renal tubular development continues until 36 weeks gestation. Data from studies in organ culture, where an antibody is used to block the epidermal growth factor receptor, suggest that blocking the EGF receptor may interfere with normal nephron development. It seems scientifically plausible, based on the drug's mechanism of action that Herceptin could potentially increase the likelihood of oligohydramnios.

At this time, the data are not robust enough to conclude that a clear association exists between the use of Herceptin during pregnancy and the occurrence of oligohydramnios; however, the data do suggest a possible association that deserves monitoring. Additional data are needed to more clearly define and understand this possible relationship. Based on a woman's individual disease state and course of progression and on risk/benefit counseling between physician and patient, some women may continue Herceptin when oligohydramnios occurs and some may stop. Some

women who continue therapy may be delivered depending on the gestational age of the fetus and other factors, and some may continue their pregnancy with fetal monitoring and ultrasound examinations. In order to optimize the clinical outcomes for pregnant women with breast cancer and their babies, women using Herceptin during pregnancy should be monitored for oligohydramnios. If and when oligohydramnios occurs, risk/benefit counseling should occur and fetal testing should begin.

While oligohydramnios is not a classically teratogenic effect, the oligohydramnios may be caused by an untoward effect of Herceptin on nephron growth and function.

RECOMMENDATIONS

1. The pregnancy category for Herceptin (trastuzumab) should be changed to a "D" based on the available human data that suggest a possible teratogenic effect leading to oligohydramnios.

2. The pregnancy portion of the Herceptin label should include information about the known cases of oligohydramnios that occurred with use of Herceptin during pregnancy.

3. The label should recommend that pregnant women using Herceptin undergo screening for oligohydramnios with obstetrical ultrasound examination at regular intervals.

4. If oligohydramnios occurs, the obstetrician should begin fetal testing appropriate for the gestational age of the fetus and consistent with the standards of care for the community. This testing should continue on a regular basis until one of two conditions is met:

    a. Herceptin therapy is discontinued and oligohydramnios resolves
    b. Delivery.

5. In cases where the physician and patient decide to continue Herceptin therapy for maternal reasons despite the presence of oligohydramnios, additional intravenous hydration should be considered. With other forms of chemotherapy during pregnancy, transient oligohydramnios has been observed, and extra hydration sometimes mitigates this effect.

6. Include contact information for the Cancer and Childbirth Registry and encourage enrollment of pregnant patients using Herceptin.

7. Please see Appendix B for suggested draft language for the pregnancy and nursing mothers portions of the label.

INTRODUCTION

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the Erb-2/Her2/neu receptor (epithelial growth factor receptor 2 protein). It is indicated as single agent therapy in metastatic, Her2-overexpressing breast

cancer and as part of a chemotherapy regimen for Her2-overexpressing, node positive breast cancer. The Division of Biologic Oncology Products (DBOP) consulted the Maternal Health Team (MHT) regarding the potential need for changes in labeling based on 18 case reports of oligohydramnios associated with Herceptin use during pregnancy. While the Pregnancy and Lactation Labeling Team (PLT, now the Maternal Health Team) reviewed this issue in September 2004, DBOP would like the issue revisited in light of additional reported oligohydramnios cases and the drug's relatively new indication as adjuvant therapy for breast cancer. DBOP is concerned about potential increased use of Herceptin among women of reproductive age women with breast cancer.

BACKGROUND

While breast cancer is primarily a disease of older women, with a median age at diagnosis of 61 years, seven to 14% of breast cancers are diagnosed in women less than 40 years of age. [7,10] With delay of childbearing by many women into their 30's and even 40's, breast cancer (treated, recurrent, or newly diagnosed) is seen with increasing frequency in pregnancy. Up to one in 3000 live births is complicated by breast cancer, and this number does not include pregnancy terminations done for the mother's condition. [7] Breast cancer tumors in women under the age of 40 years tend to be larger, more aggressive, less differentiated, and lymph-node positive. Younger women with breast cancer tend to have tumors that are more likely to be estrogen and progesterone receptor negative and Her-2/neu positive. They experience higher disease-related mortality and shorter disease-free survival. [10]

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the Erb-2/Her2/neu receptor. In 1998, FDA approved Herceptin (BLA 103792) alone and in combination with paclitaxel (chemotherapy-nieve patients only) for the treatment of metastatic breast cancer in women with HER2-overexpressing metastatic breast cancer. On November 16, 2006, FDA approved Herceptin as part of an adjuvant treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel in women with HER2-overexpressing, node-positive breast cancer.

In 2004, the Division consulted PLT on whether information on five cases of oligohydramnios that occurred with Herceptin use during pregnancy should be included in labeling. At that time, Gerard Nahum MD, medical officer, reviewed information submitted by the sponsor on 23 women with breast cancer exposed to Herceptin during pregnancy. In all cases, the women were also exposed to other chemotherapeutic agents concurrently. Among 12 pregnancies that resulted in live births, eight of the women had metastatic disease (one of these women had two pregnancies), and three used Herceptin off-label in the adjuvant setting. The timing of exposure during pregnancy varied. Oligohydramnios occurred in five of these 12 pregnancies, and two of these cases involved another factor that could have contributed to the occurrence of oligohydramnios – one case of trisomy-21 and one case of severe intra-uterine growth restriction (IUGR). At that time, the PLT did not recommend including information on the isolated case reports of oligohydramnios in drug product labeling. The concomitant chemotherapy, the variable time of exposure during pregnancy, and an adverse selection testing bias based on maternal disease combined with a probability of a false-positive diagnosis of oligohydramnios were all variables that supported PLT's conclusion that this information should not be included

in product labeling. The team felt that the data was not robust enough to support a potential association between the occurrence of oligohydramnios and the use of Herceptin in these women. The most recently approved label (November 2006) includes the following statement:

> In the postmarketing setting, oligohydramnios has been reported in women who received Herceptin during pregnancy, either in combination with chemotherapy or as a single agent. Given the limited number of reported cases, the high background rate of occurrence of oligohydramnios, the lack of clear temporal relationships between drug use and clinical findings, and the lack of supportive findings in animal studies, an association between Herceptin and oligohydramnios has not been established.

Oligohydramnios is a reduced volume of amniotic fluid around the fetus, and anhydramnios is the absence of fluid around the fetus. In utero, the placenta is primarily responsible for maintaining fetal homeostasis. Fetal urine formation begins by 12 weeks of gestation and is the main constituent of amniotic fluid. [2] Amniotic fluid volume peaks at an average of one liter at 36 weeks gestation and then slowly declines. Often, decreased fluid volume occurs in pregnancies that continue post-term (beyond 40 weeks gestation), and in this situation, oligohydramnios is a reason to deliver the patient. Prior to term, oligohydramnios is far less common and is often associated with a poor prognosis. Different ultrasound methods have been used to assess the amount of amniotic fluid. Phelan et al (1987) described quantifying amniotic fluid by adding the vertical depths of the largest pocket of fluid in each of four equal uterine quadrants. This measurement is called the amniotic fluid index (AFI) and is widely used in clinical practice and as part of the biophysical profile (BPP), a form of antenatal testing that evaluates AFI, fetal tone, fetal movement, fetal breathing, and fetal heart rate pattern (nonstress test, NST) over a 30 minute period of time. An AFI < 5 cm is defined as oligohydramnios. The other widely accepted ultrasonographic method of defining oligohydramnios is the lack of a vertical pocket of amniotic fluid at least 2 cm deep. A number of studies suggest that while the AFI is a more accurate way of estimating actual amniotic fluid volume, none of the ultrasound assessments of amniotic fluid volume accurately predict fetal tolerance of labor or neonatal outcomes. [14]

Decreased amniotic fluid may be associated with maternal or fetal problems. Such maternal conditions include preterm premature rupture of membranes (PPROM) or conditions that affect placental function or vascularization (postterm pregnancy, preeclampsia). Maternal use of ACE inhibitors can also cause oligohydramnios. Fetal conditions almost always associated with oligohydramnios include fetal urinary tract obstruction or renal agenesis (Potter syndrome). Fifteen to 25% of cases of preterm oligohydramnios are associated with fetal anomalies. However, otherwise normal fetuses may experience the following consequences of early-onset, severe oligohydramnios: musculoskeletal deformities (like clubfoot, limb contractures), pulmonary hypoplasia, and/or serious deformities due to fetal part entrapment in amniotic bands. When oligohydramnios is accompanied by intrauterine growth restriction, the risk of fetal morbidity is increased. In these situations, fetal surveillance is important and delivery is often recommended for fetal or maternal indications. While gestational age is a consideration, in these

situations, fetal or maternal compromise usually overrides the potential complications from preterm delivery. [14]

Oligohydramnios detected before 36 weeks gestation with normal fetal anatomy by ultrasound can be managed expectantly along with antepartum fetal testing. [14] Antepartum fetal testing is most often performed once or twice weekly using a combination of NSTs and BPPs. The contraction stress test (CST) has the best predictive values for fetal well being during the seven days following testing but most often is not used routinely due to the possible increased risk of preterm labor.

Four of five studies suggest that maternal hydration can increase AFI, but the effect dissipates by 24 hours following fluid administration. Fluid restriction or dehydration can lower the AFI.

REVIEW OF DATA

To complete this consult, this reviewer reviewed and/or looked for the following information:

- 19 MedWatch reports that reported on eight unique cases of oligohydramnios
- Published literature on oligohydramnios associated with Herceptin use during pregnancy
- Published literature on oligohydramnios associated with pregnancies in patients with cancer or pregnancies in patients with cancer receiving chemotherapy
- Published literature on the role of epidermal growth factor in renal development.

Renal development and epidermal growth factor

Based on current data about the role that epithelial growth factor plays in renal development, some scientists and clinicians suspect that Herceptin has a potential to cause fetal adverse effects with in-utero exposure.

During embryonic development, three sets of renal organs develop sequentially: the pronephros, the mesonephros, and finally, the metanephros, which persist to become the mature kidneys. The ureteric bud grows from the mesonephric duct after the fourth week of gestation. The Wolffian duct grows caudally, passing the pronephros and mesonephros to approach the metanephric mesenchyme. As this occurs, growth factor signaling from the metanephric mesenchyme transitions from insulin growth factor-II (IGF-II) to glial-derived neurotrophic factor (GDNF). Wilm's tumor gene expression begins, suppresses IGF-II, and helps convert metanephric mesenchymal cells to epithelial cells. GDNF appears essential for promoting outpouching of the ureteric bud from the mesonephric duct. Retinoids also play an important but incompletely understood role in ureteric bud formation. Stimulation of the angiotension II receptor AT2 leads to mesenchymal apoptosis needed for ureteric bud development. [9]

The ureteric bud produces a number of soluble agents that work together to promote cellular condensation and differentiation. [9] One of these agents is epithelial growth factor (EGF), also

called transforming growth factor-α (TGF-α). TGF-α is synthesized and secreted in the embryonic kidney where it binds to the EGF receptor. The TGF-α peptide and receptors are present in the fetal human metanephros. Studies in cultured embryonic organ show that adding anti-TGF-α antibodies inhibits morphogenesis and tubulogenesisis. This suggests that TGF-α plays a role in early ureteric bud development. EGF/ TGF-α also appears to participate in rescuing uninduced mesenchymal cells from apoptosis. While the role of EGF/ TGF-α is not completely defined, it appears to play an important part in kidney organogenesis. [6]

Nephrons develop in successive stages from the inner to the outer area of the fetal kidney, in parallel with the vascular system. In humans, nephrogenesis is not completed until the 36th week of gestation. In preterm infants, the process continues following delivery. EGF/ TGF-α is one of the many factors involved in the promotion and control of nephrogenesis. [2]

Reviewer comment:

Herceptin is an IgG monoclonal antibody that blocks the human epidermal growth factor receptor 2 protein and is known to cross the placenta. Organ culture studies suggest that blocking the EGF receptor may interfere with normal nephron development.

Oligohydramnios and Herceptin use during pregnancy

Review of the published literature and MedWatch forms submitted to FDA reveal ten reported and unique pregnancies in women with breast cancer who used Herceptin during some portion of their pregnancy, nine of whom developed oligohydramnios. In one other case, a woman received two doses of Herceptin just prior to conception. Table 1 summarizes the key features of these 11 cases including the gestational ages at which Herceptin was given, the gestational age at which oligo- or anhydramnios was diagnosed, concomitant chemotherapies, whether the patient was dechallenged or rechallenged with Herceptin, and the pregnancy outcome. These cases are presented in tabular form in greater detail in Appendix A.

In cases 1 – 6, Herceptin was discontinued during pregnancy. In cases 1 – 5, the therapy was stopped due to oligohydramnios or anhydramnios. In four of these cases, there was documented reaccumulation of amniotic fluid following discontinuation of Herceptin therapy. After improvement in or resolution of oligohydramnios, one of these patients was re-challenged with Herceptin. One week after resumption of Herceptin therapy, the patient was delivered by cesarean with oligohydramnios. The fifth patient in whom Herceptin was discontinued (Case 4) received her last dose at 24 weeks gestation, and she delivered at 34 weeks by cesarean section. The MedWatch report did not include information about the reason for cesarean section at that time or the amount of amniotic fluid present prior to or at delivery. The fact that she remained pregnant for about two months following the diagnosis of oligohydramnios suggests that the amniotic fluid volume likely recovered after Herceptin therapy was stopped. The sixth patient (Case 6) discontinued Herceptin therapy during pregnancy for a maternal reason. On transthoracic echocardiography, she had a mildly reduced ventricular ejection fraction, a known cardiotoxic effect associated with Herceptin. At 25 weeks gestation, AFI was normal in this pregnancy even though Herceptin therapy was continued up until 24 weeks.[11]

In Cases 7 and 8, the patients had apparently normal pregnancies until 26 and 27 weeks respectively when the patients were diagnosed with recurrent metastatic breast cancer. In both cases, Herceptin therapy was started in combination with paclitaxel or vinorelbine and continued until delivery. In case 7, the patient received Herceptin and paclitaxel at 26 and 29 weeks

Table 1: Summary of 11 reported cases of Herceptin exposure during pregnancy: nine with oligohydramnios and two without oligohydramnios

Case	Gestational age (weeks)		Other chemo	De-challenge	Re-challenge	Outcome
	Herceptin exposure	Oligo- or anhydramnios				
1	0 – 26	26	None	Yes	Yes	AFI increased after dechallenge. Delivered at 29 wks by C/S with oligohydramnios one week after rechallenge.
2	0 – 7; 14 – 32	32	Zoladex	Yes	No	At 36 weeks, spontaneous labor and normal vaginal delivery. Trisomy 21.
3	0 – 20	23	None	Yes	No	AF reappeared at 25 weeks and normal at 32 weeks. Normal delivery at 37.5 wks.
4	0 – 24	25+	None	Yes	No	Delivered by C/S at 34 wks. Unknown reason for C/S.
5	0 – 24	None	None	Yes	No	Herceptin treatment through 24 wks gestation. Normal AFI at 25 wks. Normal infant delivered by C/S at 37 wks.
6	23 – 27	30	Docetaxel	Yes	No	At 33 wks, reaccumulating AF. Delivered by C/S for maternal reasons at 36 wks. Normal infant.
7	26 – 29	31 – 32	Paclitaxel	No	No	Due to anhydramnios with IUGR, fetal lung maturation with steroids and C/S at 32 weeks. Decreased neonatal renal function.
8	27 – del	After starting treatment	Vinorelbine	No	No	Treatment continued for maternal reasons. Extra IV hydration with weekly tx. Oligohydramnios persistent. Induction and delivery 35 wks
9	0 – del	26	None	No	No	C/S at 36 weeks. Baby with limb deformities. Died of pulmonary hypoplasia at 6 hrs
10	0 – 24	24	? Vinorelbine	No	No	Therapeutic abortion twin gestation at 24 weeks. "Lungs not developing properly"
11	-4 - 0	None	None	No	No	Normal pregnancy

gestation.[1] Within a couple of weeks of the last Herceptin dose, anhydramnios was diagnosed by ultrasound. The physicians administered steroids to mature the fetal lungs and delivered the baby by cesarean section at 32 weeks gestation, three weeks after the last dose of Herceptin. The baby had decreased renal function, which normalized over the first four weeks of life.

Reviewer comment:

Based on the severity of the mother's disease and rates of morbidity and mortality for a 32 week premature infant with anhydramnios, the obstetrician and oncologist may have decided that it was in the best interest of the mother and baby to proceed with delivery. In a different disease state situation, the clinicians may have opted for discontinuation of Herception therapy and expectant management with antepartum surveillance. Based on other cases reviewed here, it is possible that amniotic fluid may have reaccumulated with this more conservative management plan. It is interesting to note that this infant had compromised renal function at the time of delivery. This was not seen in the other Herceptin-exposed infants. While it is scientifically plausible that the decrease in renal function could be related to epithelial growth factor receptor blockade by Herceptin, there are not enough data to support such a conclusion.

In Case 8, the mother was also diagnosed with metastatic recurrence of breast cancer mid-pregnancy.[4] She began Herceptin and vinorelbine therapy at 27 weeks gestation and developed oligohydramnios shortly thereafter. Due to her condition, weekly Herceptin and vinorelbine therapy continued up to and through delivery but she received extra IV hydration with each treatment. The oligohydramnios persisted but was not progressive, and the patient underwent induction of labor at 35 weeks. She delivered a healthy infant by vaginal delivery and there were no complications.

In cases 9 and 10, the mothers received Herceptin therapy throughout the course of their pregnancies, and both had poor pregnancy outcomes. One mother continued Herceptin mono-therapy from prior to conception through delivery at 36 weeks. Oligohydramnios was diagnosed at 26 weeks gestation. Following counseling, the patient decided to continue the pregnancy and Herceptin therapy. The baby was delivered by cesarean at 36 weeks gestation with limb deformities and pulmonary hypoplasia. It died at six hours of life. Case 10 was a woman with a twin gestation receiving Herceptin monotherapy. At 24 weeks gestation, ultrasound revealed olighohydramnios and evidence that the "lungs were not developing properly." She chose to undergo therapeutic abortion at that time.

Case 11 is a published case of a woman who received two doses of Herceptin four weeks prior to and three days prior to conception. She did not receive any additional chemotherapy during her pregnancy. She had a normal pregnancy and delivery, and the baby had no complications.[12]

Chemotherapy and Pregnancy

A toxnet search found the word "oligohydramnios" associated with the following drugs: captopril, quinapril, losartan, indomethacin, enalapril, celcoxib, benazepril, rofecoxib, valdecoxib, and lisinopril. Other than ACE inhibitors and NSAIDs, no other drugs were associated with oligohydramnios in the Toxnet search.

A Toxnet search with the terms "vinorelbine and oligohydramnios" and "cancer and oligohydramnios" yielded only one informative and relevant article not already presented in this review. In 1997, Cuvier et al reported on three women with breast cancer treated with 5-fluorouracil (5-FU) and vinorelbine during pregnancy. The women began therapy at 24 – 29

weeks gestation. After two rounds of 5-FU and vinorelbine chemotherapy, one woman received six courses of cyclophosphamide and epidoxorubicin due to disease progression. Two women had spontaneous labor and vaginal deliveries at 37 and 41 weeks, and the third woman (the one who received four chemotherapeutic agents) delivered at 34 weeks by cesarean section. It appears that none of these women developed oligohydramnios; however, the reason for the cesarean delivery at 34 weeks was not provided in the article. All three children had normal development at 23 – 35 months of age.[3]

A PubMed search using the search terms "paclitaxel and oligohydramnios", " docetaxel and oligohydramnios", and "vinorelbine and oligohydramnios," found only the article by Bader et al that reports one of the oligohydramnios cases associated with Herceptin use with paclitaxel during pregnancy. A search with the terms "cancer and oligohydramnios" found three relevant articles. Two involved Herceptin cases already discussed in this review (Watson and Bader) and the other was a case report of a woman diagnosed with acute lymphocytic leukemia at 25 weeks gestation.[5] A detailed obstetrical ultrasound at that time revealed fetal growth at the 35th percentile, a normal AFI, and normal umbilical artery Doppler systolic-diastolic ratio. At 26 weeks gestation, the patient began intensive multi-agent chemotherapy: cyclophosphamide, intrathecal methotrexate, daunorubicin, vincristine, 6-mercaptopurine, cytarabine, L-asparaginase, and prednisone. After each course of chemotherapy, transient oligohydramnios occurred with the AFI decreasing to 2.0 – 3.4 cm and recovering to normal over 6-7 days. The patient went into labor spontaneously at 36 2/7 weeks gestation. There was thick meconium at rupture of membranes. This patient underwent extensive fetal monitoring during the pregnancy. Weekly non-stress tests began at 28 weeks gestation and were done twice weekly starting at 32 weeks. Ultrasound assessments of amniotic fluid were done weekly once chemotherapy began. Additional factors during this pregnancy included maternal anemia (transfusion for a hematocrit of 22%) and antibiotic treatment for a MRSA infection of indwelling Hickman catheter.[5]

Kelly et al[7] published a review article in 2006 on the options for systemic therapy in pregnant patients with breast cancer. The authors included eight studies that reported outcomes for women treated with chemotherapy during pregnancy for a variety of cancers. Three percent of babies had a congenital anomaly, which is the same as the background rate in the population. Fetal death, spontaneous abortion, prematurity, and fetal complications occurred more often in babies born to leukemic patients compared to those born to women with other tumor types. No cases of oligohydramnios were reported, but this reviewer did not review all of the original articles in this series. The largest included series was by Germann et al (2004) and did not describe any diagnoses of oligohydramnios or anhydramnios.

The Cancer and Childbirth Registry has enrolled about 92 pregnant women with breast cancer. This reviewer spoke with the registry director, Dr. Elyce Cardonick, a maternal-fetal-medicine specialist. Dr. Cardonick stated that she has seen cases of borderline oligohydramnios in pregnant women with breast cancer following a round of chemotherapy but additional IV hydration administered with the chemotherapy reversed the process. She has not seen severe oligohydramnios or anhydramnios associated with chemotherapy treatment for breast cancer during pregnancy.

DISCUSSION/CONCLUSIONS

Herceptin (trastuzumab) is a recombinant IgG humanized monoclonal antibody that binds to the epidermal growth receptor 2. It is effective for the treatment of Her-2 overexpressing metastatic breast cancers as monotherapy and for primary node-positive breast cancers as part of an adjuvant chemotherapy regimen. There are nine unique reports of oligohydramnios associated with Herceptin use in pregnancy both in the published literature and post-marketing reports in the AERS database. In four, and possibly five, of these cases, the amniotic fluid volume has recovered following discontinuation of Herceptin therapy. There is one case with both a positive dechallenge and rechallenge. The current label mentions the existence of a limited number of post-marketing cases of oligohydramnios and states that no association between oligohydramnios and the use of Herceptin has been established.

Pre-clinical data suggest an important role for epidermal growth factor in renal development. Human renal tubular development continues until 36 weeks gestation. Data from studies in organ culture, where an antibody is used to block the epidermal growth factor receptor, suggest that blocking the EGF receptor may interfere with normal nephron development. It seems scientifically plausible, based on the drug's mechanism of action that Herceptin could potentially increase the likelihood of oligohydramnios.

Oligohydramnios (decreased amniotic fluid volume) and anhydramnios (no amniotic fluid), in the absence of premature rupture of membranes, can be related to chronic fetal hypoxia, decreased or absent fetal renal function, poor placental function, and some fetal anomalies. In preterm pregnancies, the presence of oligohydramnios is associated with increased fetal morbidity, which is due in part to an increased risk of cord compression and due in part to the underlying condition that caused the oligohydramnios.

At this time, the data are not robust enough to conclude that a clear association exists between the use of Herceptin during pregnancy and the occurrence of oligohydramnios; however, the data do suggest a possible association that deserves monitoring. Additional data are needed to more clearly define and understand this possible relationship. If additional data further support an association between Herceptin use during pregnancy and oligohydramnios, then an attempt should be made to answer the following questions:

1. During which periods of gestation is Herceptin exposure associated with an increased risk of oligohydramnios?

2. Does the risk vary with the Herceptin dose and frequency of administration?

3. Does additional IV hydration either at the time of chemotherapy or in between courses of therapy alter the frequency or severity of oligohydramnios?

4. With reference to the time of Herceptin administration, when does the AFI decline and when does it recover?

Based on a woman's individual disease state and course of progression and on risk/benefit counseling between physician and patient, some women may continue Herceptin when oligohydramnios occurs and some may stop. Some women who continue therapy may be delivered depending on the gestational age of the fetus and other factors, and some may continue their pregnancy with fetal monitoring and ultrasound examinations. In order to optimize the clinical outcomes for pregnant women with breast cancer and their babies, women using Herceptin during pregnancy should be monitored for oligohydramnios. If and when oligohydramnios occurs, risk/benefit counseling should occur and fetal testing should begin.

While oligohydramnios is not a classically teratogenic effect, the oligohydramnios may be caused by an untoward effect of Herceptin on nephron growth and function.

RECOMMENDATIONS

1. The pregnancy category for Herceptin (trastuzumab) should be changed to a "D" based on the available human data that suggest a possible teratogenic effect leading to oligohydramnios.

2. The pregnancy portion of the Herceptin label should include information about the known cases of oligohydramnios that occurred with use of Herceptin during pregnancy.

3. The label should recommend that pregnant women using Herceptin undergo screening for oligohydramnios with obstetrical ultrasound examination at regular intervals.

4. If oligohydramnios occurs, the obstetrician should begin fetal testing appropriate for the gestational age of the fetus and consistent with the standards of care for the community. This testing should continue on a regular basis until one of two conditions is met:

    a. Herceptin therapy is discontinued and oligohydramnios resolves
    b. Delivery.

5. In cases where the physician and patient decide to continue Herceptin therapy for maternal reasons despite the presence of oligohydramnios, additional intravenous hydration should be considered. With other forms of chemotherapy during pregnancy, transient oligohydramnios has been observed, and extra hydration sometimes mitigates this effect.

6. Include contact information for the Cancer and Childbirth Registry and encourage enrollment of pregnant patients using Herceptin.

7. Please see Appendix B for suggested draft language for the pregnancy and nursing mothers portions of the label.

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Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
(b) (6) Table 1 Case1	32	(b) (6) (pre-conception) to (b) (6) (26 weeks gestation)	None	Recurrent breast cancer at 14 weeks gestation. Started on Herceptin 480 mg IV Q 3 weeks. US at about 26 weeks showed oligohydramnios with normal fetal growth. Hospitalized for bedrest and corticosteroids. Herceptin stopped the next day. Amniotic fluid increased. Weekly Herceptin resumed. Received one dose Herceptin 480 mg IV at 28 weeks gestation. Delivered one week later. Gestational age information is not completely consistent in MedWatch report.	By best information, preterm male infant delivered by cesarean section for breech position and oligohydramnios at 29 weeks gestation. Weight=1455g; Apgars 2/3/5. To NICU for respiratory distress and chronic lung disease. Ventilated for 2 weeks. Hospitalized for 3 months for prematurity.
(b) (6) Table 1 Case2	38	Before pregnancy. Stopped for gestational weeks 7-14. Resumed gestational weeks 14-32.	Zoladex	Patient treated for metastatic breast CA with Taxotere and Hercptin until July 2003 when pregnancy diagnosed. Borderline decreased amniotic fluid at 28 weeks. Oligohydramnios diagnosed at 32 weeks. Fetal monitoring in hospital. Herceptin stopped. Mother had gestational diabetes and hypertension.	Spontaneous labor and normal vaginal delivery at 36.2 weeks. Male infant, 6 lbs, 10 oz., Apgars 8/9. Down's Syndrome. Discharged on 4th day of life.
(b) (6) Table 1 Case 3	28	Herceptin 6 mg/kg Q 3 weeks from (b) (6) (time of conception/implantation) until 20 weeks gestation	None	Patient diagnosed with poorly differentiated carcinoma (grade III) with perinodal involvement and HER-2/neu positivity. Treated with XRT and 3 cycles doxorubicin and cyclophosphamide and 3 cycles paclotaxel. Started Herceptin near conception. Pregnancy diagnosed at 23 weeks with anhydramnios. Herceptin stopped. Amniotic fluid started to reaccumulate at 25 weeks and was normal at 32 weeks gestation. This case was published.	Induction of labor and normal vaginal delivery of a living female infant at 37.5 weeks gestation (2960 g, Apgars 8/9) Baby had normal renal function and no evidence of pulmonary hypoplasia. Normal placenta. Baby had normal growth at six months of age. Watson et al (2005). See references.
(b) (6) Table 1 Case 4	29	Two years of Herceptin therapy prior to pregnancy. Herceptin discontinued after dose at about 24 weeks gestation	None	Pregnancy diagnosed and confirmed by US at 17 weeks gestation. Herceptin given at 15 weeks and probably discontinued after treatment at 24 weeks gestation. Borderline low amniotic fluid at 25 weeks gestation progressed to oligohydramnios.	Normal preterm female infant delivered by cesarean section at 34 weeks gestation.
(b) (6) Table 1 Case 10	30	Herceptin prior to and throughout pregnancy	Possibly vinorelbine	Twin pregnancy with oligohydramnios diagnosed at 24 weeks gestation. According to the report, there was "evidence that the lungs were not developing properly" and were considered incompatible with life. Mother had a therapeutic abortion.	Therapeutic abortion after 24 weeks gestation.

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
(b) (6) Table 1 Case 8	26	Herceptin started at 27 weeks gestation	Vinorelbine	Patient diagnosed and treated for Grade III infiltrating ductal carcinoma with positive nodes. She completed treatment with Herceptin, paclitaxel, 5-FU, epirubicin, and cyclophosphamide through a clinical trial. Fourteen months after diagnosis, she presented with right upper quadrant pain and a 27 week pregnancy. Multiple imaging studies including ultrasound were performed. She had multiple hepatic metastases and increased LFTs. Patient was treated with Herceptin (4mg/kg load and 2 mg/kg per week) and vinorelbine (weekly x 3, then 1 week rest). She was seen weekly by a high risk obstetrician and oncologist. After starting treatment, oligohydramnios was noted. This was thought secondary to fluid shifts or systemic therapy. Extra IV hydration given with each chemotherapy treatment. Weekly fetal monitoring. AFIs remained low. Decreased fetal movement at 34 5/7 weeks with occasional, mild fetal heart decelerations.	Induction of labor at 34 5/7 weeks with normal vaginal delivery of a healthy male infant (5 lbs, 11 oz; Apgars 9/9/10). Normal and healthy at six months of age. Fanale et al (2005). See references.
(b) (6) Table 1 Case 9	36	Herceptin throughout pregnancy	None	Patient previously diagnosed with breast cancer. Being treated with Herceptin 441 mg Q 3 weeks. Pregnancy confirmed and dated by 26 week ultrasound. Anhydramnios diagnosed. Patient counseled and chose to continue pregnancy.	Female infant delivered by cesarean section at about 36 weeks gestation (2690 g, Apgars 8/8). Baby had lower limb deformities and died of pulmonary hypoplasia at 6 hours of life.
(b) (6) Table 1 Case 7	38	Herceptin at 26 and 29 weeks gestation	Paclitaxel	Seven years prior to pregnancy, the patient was diagnosed with Stage I breast cancer. She was treated with six cycles of cyclophosphamide, methotrexate, and 5-FU followed by XRT and 5 years of tamoxifen. At 17 weeks gestation, the patient developed paresthesia and hypoesthesia of the left arm and cervical neck pain. On MRI, there was metastatic infiltration and collapse of the second cervical vertebrae with spinal compression and metastases in the fourth thoracic vertebrae and femur. Between 26 and 32 weeks gestation, the patient received two treatments of Herceptin and paclitaxel. On US, the fetal abdominal circumference stopped increasing and the amniotic fluid volume decreased nearly to anhydramnios. Corticosteroids given for fetal lung maturation.	Delivery of living infant by cesarean section for anhydramnios, fetal growth restriction, and suspected fetal renal failure. Normal placenta. Admitted to NICU with signs of bacterial sepsis and decreased renal function. Renal function normalized by day of life 28, and the baby was discharged home. Normal development at 12 weeks of age. Bader et al (2007). See references.

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
J Clin Onc 01/10/06 Table 1 Case 11	30	3.5 weeks and 3 days prior to conception	None	Patient diagnosed with multifocal grade 2 invasive ductal adenocarcinoma of the right breast with two of five nodes positive. Estrogen and progesterone receptor negative. Her-2/neu positive. Had been trying to conceive. Treated with four cycles of epirubicin followed by four cycles of cyclophosphamide, methotrexate, and 5-FU over six months. Due to incomplete excision and strong family history of breast CA, had a bilateral mastectomy followed by radiotherapy to the right chest wall. Enrolled in Herceptin Adjuvant trial (HERA) and randomized to trastuzumab treatment every three weeks. Had a positive pregnancy test before third treatment cycle. Conceived three days after second dose. Withdrew from trial.	Spontaneous vaginal delivery of a healthy female infant at full term. No complications. Waterston and Graham (2006). See references.
Reprod Tox 06/07 Table 1 Case 5	32	Throughout pregnancy until 24 weeks gestation	None	Patient diagnosed with Her-2/neu positive breast cancer during her first pregnancy. She underwent radical mastectomy and therapeutic abortion. Treated with paclitaxel and carboplatin. Six months after completing chemotherapy, diagnosed with lung metastases. Treated with paclitaxel, carboplatin, and trastuzumab. Eighteen months later had a single brain metastasis treated with surgery and radiation. After one year of ongoing treatment with trastuzumab alone and no recurrence, the patient presented with a five week viable pregnancy. Treatment was continued and the pregnancy progressed normally until trans-thoracic echocardiography revealed an asymptomatic mild low ejection fraction at 18 weeks. Fetal growth and anatomical survey were normal. Repeat maternal echo at 24 weeks was unchanged but trstuzumab was discontinued. Fetal US at 25 weeks gestation showed normal growth, AFI, and BPP.	Cesarean delivery (for breech presentation) of a healthy female infant at 37 weeks gestation. Normal placental pathology without metastases. Shrim et al (20007). See references.

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
Obstet Gynecol 08/07	28	23, 26, and 27 weeks gestation	Docetaxel	(Australia) Patient was diagnosed with left infiltrating ductal carcinoma, grade 2, stage T2N2M0 in (b) (6) (b) (6). She had a radical mastectomy and lymphadenectomy with 18 of 18 nodes positive. The tumor was E/P receptor negative and human epidermal growth factor 2 (Her-2/neu) positive. She was treated with chemotherapy and radiotherapy. At 20 weeks gestation, MRI revealed brachial plexus and pulmonary metastases. She was treated with three cycles of docetaxel and trastuzumab at 23, 26, and 27 weeks gestation. A fetal ultrasound was done at 30 weeks for clinical suspicion of fetal growth restriction. The ultrasound showed fetal growth measurements at <5th percentile consistent with IUGR and anhydramnios. Chemotherapy was held until after delivery. Two doses of betamethasone were given for fetal lung maturation in case delivery was needed. At 33 weeks, amniotic fluid was reaccumulating. Due to the patient's advanced disease state, she was delivered at 36 weeks.	Cesarean delivery for breech presentation at 362/7 weeks due to maternal disease state. Small amount of clear amniotic fluid at delivery. Living male infant, 2230 g, Apgars 7/9. Normal neonatal urine output. No complications. Sekar and Stone (2007). See references.

Appendix B: Proposed Changes to Current Pregnancy Labeling Language

Suggested deletions are indicated with strikeouts, and suggested insertions are indicated with an underline.

(b) (4)

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

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

M E M O R A N D U M

Date: August 17, 2007 **Date Consulted:** May 29, 2007

From: Karen B. Feibus, M.D. 8/28/07
Medical Team Leader, Pediatric and Maternal Health Staff

Through: Lisa Mathis, MD 8/28/07
Associate Director, Pediatric and Maternal Health Staff

Sandra Kweder, MD 8/28/07
Deputy Director, Office of New Drugs

To: Division of Biological Oncology Products

Drug: Trastuzumab (Herceptin®)

Subject: Case reports of oligohydramnios associated with Herceptin use during pregnancy. Are changes needed in the pregnancy section of labeling?

Materials Reviewed:

- 19 MedWatch reports that reported on eight unique cases of oligohydramnios
- Published literature on oligohydramnios associated with Herceptin use during pregnancy
- Published literature on oligohydramnios associated with pregnancies in patients with cancer or pregnancies in patients with cancer receiving chemotherapy
- Published literature on the role of epidermal growth factor in renal development.

Consult Question:

Should available information on the 18 case reports of oligohydramnios with Herceptin® use during pregnancy lead to changes in labeling of the drug for use during pregnancy?

EXECUTIVE SUMMARY

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the Erb-2/Her2/neu receptor (epithelial growth factor 2 protein). In 1998, FDA approved Herceptin (BLA 103792) alone and in combination with paclitaxel (chemotherapy-nieve patients only) for the treatment of metastatic breast cancer in women with HER2-overexpressing metastatic breast cancer. On November 16, 2006, FDA approved Herceptin as part of an adjuvant treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel in women with HER2-overexpressing, node-positive breast cancer. Up to one in 3000 live births is complicated by breast cancer. [7]

The Division of Biologic Oncology Products (DBOP) consulted the Maternal Health Team (MHT) regarding the potential need for changes in labeling based on 18 case reports of oligohydramnios associated with Herceptin use during pregnancy. The Pregnancy and Lactation Labeling Team (PLT, now the Maternal Health Team) reviewed this issue in September 2004, when there were five known cases of oligohydramnios associated with Herceptin use in pregnancy, and at that time, PLT felt that the data was confounded and not robust enough to include in labeling. The current label mentions the existence of a limited number of post-marketing cases of oligohydramnios and states that no association between oligohydramnios and the use of Herceptin has been established. DBOP would like MHT to revisit this issue in light of additional reported oligohydramnios cases and the drug's relatively new indication as adjuvant therapy for breast cancer. DBOP is concerned about potential increased use of Herceptin among women of reproductive age women with breast cancer.

Currently, there are nine unique reports of oligohydramnios associated with Herceptin use in pregnancy both in the published literature and post-marketing reports in the AERS database. In four, and possibly five, of these cases, the amniotic fluid volume has recovered following discontinuation of Herceptin therapy. There is one case with both a positive dechallenge and rechallenge. Transient oligohydramnios has occasionally been reported following courses of chemotherapy with other agents, but the amniotic fluid volume has generally recovered in a short period of time. Sometimes clinicians have used additional intravenous hydration in an attempt to compensate for fluid compartment shifts and blunt this effect following chemotherapy.

Pre-clinical data suggest an important role for epidermal growth factor in renal development. Human renal tubular development continues until 36 weeks gestation. Data from studies in organ culture, where an antibody is used to block the epidermal growth factor receptor, suggest that blocking the EGF receptor may interfere with normal nephron development. It seems scientifically plausible, based on the drug's mechanism of action that Herceptin could potentially increase the likelihood of oligohydramnios.

At this time, the data are not robust enough to conclude that a clear association exists between the use of Herceptin during pregnancy and the occurrence of oligohydramnios; however, the data do suggest a possible association that deserves monitoring. Additional data are needed to more clearly define and understand this possible relationship. Based on a woman's individual disease state and course of progression and on risk/benefit counseling between physician and patient, some women may continue Herceptin when oligohydramnios occurs and some may stop. Some

women who continue therapy may be delivered depending on the gestational age of the fetus and other factors, and some may continue their pregnancy with fetal monitoring and ultrasound examinations. In order to optimize the clinical outcomes for pregnant women with breast cancer and their babies, women using Herceptin during pregnancy should be monitored for oligohydramnios. If and when oligohydramnios occurs, risk/benefit counseling should occur and fetal testing should begin.

RECOMMENDATIONS

1. The pregnancy portion of the Herceptin (tratuzumab) label should include information about the known cases of oligohydramnios that occurred with use of Herceptin during pregnancy.

2. The label should recommend that pregnant women using Herceptin undergo routine obstetrical ultrasound examination following each treatment with Herceptin to screen for oligohydramnios.

3. If oligohydramnios occurs, the obstetrician should begin fetal testing appropriate for the gestational age of the fetus and consistent with the standards of care for the community. This testing should continue on a regular basis until one of two conditions is met:

    a. Herceptin therapy is discontinued and oligohydramnios resolves
    b. Delivery.

4. In cases where the physician and patient decide to continue Herceptin therapy for maternal reasons despite the presence of oligohydramnios, additional intravenous hydration should be considered. With other forms of chemotherapy during pregnancy, transient oligohydramnios has been observed, and extra hydration sometimes mitigates this effect.

5. Include contact information for the Cancer and Childbirth Registry and encourage enrollment of pregnant patients using Herceptin.

6. If it would be helpful to the Division, the Maternal Health Team would be happy to provide draft language for the pregnancy portion of the label. (Please see Appendix B.)

INTRODUCTION

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the Erb-2/Her2/neu receptor (epithelial growth factor receptor 2 protein). It is indicated as single agent therapy in metastatic, Her2-overexpressing breast cancer and as part of a chemotherapy regimen for Her2-overexpressing, node positive breast cancer. The Division of Biologic Oncology Products (DBOP) consulted the Maternal Health Team (MHT) regarding the potential need for changes in labeling based on 18 case reports of oligohydramnios associated with Herceptin use during pregnancy. While the Pregnancy and Lactation Labeling Team (PLT, now the Maternal Health Team) reviewed this issue in

September 2004, DBOP would like the issue revisited in light of additional reported oligohydramnios cases and the drug's relatively new indication as adjuvant therapy for breast cancer. DBOP is concerned about potential increased use of Herceptin among women of reproductive age women with breast cancer.

BACKGROUND

While breast cancer is primarily a disease of older women, with a median age at diagnosis of 61 years, seven to 14% of breast cancers are diagnosed in women less than 40 years of age. [7,10] With delay of childbearing by many women into their 30's and even 40's, breast cancer (treated, recurrent, or newly diagnosed) is seen with increasing frequency in pregnancy. Up to one in 3000 live births is complicated by breast cancer, and this number does not include pregnancy terminations done for the mother's condition. [7] Breast cancer tumors in women under the age of 40 years tend to be larger, more aggressive, less differentiated, and lymph-node positive. Younger women with breast cancer tend to have tumors that are more likely to be estrogen and progesterone receptor negative and Her-2/neu positive. They experience higher disease-related mortality and shorter disease-free survival. [10]

Herceptin (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the Erb-2/Her2/neu receptor. In 1998, FDA approved Herceptin (BLA 103792) alone and in combination with paclitaxel (chemotherapy-nieve patients only) for the treatment of metastatic breast cancer in women with HER2-overexpressing metastatic breast cancer. On November 16, 2006, FDA approved Herceptin as part of an adjuvant treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel in women with HER2-overexpressing, node-positive breast cancer.

In 2004, the Division consulted PLT on whether information on five cases of oligohydramnios that occurred with Herceptin use during pregnancy should be included in labeling. At that time, Gerard Nahum MD, medical officer, reviewed information submitted by the sponsor on 23 women with breast cancer exposed to Herceptin during pregnancy. In all cases, the women were also exposed to other chemotherapeutic agents concurrently. Among 12 pregnancies that resulted in live births, eight of the women had metastatic disease (one of these women had two pregnancies), and three used Herceptin off-label in the adjuvant setting. The timing of exposure during pregnancy varied. Oligohydramnios occurred in five of these 12 pregnancies, and two of these cases involved another factor that could have contributed to the occurrence of oligohydramnios – one case of trisomy-21 and one case of severe intra-uterine growth restriction (IUGR). At that time, the PLT did not recommend including information on the isolated case reports of oligohydramnios in drug product labeling. The concomitant chemotherapy, the variable time of exposure during pregnancy, and an adverse selection testing bias based on maternal disease combined with a probability of a false-positive diagnosis of oligohydramnios were all variables that supported PLT's conclusion that this information should not be included in product labeling. The team felt that the data was not robust enough to support a potential association between the occurrence of oligohydramnios and the use of Herceptin in these women. The most recently approved label (November 2006) includes the following statement:

In the postmarketing setting, oligohydramnios has been reported in women who received Herceptin during pregnancy, either in combination with chemotherapy or as a single agent. Given the limited number of reported cases, the high background rate of occurrence of oligohydramnios, the lack of clear temporal relationships between drug use and clinical findings, and the lack of supportive findings in animal studies, an association between Herceptin and oligohydramnios has not been established.

Oligohydramnios is a reduced volume of amniotic fluid around the fetus, and anhydramnios is the absence of fluid around the fetus. In utero, the placenta is primarily responsible for maintaining fetal homeostasis. Fetal urine formation begins by 12 weeks of gestation and is the main constituent of amniotic fluid. [2] Amniotic fluid volume peaks at an average of one liter at 36 weeks gestation and then slowly declines. Often, decreased fluid volume occurs in pregnancies that continue post-term (beyond 40 weeks gestation), and in this situation, oligohydramnios is a reason to deliver the patient. Prior to term, oligohydramnios is far less common and is often associated with a poor prognosis. Different ultrasound methods have been used to assess the amount of amniotic fluid. Phelan et al (1987) described quantifying amniotic fluid by adding the vertical depths of the largest pocket of fluid in each of four equal uterine quadrants. This measurement is called the amniotic fluid index (AFI) and is widely used in clinical practice and as part of the biophysical profile (BPP), a form of antenatal testing that evaluates AFI, fetal tone, fetal movement, fetal breathing, and fetal heart rate pattern (nonstress test, NST) over a 30 minute period of time. An AFI < 5 cm is defined as oligohydramnios. The other widely accepted ultrasonographic method of defining oligohydramnios is the lack of a vertical pocket of amniotic fluid at least 2 cm deep. A number of studies suggest that while the AFI is a more accurate way of estimating actual amniotic fluid volume, none of the ultrasound assessments of amniotic fluid volume accurately predict fetal tolerance of labor or neonatal outcomes. [14]

Decreased amniotic fluid may be associated with maternal or fetal problems. Such maternal conditions include preterm premature rupture of membranes (PPROM) or conditions that affect placental function or vascularization (postterm pregnancy, preeclampsia). Maternal use of ACE inhibitors can also cause oligohydramnios. Fetal conditions almost always associated with oligohydramnios include fetal urinary tract obstruction or renal agenesis (Potter syndrome). Fifteen to 25% of cases of preterm oligohydramnios are associated with fetal anomalies. However, otherwise normal fetuses may experience the following consequences of early-onset, severe oligohydramnios: musculoskeletal deformities (like clubfoot, limb contractures), pulmonary hypoplasia, and/or serious deformities due to fetal part entrapment in amniotic bands. When oligohydramnios is accompanied by intrauterine growth restriction, the risk of fetal morbidity is increased. In these situations, fetal surveillance is important and delivery is often recommended for fetal or maternal indications. While gestational age is a consideration, in these situations, fetal or maternal compromise usually overrides the potential complications from preterm delivery. [14]

Oligohydramnios detected before 36 weeks gestation with normal fetal anatomy by ultrasound can be managed expectantly along with antepartum fetal testing. [14] Antepartum fetal testing is most often performed once or twice weekly using a combination of NSTs and BPPs. The contraction stress test (CST) has the best predictive values for fetal well being during the seven days following testing but most often is not used routinely due to the possible increased risk of preterm labor.

Four of five studies suggest that maternal hydration can increase AFI, but the effect dissipates by 24 hours following fluid administration. Fluid restriction or dehydration can lower the AFI.

REVIEW OF DATA

To complete this consult, this reviewer reviewed and/or looked for the following information:

- 19 MedWatch reports that reported on eight unique cases of oligohydramnios
- Published literature on oligohydramnios associated with Herceptin use during pregnancy
- Published literature on oligohydramnios associated with pregnancies in patients with cancer or pregnancies in patients with cancer receiving chemotherapy
- Published literature on the role of epidermal growth factor in renal development.

Renal development and epidermal growth factor

Based on current data about the role that epithelial growth factor plays in renal development, some scientists and clinicians suspect that Herceptin has a potential to cause fetal adverse effects with in-utero exposure.

During embryonic development, three sets of renal organs develop sequentially: the pronephros, the mesonephros, and finally, the metanephros, which persist to become the mature kidneys. The ureteric bud grows from the mesonephric duct after the fourth week of gestation. The Wolffian duct grows caudally, passing the pronephros and mesonephros to approach the metanephric mesenchyme. As this occurs, growth factor signaling from the metanephric mesenchyme transitions from insulin growth factor-II (IGF-II) to glial-derived neurotrophic factor (GDNF). Wilm's tumor gene expression begins, suppresses IGF-II, and helps convert metanephric mesenchymal cells to epithelial cells. GDNF appears essential for promoting outpouching of the ureteric bud from the mesonephric duct. Retinoids also play an important but incompletely understood role in ureteric bud formation. Stimulation of the angiotension II receptor AT2 leads to mesenchymal apoptosis needed for ureteric bud development. [9]

The ureteric bud produces a number of soluble agents that work together to promote cellular condensation and differentiation. [9] One of these agents is epithelial growth factor (EGF), also called transforming growth factor-α (TGF-α). TGF-α is synthesized and secreted in the embryonic kidney where it binds to the EGF receptor. The TGF-α peptide and receptors are present in the fetal human metanephros. Studies in cultured embryonic organ show that adding

anti-TGF-α antibodies inhibits morphogenesis and tubulogenesisis. This suggests that TGF-α plays a role in early ureteric bud development. EGF/ TGF-α also appears to participate in rescuing uninduced mesenchymal cells from apoptosis. While the role of EGF/ TGF-α is not completely defined, it appears to play an important part in kidney organogenesis. [6]

Nephrons develop in successive stages from the inner to the outer area of the fetal kidney, in parallel with the vascular system. In humans, nephrogenesis is not completed until the 36th week of gestation. In preterm infants, the process continues following delivery. EGF/ TGF-α is one of the many factors involved in the promotion and control of nephrogenesis. [2]

Reviewer comment:

Herceptin is an IgG monoclonal antibody that blocks the human epidermal growth factor receptor 2 protein and is known to cross the placenta. Organ culture studies suggest that blocking the EGF receptor may interfere with normal nephron development.

Oligohydramnios and Herceptin use during pregnancy

Review of the published literature and MedWatch forms submitted to FDA reveal ten reported and unique pregnancies in women with breast cancer who used Herceptin during some portion of their pregnancy, nine of whom developed oligohydramnios. In one other case, a woman received two doses of Herceptin just prior to conception. Table 1 summarizes the key features of these 11 cases including the gestational ages at which Herceptin was given, the gestational age at which oligo- or anhydramnios was diagnosed, concomitant chemotherapies, whether the patient was dechallenged or rechallenged with Herceptin, and the pregnancy outcome. These cases are presented in tabular form in greater detail in Appendix A.

In cases 1 – 6, Herceptin was discontinued during pregnancy. In cases 1 – 5, the therapy was stopped due to oligohydramnios or anhydramnios. In four of these cases, there was documented reaccumulation of amniotic fluid following discontinuation of Herceptin therapy. After improvement in or resolution of oligohydramnios, one of these patients was re-challenged with Herceptin. One week after resumption of Herceptin therapy, the patient was delivered by cesarean with oligohydramnios. The fifth patient in whom Herceptin was discontinued (Case 4) received her last dose at 24 weeks gestation, and she delivered at 34 weeks by cesarean section. The MedWatch report did not include information about the reason for cesarean section at that time or the amount of amniotic fluid present prior to or at delivery. The fact that she remained pregnant for about two months following the diagnosis of oligohydramnios suggests that the amniotic fluid volume likely recovered after Herceptin therapy was stopped. The sixth patient (Case 6) discontinued Herceptin therapy during pregnancy for a maternal reason. On transthoracic echocardiography, she had a mildly reduced ventricular ejection fraction, a known cardiotoxic effect associated with Herceptin. At 25 weeks gestation, AFI was normal in this pregnancy even though Herceptin therapy was continued up until 24 weeks.[11]

In Cases 7 and 8, the patients had apparently normal pregnancies until 26 and 27 weeks respectively when the patients were diagnosed with recurrent metastatic breast cancer. In both cases, Herceptin therapy was started in combination with paclitaxel or vinorelbine and continued until delivery. In case 7, the patient received Herceptin and paclitaxel at 26 and 29 weeks

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Table 1: Summary of 11 reported cases of Herceptin exposure during pregnancy: nine with oligohydramnios and two without oligohydramnios

Case	Gestational age (weeks): Herceptin exposure	Gestational age (weeks): Oligo- or anhydramnios	Other chemo	De-challenge	Re-challenge	Outcome
1	0 – 26	26	None	Yes	Yes	AFI increased after dechallenge. Delivered at 29 wks by C/S with oligohydramnios one week after rechallenge.
2	0 – 7; 14 – 32	32	Zoladex	Yes	No	At 36 weeks, spontaneous labor and normal vaginal delivery. Trisomy 21.
3	0 – 20	23	None	Yes	No	AF reappeared at 25 weeks and normal at 32 weeks. Normal delivery at 37.5 wks.
4	0 – 24	25+	None	Yes	No	Delivered by C/S at 34 wks. Unknown reason for C/S.
5	0 – 24	None	None	Yes	No	Herceptin treatment through 24 wks gestation. Normal AFI at 25 wks. Normal infant delivered by C/S at 37 wks.
6	23 – 27	30	Docetaxel	Yes	No	At 33 wks, reaccumulating AF. Delivered by C/S for maternal reasons at 36 wks. Normal infant.
7	26 – 29	31 – 32	Paclitaxel	No	No	Due to anhydramnios with IUGR, fetal lung maturation with steroids and C/S at 32 weeks. Decreased neonatal renal function.
8	27 – del	After starting treatment	Vinorelbine	No	No	Treatment continued for maternal reasons. Extra IV hydration with weekly tx. Oligohydramnios persistent. Induction and delivery 35 wks
9	0 – del	26	None	No	No	C/S at 36 weeks. Baby with limb deformities. Died of pulmonary hypoplasia at 6 hrs
10	0 – 24	24	? Vinorelbine	No	No	Therapeutic abortion twin gestation at 24 weeks. "Lungs not developing properly"
11	-4 - 0	None	None	No	No	Normal pregnancy

gestation.[1] Within a couple of weeks of the last Herceptin dose, anhydramnios was diagnosed by ultrasound. The physicians administered steroids to mature the fetal lungs and delivered the baby by cesarean section at 32 weeks gestation, three weeks after the last dose of Herceptin. The baby had decreased renal function, which normalized over the first four weeks of life.

Reviewer comment:

Based on the severity of the mother's disease and rates of morbidity and mortality for a 32 week premature infant with anhydramnios, the obstetrician and oncologist may have decided that it was in the best interest of the mother and baby to proceed with delivery. In a different disease state situation, the clinicians may have opted for discontinuation of Herception therapy and expectant management with antepartum surveillance. Based on other cases

reviewed here, it is possible that amniotic fluid may have reaccumulated with this more conservative management plan. It is interesting to note that this infant had compromised renal function at the time of delivery. This was not seen in the other Herceptin-exposed infants. While it is scientifically plausible that the decrease in renal function could be related to epithelial growth factor receptor blockade by Herceptin, there are not enough data to support such a conclusion.

In Case 8, the mother was also diagnosed with metastatic recurrence of breast cancer mid-pregnancy.[4] She began Herceptin and vinorelbine therapy at 27 weeks gestation and developed oligohydramnios shortly thereafter. Due to her condition, weekly Herceptin and vinorelbine therapy continued up to and through delivery but she received extra IV hydration with each treatment. The oligohydramnios persisted but was not progressive, and the patient underwent induction of labor at 35 weeks. She delivered a healthy infant by vaginal delivery and there were no complications.

In cases 9 and 10, the mothers received Herceptin therapy throughout the course of their pregnancies, and both had poor pregnancy outcomes. One mother continued Herceptin mono-therapy from prior to conception through delivery at 36 weeks. Oligohydramnios was diagnosed at 26 weeks gestation. Following counseling, the patient decided to continue the pregnancy and Herceptin therapy. The baby was delivered by cesarean at 36 weeks gestation with limb deformities and pulmonary hypoplasia. It died at six hours of life. Case 10 was a woman with a twin gestation receiving Herceptin monotherapy. At 24 weeks gestation, ultrasound revealed olighohydramnios and evidence that the "lungs were not developing properly." She chose to undergo therapeutic abortion at that time.

Case 11 is a published case of a woman who received two doses of Herceptin four weeks prior to and three days prior to conception. She did not receive any additional chemotherapy during her pregnancy. She had a normal pregnancy and delivery, and the baby had no complications.[12]

Chemotherapy and Pregnancy

A toxnet search found the word "oligohydramnios" associated with the following drugs: captopril, quinapril, losartan, indomethacin, enalapril, celcoxib, benazepril, rofecoxib, valdecoxib, and lisinopril. Other than ACE inhibitors and NSAIDs, no other drugs were associated with oligohydramnios in the Toxnet search.

A Toxnet search with the terms "vinorelbine and oligohydramnios" and "cancer and oligohydramnios" yielded only one informative and relevant article not already presented in this review. In 1997, Cuvier et al reported on three women with breast cancer treated with 5-fluorouracil (5-FU) and vinorelbine during pregnancy. The women began therapy at 24 – 29 weeks gestation. After two rounds of 5-FU and vinorelbine chemotherapy, one woman received six courses of cyclophosphamide and epidoxorubicin due to disease progression. Two women had spontaneous labor and vaginal deliveries at 37 and 41 weeks, and the third woman (the one who received four chemotherapeutic agents) delivered at 34 weeks by cesarean section. It appears that none of these women developed oligohydramnios; however, the reason for the

cesarean delivery at 34 weeks was not provided in the article. All three children had normal development at 23 – 35 months of age.[3]

A PubMed search using the search terms "paclitaxel and oligohydramnios", " docetaxel and oligohydramnios", and "vinorelbine and oligohydramnios," found only the article by Bader et al that reports one of the oligohydramnios cases associated with Herceptin use with paclitaxel during pregnancy. A search with the terms "cancer and oligohydramnios" found three relevant articles. Two involved Herceptin cases already discussed in this review (Watson and Bader) and the other was a case report of a woman diagnosed with acute lymphocytic leukemia at 25 weeks gestation.[5] A detailed obstetrical ultrasound at that time revealed fetal growth at the 35th percentile, a normal AFI, and normal umbilical artery Doppler systolic-diastolic ratio. At 26 weeks gestation, the patient began intensive multi-agent chemotherapy: cyclophosphamide, intrathecal methotrexate, daunorubicin, vincristine, 6-mercaptopurine, cytarabine, L-asparaginase, and prednisone. After each course of chemotherapy, transient oligohydramnios occurred with the AFI decreasing to 2.0 – 3.4 cm and recovering to normal over 6-7 days. The patient went into labor spontaneously at 36 2/7 weeks gestation. There was thick meconium at rupture of membranes. This patient underwent extensive fetal monitoring during the pregnancy. Weekly non-stress tests began at 28 weeks gestation and were done twice weekly starting at 32 weeks. Ultrasound assessments of amniotic fluid were done weekly once chemotherapy began. Additional factors during this pregnancy included maternal anemia (transfusion for a hematocrit of 22%) and antibiotic treatment for a MRSA infection of indwelling Hickman catheter.[5]

Kelly et al[7] published a review article in 2006 on the options for systemic therapy in pregnant patients with breast cancer. The authors included eight studies that reported outcomes for women treated with chemotherapy during pregnancy for a variety of cancers. Three percent of babies had a congenital anomaly, which is the same as the background rate in the population. Fetal death, spontaneous abortion, prematurity, and fetal complications occurred more often in babies born to leukemic patients compared to those born to women with other tumor types. No cases of oligohydramnios were reported, but this reviewer did not review all of the original articles in this series. The largest included series was by Germann et al (2004) and did not describe any diagnoses of oligohydramnios or anhydramnios.

The Cancer and Childbirth Registry has enrolled about 92 pregnant women with breast cancer. This reviewer spoke with the registry director, Dr. Elyce Cardonick, a maternal-fetal-medicine specialist. Dr. Cardonick stated that she has seen cases of borderline oligohydramnios in pregnant women with breast cancer following a round of chemotherapy but additional IV hydration administered with the chemotherapy reversed the process. She has not seen severe oligohydramnios or anhydramnios associated with chemotherapy treatment for breast cancer during pregnancy.

DISCUSSION/CONCLUSIONS

Herceptin (trastuzumab) is a recombinant IgG humanized monoclonal antibody that binds to the epidermal growth receptor 2. It is effective for the treatment of Her-2 overexpressing metastatic breast cancers as monotherapy and for primary node-positive breast cancers as part of an

adjuvant chemotherapy regimen. There are nine unique reports of oligohydramnios associated with Herceptin use in pregnancy both in the published literature and post-marketing reports in the AERS database. In four, and possibly five, of these cases, the amniotic fluid volume has recovered following discontinuation of Herceptin therapy. There is one case with both a positive dechallenge and rechallenge. The current label mentions the existence of a limited number of post-marketing cases of oligohydramnios and states that no association between oligohydramnios and the use of Herceptin has been established.

Pre-clinical data suggest an important role for epidermal growth factor in renal development. Human renal tubular development continues until 36 weeks gestation. Data from studies in organ culture, where an antibody is used to block the epidermal growth factor receptor, suggest that blocking the EGF receptor may interfere with normal nephron development. It seems scientifically plausible, based on the drug's mechanism of action that Herceptin could potentially increase the likelihood of oligohydramnios.

Oligohydramnios (decreased amniotic fluid volume) and anhydramnios (no amniotic fluid), in the absence of premature rupture of membranes, can be related to chronic fetal hypoxia, decreased or absent fetal renal function, poor placental function, and some fetal anomalies. In preterm pregnancies, the presence of oligohydramnios is associated with increased fetal morbidity, which is due in part to an increased risk of cord compression and due in part to the underlying condition that caused the oligohydramnios.

At this time, the data are not robust enough to conclude that a clear association exists between the use of Herceptin during pregnancy and the occurrence of oligohydramnios; however, the data do suggest a possible association that deserves monitoring. Additional data are needed to more clearly define and understand this possible relationship. If additional data further support an association between Herceptin use during pregnancy and oligohydramnios, then an attempt should be made to answer the following questions:

1. During which periods of gestation is Herceptin exposure associated with an increased risk of oligohydramnios?

2. Does the risk vary with the Herceptin dose and frequency of administration?

3. Does additional IV hydration either at the time of chemotherapy or in between courses of therapy alter the frequency or severity of oligohydramnios?

4. With reference to the time of Herceptin administration, when does the AFI decline and when does it recover?

Based on a woman's individual disease state and course of progression and on risk/benefit counseling between physician and patient, some women may continue Herceptin when oligohydramnios occurs and some may stop. Some women who continue therapy may be delivered depending on the gestational age of the fetus and other factors, and some may continue their pregnancy with fetal monitoring and ultrasound examinations. In order to optimize the clinical outcomes for pregnant women with breast cancer and their babies, women using

Herceptin during pregnancy should be monitored for oligohydramnios. If and when oligohydramnios occurs, risk/benefit counseling should occur and fetal testing should begin.

RECOMMENDATIONS

1. The pregnancy portion of the Herceptin (tratuzumab) label should include information about the known cases of oligohydramnios that occurred with use of Herceptin during pregnancy.

2. The label should recommend that pregnant women using Herceptin undergo routine obstetrical ultrasound examination following each treatment with Herceptin to screen for oligohydramnios.

3. If oligohydramnios occurs, the obstetrician should begin fetal testing appropriate for the gestational age of the fetus and consistent with the standards of care for the community. This testing should continue on a regular basis until one of two conditions is met:

    a. Herceptin therapy is discontinued and oligohydramnios resolves
    b. Delivery.

4. In cases where the physician and patient decide to continue Herceptin therapy for maternal reasons despite the presence of oligohydramnios, additional intravenous hydration should be considered. With other forms of chemotherapy during pregnancy, transient oligohydramnios has been observed, and extra hydration sometimes mitigates this effect.

5. Include contact information for the Cancer and Childbirth Registry and encourage enrollment of pregnant patients using Herceptin.

6. If it would be helpful to the Division, the Maternal Health Team would be happy to provide draft language for the pregnancy and lactation portions of the label. (Please see Appendix B.)

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APPEARS THIS WAY ON ORIGINAL

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
(b) (6) Table 1 Case1	32	(b) (6) (pre-conception) to (b) (6) (26 weeks gestation)	None	Recurrent breast cancer at 14 weeks gestation. Started on Herceptin 480 mg IV Q 3 weeks. US at about 26 weeks showed oligohydramnios with normal fetal growth. Hospitalized for bedrest and corticosteroids. Herceptin stopped the next day. Amniotic fluid increased. Weekly Herceptin resumed. Received one dose Herceptin 480 mg IV at 28 weeks gestation. Delivered one week later. Gestational age information is not completely consistent in MedWatch report.	By best information, preterm male infant delivered by cesarean section for breech position and oligohydramnios at 29 weeks gestation. Weight=1455g; Apgars 2/3/5. To NICU for respiratory distress and chronic lung disease. Ventilated for 2 weeks. Hospitalized for 3 months for prematurity.
(b) (6) Table 1 Case2	38	Before pregnancy. Stopped for gestational weeks 7-14. Resumed gestational weeks 14-32.	Zoladex	Patient treated for metastatic breast CA with Taxotere and Hercptin until July 2003 when pregnancy diagnosed. Borderline decreased amniotic fluid at 28 weeks. Oligohydramnios diagnosed at 32 weeks. Fetal monitoring in hospital. Herceptin stopped. Mother had gestational diabetes and hypertension.	Spontaneous labor and normal vaginal delivery at 36.2 weeks. Male infant, 6 lbs, 10 oz., Apgars 8/9. Down's Syndrome. Discharged on 4th day of life.
(b) (6) Table 1 Case 3	28	Herceptin 6 mg/kg Q 3 weeks from (b) (6) (b) (6) (time of conception/implantation) until 20 weeks gestation	None	Patient diagnosed with poorly differentiated carcinoma (grade III) with perinodal involvement and HER-2/neu positivity. Treated with XRT and 3 cycles doxorubicin and cyclophosphamide and 3 cycles paclotaxel. Started Herceptin near conception. Pregnancy diagnosed at 23 weeks with anhydramnios. Herceptin stopped. Amniotic fluid started to reaccumulate at 25 weeks and was normal at 32 weeks gestation. This case was published.	Induction of labor and normal vaginal delivery of a living female infant at 37.5 weeks gestation (2960 g, Apgars 8/9) Baby had normal renal function and no evidence of pulmonary hypoplasia. Normal placenta. Baby had normal growth at six months of age. Watson et al (2005). See references.
(b) (6) Table 1 Case 4	29	Two years of Herceptin therapy prior to pregnancy. Herceptin discontinued after dose at about 24 weeks gestation	None	Pregnancy diagnosed and confirmed by US at 17 weeks gestation. Herceptin given at 15 weeks and probably discontinued after treatment at 24 weeks gestation. Borderline low amniotic fluid at 25 weeks gestation progressed to oligohydramnios.	Normal preterm female infant delivered by cesarean section at 34 weeks gestation.
(b) (6) Table 1 Case 10	30	Herceptin prior to and throughout pregnancy	Possibly vinorelbine	Twin pregnancy with oligohydramnios diagnosed at 24 weeks gestation. According to the report, there was "evidence that the lungs were not developing properly" and were considered incompatible with life. Mother had a therapeutic abortion.	Therapeutic abortion after 24 weeks gestation.

APPEARS THIS WAY ON ORIGINAL

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Maternal Age at Conception (yrs)	Dates and Gestational Age of Herceptin therapy	Other Current tx	Pertinent Perinatal History	Fetal outcome
(b) (6) Table 1 Case 8	26	Herceptin started at 27 weeks gestation	Vinorelbine	Patient diagnosed and treated for Grade III infiltrating ductal carcinoma with positive nodes. She completed treatment with Herceptin, paclitaxel, 5-FU, epirubicin, and cyclophosphamide through a clinical trial. Fourteen months after diagnosis, she presented with right upper quadrant pain and a 27 week pregnancy. Multiple imaging studies including ultrasound were performed. She had multiple hepatic metastases and increased LFTs. Patient was treated with Herceptin (4mg/kg load and 2 mg/kg per week) and vinorelbine (weekly x 3, then 1 week rest). She was seen weekly by a high risk obstetrician and oncologist. After starting treatment, oligohydramnios was noted. This was thought secondary to fluid shifts or systemic therapy. Extra IV hydration given with each chemotherapy treatment. Weekly fetal monitoring. AFIs remained low. Decreased fetal movement at 34 5/7 weeks with occasional, mild fetal heart decelerations.	Induction of labor at 34 5/7 weeks with normal vaginal delivery of a healthy male infant (5 lbs, 11 oz; Apgars 9/9/10). Normal and healthy at six months of age. Fanale et al (2005). See references.
(b) (6) Table 1 Case 9	36	Herceptin throughout pregnancy	None	Patient previously diagnosed with breast cancer. Being treated with Herceptin 441 mg Q 3 weeks. Pregnancy confirmed and dated by 26 week ultrasound. Anhydramnios diagnosed. Patient counseled and chose to continue pregnancy.	Female infant delivered by cesarean section at about 36 weeks gestation (2690 g, Apgars 8/8). Baby had lower limb deformities and died of pulmonary hypoplasia at 6 hours of life.
(b) (6) Table 1 Case 7	38	Herceptin at 26 and 29 weeks gestation	Paclitaxel	Seven years prior to pregnancy, the patient was diagnosed with Stage I breast cancer. She was treated with six cycles of cyclophosphamide, methotrexate, and 5-FU followed by XRT and 5 years of tamoxifen. At 17 weeks gestation, the patient developed paresthesia and hypoesthesia of the left arm and cervical neck pain. On MRI, there was metastatic infiltration and collapse of the second cervical vertebrae with spinal compression and metastases in the fourth thoracic vertebrae and femur. Between 26 and 32 weeks gestation, the patient received two treatments of Herceptin and paclitaxel. On US, the fetal abdominal circumference stopped increasing and the amniotic fluid volume decreased nearly to anhydramnios. Corticosteroids given for fetal lung maturation.	Delivery of living infant by cesarean section for anhydramnios, fetal growth restriction, and suspected fetal renal failure. Normal placenta. Admitted to NICU with signs of bacterial sepsis and decreased renal function. Renal function normalized by day of life 28, and the baby was discharged home. Normal development at 12 weeks of age. Bader et al (2007). See references.

APPEARS THIS WAY ON ORIGINAL

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
J Clin Onc 01/10/06 Table 1 Case 11	30	3.5 weeks and 3 days prior to conception	None	Patient diagnosed with multifocal grade 2 invasive ductal adenocarcinoma of the right breast with two of five nodes positive. Estrogen and progesterone receptor negative. Her-2/neu positive. Had been trying to conceive. Treated with four cycles of epirubicin followed by four cycles of cyclophosphamide, methotrexate, and 5-FU over six months. Due to incomplete excision and strong family history of breast CA, had a bilateral mastectomy followed by radiotherapy to the right chest wall. Enrolled in Herceptin Adjuvant trial (HERA) and randomized to trastuzumab treatment every three weeks. Had a positive pregnancy test before third treatment cycle. Conceived three days after second dose. Withdrew from trial.	Spontaneous vaginal delivery of a healthy female infant at full term. No complications. Waterston and Graham (2006). See references.
Reprod Tox 06/07 Table 1 Case 5	32	Throughout pregnancy until 24 weeks gestation	None	Patient diagnosed with Her-2/neu positive breast cancer during her first pregnancy. She underwent radical mastectomy and therapeutic abortion. Treated with paclitaxel and carboplatin. Six months after completing chemotherapy, diagnosed with lung metastases. Treated with paclitaxel, carboplatin, and trastuzumab. Eighteen months later had a single brain metastasis treated with surgery and radiation. After one year of ongoing treatment with trastuzumab alone and no recurrence, the patient presented with a five week viable pregnancy. Treatment was continued and the pregnancy progressed normally until trans-thoracic echocardiography revealed an asymptomatic mild low ejection fraction at 18 weeks. Fetal growth and anatomical survey were normal. Repeat maternal echo at 24 weeks was unchanged but trstuzumab was discontinued. Fetal US at 25 weeks gestation showed normal growth, AFI, and BPP.	Cesarean delivery (for breech presentation) of a healthy female infant at 37 weeks gestation. Normal placental pathology without metastases. Shrim et al (20007). See references.

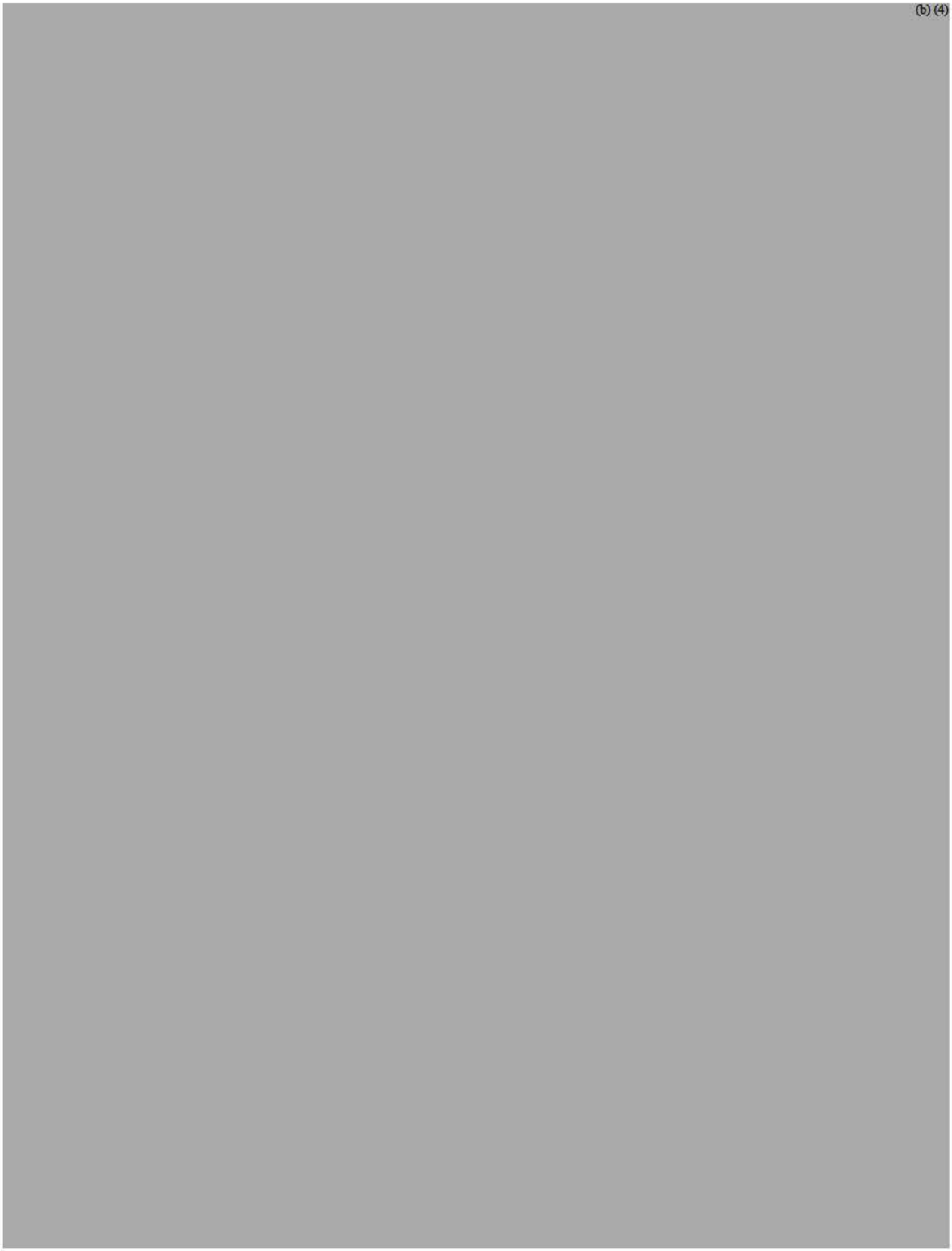
APPEARS THIS WAY ON ORIGINAL

Appendix A:
Detailed Summary of MedWatch case reports and published cases of oligohydramnios among pregnant women using Herceptin®

Source/ Case	Patient Age (yrs)	Dates and Gestational age of Herceptin therapy	Other Current tx	Pertinent Perinatal history	Fetal outcome
Obstet Gynecol 08/07	28	23, 26, and 27 weeks gestation	Docetaxel	(Australia) Patient was diagnosed with left infiltrating ductal carcinoma, grade 2, stage T2N2M0 in (b) (6) She had a radical mastectomy and lymphadenectomy with 18 of 18 nodes positive. The tumor was E/P receptor negative and human epidermal growth factor 2 (Her-2/neu) positive. She was treated with chemotherapy and radiotherapy. At 20 weeks gestation, MRI revealed brachial plexus and pulmonary metastases. She was treated with three cycles of docetaxel and trastuzumab at 23, 26, and 27 weeks gestation. A fetal ultrasound was done at 30 weeks for clinical suspicion of fetal growth restriction. The ultrasound showed fetal growth measurements at <5th percentile consistent with IUGR and anhydramnios. Chemotherapy was held until after delivery. Two doses of betamethasone were given for fetal lung maturation in case delivery was needed. At 33 weeks, amniotic fluid was reaccumulating. Due to the patient's advanced disease state, she was delivered at 36 weeks.	Cesarean delivery for breech presentation at 362/7 weeks due to maternal disease state. Small amount of clear amniotic fluid at delivery. Living male infant, 2230 g, Apgars 7/9. Normal neonatal urine output. No complications. Sekar and Stone (2007). See references.

Appendix B: Proposed Changes to Current Pregnancy Labeling Language

Suggested deletions are indicated with strikeouts, and suggested insertions are indicated with an underline.



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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103792Orig1s5175

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: June 12, 2006

From: *Monica Hughes, M.S.; DBOP/OODP/CDER*

Subject: Meeting Minutes to IND 4517 (Prior to the meeting, draft FDA comments to Genentech's questions were provided by facsimile on May 31, 2006). These final meeting minutes incorporate the draft comments and additional discussion from the meeting.

Meeting Type: Type B
Meeting Category: Pre-sBLA, IND 4517
Meeting Date and Time: May 31, 2006: 1:30PM-3:00PM EST
Meeting Format: Teleconference
Product: Trastuzumab [Humanized Monoclonal Antibody (Genentech) p185HER2/neu]
Meeting Requestor/Sponsor: Genentech, Incorporated

Background: Genentech submitted an sBLA in February 2006, which is currently under Agency review, and included a joint analysis of data from 2 NCI cooperative group studies (NSABP B-31 and NCCTG N9831) to support a labeling change to the indication statement to include the use of Herceptin, as an adjunct to chemotherapy (sequential doxorubicin plus cyclophosphamide followed by paclitaxel) for the post-surgical adjuvant treatment of HER-2 overexpressing, node-positive or high-risk node-negative, breast cancer as discussed during the July 7, 2005, pre-sBLA meeting. The dosage regimen will consist of Herceptin administered on a weekly schedule, initiated concurrently with paclitaxel, for a maximum of 52 doses.

Genentech is proposing to file a separate sBLA to expand the Herceptin label in support of additional adjuvant chemotherapy regimens, initiated concurrently with chemotherapy or following the completion of chemotherapy. Pharmacokinetic data from the HERA trial and two other studies conducted in patients with metastatic breast cancer (BO15935, and WO16229) are intended to support the addition of every-3-week dosing (following completion of adjuvant chemotherapy) to the dosage and administration section of the label.

May 31, 2006: IND 4517 Teleconference with Genentech, Inc.

BCIRG.006 was a large, international, randomized trial comparing three adjuvant treatment strategies in patients with HER2-positive, early-stage breast cancer who were either node-positive or high-risk node-negative:

(1) AC→T (four cycles of AC followed by four cycles of docetaxel at 100mg/m^2);

(2) AC→TH (same chemotherapy regimen with the addition of 52 weeks of Herceptin starting concurrently with docetaxel and continuing as monotherapy); and

(3) TCH (six cycles of docetaxel at 75mg/m^2 and carboplatin at an AUC of 6mg/mL/min every 3 weeks concurrently with Herceptin, followed by Herceptin monotherapy).

Patients were enrolled based on HER2 positivity determined by FISH at one of two designated central laboratories. Herceptin was administered weekly concurrently with chemotherapy and then every 3 weeks (6 mg/kg Q3W) in the monotherapy portion of the study for a total of 52 weeks. BCIRG.006 was conducted by Sanofi-Aventis under IND 35,555. The study was activated on December 29, 2000, with the protocols and subsequent amendments also being submitted to Genentech's IND 4517 as BCIRG.006 is being used to fulfill PMC #6 from the original Herceptin approval letter issued on September 25, 1998.

HERA (study BO16348) was an international, multi-center, randomized, three arm trial comparing 1 year and 2 years of Herceptin versus observation alone in women with HER2-positive, operable breast cancer who were either node-negative or node-positive and who have completed definitive surgery, radiotherapy (if indicated), and at least four cycles of an acceptable (neo-) adjuvant chemotherapy regimen. Patients were enrolled based on HER2 positivity (ICH 3+ or FISH+) as determined by a central laboratory. Herceptin was administered according to an every-3-week regimen (8mg/kg IV loading dose, 6mg/kg IV every 3 weeks). Hormonal therapy was prescribed for women with hormone receptor-positive tumors. HERA was sponsored by F. Hoffmann-La Roche and was conducted by BIG. Data from HERA was submitted to the EMEA on February 17, 2006, to support the use of Herceptin in early-stage breast cancer. A copy of the final study report was submitted to the FDA under BL STN 103792/5150.

Meeting Purpose: The purpose of this meeting is to gain Agency agreement on the proposed plan for the submission of an sBLA to expand the Trastuzumab (Herceptin) label in support of multiple (adjuvant) chemotherapy regimens and to support a dosing schedule of once every three weeks in the dosage and administration section of the Trastuzumab (Herceptin) label based on data from the HERA and BCIRG.006 trials.

May 31, 2006: IND 4517 Teleconference with Genentech, Inc.

Sponsor Submitted Questions and FDA Response:

QUESTIONS:

1. a. *Does the Agency agree that the proposed content for this filing is acceptable?*

FDA RESPONSE FAXED ON 5-31-06: Yes. FDA acknowledges that the sBLA will contain the following in a fully electronic eCTD submission:

- Clinical study reports for HERA, BCIRG.006, BO15935, and WO16229,
- Patient narratives for HERA and BCIRG.006 which will include (all deaths, secondary malignancies, suspected symptomatic cardiac events, pneumonitis, discontinuation of study treatment as a result of an adverse event, and adverse events that occur at an increased incidence and/or severity relative to the current Taxotere or Herceptin label),
- CRFs for patients with narratives for HERA and BCIRG.006; and,
- Raw SAS datasets (with accompanying documentation) for HERA and BCIRG.006, including PK data for patients in the HERA PK substudy. Derived datasets (with accompanying documentation) for HERA and BCIRG.006, as well as the programs that created the derived datasets. Raw datasets (with accompanying documentation) for BO15935 and WO16229.

DISCUSSION DURING TELECONFERENCE: Genentech agreed. No discussion was needed.

b. *In particular, does the existing HERA clinical study report meet the Agency's requirement for review?*

FDA RESPONSE FAXED ON 5-31-06: No. FDA is requesting that safety data, including survival data, from Arm 3 be submitted in the sBLA for the context of a safety review. In addition, FDA is requesting that all HERA related DMC minutes are included in the original sBLA submission, including the DMC meeting noting that the interim results of the 2-year Herceptin arm should not be disclosed at this time.

DISCUSSION DURING TELECONFERENCE: Genentech cannot commit to provide this data but did commit to request the data from the DMC and to ask the

DMC to put in writing if they refuse to provide the data acknowledging that the request originated from the U.S. FDA.

Genentech agreed to provide the DMC recommendations to FDA. Genentech also agreed to request the DMC minutes; if the minutes are not provided, Genentech agreed to provide a written response to the FDA indicating that the study chair refuses to provide the minutes as requested by the U.S. FDA.

c. [redacted] (b) (4)

FDA RESPONSE FAXED ON 5-31-06: [redacted] (b) (4)

DISCUSSION DURING TELECONFERENCE: Genentech agreed. No discussion was needed.

2. *Does the Agency agree with* [redacted] (b) (4)

FDA RESPONSE FAXED ON 5-31-06: No. [redacted] (b) (4)

To investigate safety and efficacy of Herceptin and the risk factors for cardiotoxicity and adequacy of monitoring for cardiotoxicity in the following settings: In a population who recently received anthracyclines and/or in population in which Herceptin is administered concurrently with anthracycline therapy (e.g., NCI-sponsored study of Herceptin + Doxil or Herceptin + prolonged infusion of doxorubicin; **In population not previously treated with anthracyclines (e.g., possible collaborative group adjuvant study of taxane/Herceptin regimen in anthracycline naive patients).**

The fulfillment of the PMC will be determined upon review of all data necessary to address the commitment. Submission of data addressing a portion of the PMC may be provided in PMC correspondence. Alternatively, all the data may be provided in a single final study report. You may wish to submit a request to replace PMC 6 with separate commitments addressing specific portions of the commitment in a final study report.

DISCUSSION DURING TELECONFERENCE: An agreement was not reached during this discussion. Both FDA and Genentech agreed to schedule a follow up teleconference to discuss the fulfillment of PMC #6.

Genentech commented on a July 2005, teleconference, with FDA in which they agreed to provide the data available for H1995g up until the study was closed, along with data from NSABP-B31, NCCTG N9831, BCIRG 006, and H1995g to fulfill PMC #6. FDA agreed to review the administrative record and discuss with Genentech at a future teleconference.

FDA noted that the review of efficacy supplements (6 or 10 months) and the review of final study reports (12 months) have different review time clocks and noted that ultimately they will be addressed under separate timelines.

3. *We would like to request Agency feedback as to whether the efficacy and safety data supplied with this proposed sBLA will support the use of Herceptin with a variety of chemotherapy regimens in the adjuvant setting?*

FDA RESPONSE FAXED ON 5-31-06: No. From the information provided, FDA notes the following:

- BCIRG.006 trial is designed to support a claim of AC followed by Taxotere in combination with weekly Herceptin for 12 weeks followed by Herceptin alone every 3 weeks for a maximum of 52 weeks and

- BCIRG.006 may also support a claim of Docetaxel in combination with Carboplatin with weekly Herceptin for 18 weeks followed by Herceptin alone every 3 weeks for a maximum duration of 52 weeks

- HERA trial is designed to support a claim for anthracycline based chemotherapy followed sequentially by 52 weeks of Herceptin given as every 3 week administration.

[redacted] (b) (4)

DISCUSSION DURING TELECONFERENCE: Genentech agreed they were requesting the claims outlined in bullets 1-3 above.

FDA noted that bullets 1 and 2 above will not support [redacted] (b) (4)

FDA stated that 3 supplements with 3 separate user fees will be required for the claims described above (bullets 1-3 consisting of 2 supplements for the BCIRG 006-basedclaims and 1 supplement for the HERA-based claim). FDA stated that one of the BCIRG 006 supplements could cross-reference the data in the other BCIRG 006 supplement. Genentech proposed and FDA agreed that no ISS or ISE would be included in module 2. Genentech stated that they will discuss this with their upper management. FDA offered a follow up teleconference with members of Genentech upper management and CDER's Office of Regulatory Policy if clarification is needed regarding the need for 3 separate supplements and user fees.

4. *We would like to request Agency feedback as to whether the efficacy, safety, and pharmacokinetic data supplied with the proposed sBLA will support the proposed change to the Herceptin dosing schedule?*

FDA RESPONSE FAXED ON 5-31-06: Inclusion of the new dosing schedule will be dependent on confirmation that the safety and efficacy data are compelling in studies which employ this dosing schedule. If the studies support labeling extension based upon demonstration of efficacy and safety, based on the summary of pharmacokinetics from the PK-substudy of the HERA trial provided in the April 28, 2006, meeting briefing package, these data may be appropriate for inclusion in the Pharmacokinetics section of the Herceptin labeling. Since this is ultimately a review issue, a final decision can only be made after evaluating the data.

DISCUSSION DURING TELECONFERENCE: Genentech agreed.

FDA RESPONSE FAXED ON 5-31-06: FDA requests that Genentech clarify the role of the pharmacokinetic data in BO 15935, and WO 16229 in support of specific labeling claims.

DISCUSSION DURING TELECONFERENCE: Genentech stated they do not intend to put this information in the package insert in either the clinical pharmacology or dosage and administration section.

FDA requested that Genentech submit the toxicology data for the HERA PK substudy and PK subsets from the metastatic disease setting. Genentech agreed and stated that it would be possible to link this data to HERA study. Genentech also agreed to provide complete datasets and study reports for BO 15935 and WO16229.

FDA RESPONSE FAXED ON 5-31-06: Please provide a separate pharmacokinetic study report and detailed dataset from clinical studies assessing the pharmacokinetic profile of Herceptin with 4 mg/kg loading dose and 2 mg/kg weekly doses in conjunction with docetaxol, including analyses assessing for evidence of drug-drug interactions.

DISCUSSION DURING TELECONFERENCE: Genentech stated that data from 16 patients in a Japanese study is available to address this request. The data available include PK data from 10 patients and would address Herceptin and docetaxol drug-drug interactions. Genentech agreed to provide a final study report and dataset translated in English, to FDA.

5. *Does the Agency agree with the proposed submission of safety data for the sBLA?*

FDA RESPONSE FAXED ON 5-31-06: No, FDA does not agree. Genentech must submit arm 3 of the HERA trial in order to allow FDA to adequately assess safety concerns.

DISCUSSION DURING TELECONFERENCE: This was discussed and captured under 1b above.

6. *Does the Agency agree with the proposed submission of Case Report Forms, financial disclosure information, datasets, and statistical programs?*

FDA RESPONSE FAXED ON 5-31-06: Yes, FDA agrees.

DISCUSSION DURING TELECONFERENCE: No discussion occurred.

Summary:

7. Genentech and FDA agreed to follow up on question 4. FDA agreed to review the administrative record for discussions in July 2005 and to have a follow up teleconference to discuss PMC #6.

8. Genentech agreed to request both the DMC to release the interim data for the 2-year Herceptin arm to the U.S. FDA along with the DMC minutes. Genentech agreed that if the HERA steering committee refuses either request, Genentech will provide correspondence stating, in writing, that the HERA steering committee and/or the DMC refuses to provide this information to the FDA. FDA agreed that if the DMC refuses these requests, that the final study report is acceptable provided there is written documentation that the HERA steering committee refused to provide data to the U.S. FDA.

9. Genentech agreed to discuss the number of supplements and claims with upper management and get back to the FDA if further clarification was needed.

10. Genentech agreed to provide all PK data (including final study reports and datasets) for the Japanese study discussed, along with BO 15935 and WO16229, and the HERA PK substudy to both the HERA and BCIRG 006 supplements.

May 31, 2006: IND 4517 Teleconference with Genentech, Inc.

Attendees:

FDA Attendees:
Monica Hughes, M.S.
Karen Jones
Patricia Keegan, M.D.
Kaushikkumar Shastri, M.D.
Lydia Martynec, M.D.
Laura (Hong) Lu, Ph.D.
Iftekar Mahmood, Ph.D.
Nam Atiqur Rahman, Ph.D.

Genentech Attendees:
David Allison
Nancy Boman
Cheryl Jones
Jacqueline Lackey
Paul Pisacane
Josina Reddy
James Reimann
Leonard Reyno
Chang-Heok Soh
Li Zheng

Other Participants:
Diane Louie, Sanofi-Aventis