

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125409Orig1s000

OTHER REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Office of Compliance
Division of Manufacturing and Product Quality
10903 New Hampshire Avenue
Silver Spring, MD 20993

Memorandum

Date: 5/31/2012

From: Shawn Gould, Consumer Safety Officer 
New Drug Manufacturing Assessment Branch

Subject: OMPQ compliance evaluation for facilities listed in support of BLA 125409:
Recommendation to withhold due to CGMP deviations at Genentech in
Vacaville, CA

Through: Tara Goen, Acting Branch Chief 
New Drug Manufacturing Assessment Branch

David Doleski, Acting Division Director 
Division of Manufacturing and Product Quality

Steve Lynn, Acting Director 
Office of Manufacturing and Product Quality

To: BLA 125409 file

Applicant: Genentech
1 DNA Way
South San Francisco, CA 94080

Establishment: Genentech
100 New Horizon Way
Vacaville, CA 95688-9431
FEI: 3002902534

The Office of Manufacturing and Product Quality (OMPQ) has completed its review of the establishment inspection report (EIR) for the March 19 – 28, 2012 inspection and post-inspectional information for the Genentech facility located in Vacaville, CA. Pre-license coverage for BLA 125409 (Pertuzumab) was provided during the inspection.

During the inspection, Genentech communicated to the inspection team that there were production problems. However, the issues remained under investigation through the inspection and the Agency planned to follow-up on the issues through the Review process. After the inspection, further information was communicated to the Agency by Genentech that the firm was unable to reproducibly and reliably manufacture drug substance. OMPQ recommends withholding approval of BLA 125409 due to significant GMP deficiencies for the pending

Genentech – Vacaville, CA
FEI 3002902534
BLA 125409

application. Specifically, the establishment has not demonstrated that the product can be reliably manufactured at commercial scale and meet its critical quality attributes¹:

- Investigations...demonstrate that the establishment has not appropriately evaluated failures

The investigation into the (b) (4) (b) (4) for Pertuzumab drug substance is inadequate and remains open. Of a total of (b) (4) (b) (4) Genentech has not yet determined the most probable reason(s) for the failures and taken appropriate corrective action to resolve the issue(s). The investigation is inadequate in that: (b) (4) to determine if the Master Cell Bank was impacted by (or was the source of) these issues; and (2) The effect (b) (4) drug substance quality, safety, or identity has not been established.

- The commercial process is not scientifically and objectively justified

Recent failures in the Pertuzumab manufacturing campaign demonstrate the inability to implement a reliable process to consistently produce drug substance lots. The effect of (b) (4) on drug substance quality, safety, or identity has not been established.

In summary, OMPQ has a lack of confidence that future lots of drug substance will be of acceptable quality and that the facility is ready to manufacture Pertuzumab in conformance with CGMPs. The Vacaville facility does not currently meet the standards designed to assure that the biologic product continues to be safe, pure, and potent. Thus, the Office of Compliance, Office of Manufacturing and Product Quality, recommends withholding approval of BLA 125409.

If you have any questions, please contact Shawn Gould at 301-796-3759.

cc:

Shared Drive\\cdnas\OCS1\OC_320\HFD-323\Domestic PAI Case Management
NGMAB Team Leader
NDMAB Branch Chief
BMAB Branch Chief
BMAB Team Leader
OPS / OBP / DMA Division Director
OND RPM

¹ Refer to Pre-Approval Inspections, Compliance Program Guidance Manual 7346.832, page 28, #8

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/s/

MAHESH R RAMANADHAM

06/07/2012

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

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

Memorandum

Date: June 1, 2012

To: Amy Tilley – Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

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

Subject: OPDP comments on draft product labeling for Perjeta (pertuzumab) injection
(Perjeta)
BLA 125409

As requested in your consult dated February 3, 2012, OPDP has reviewed the draft labeling, Package Insert (PI) for Perjeta.

OPDP's comments are based on the proposed (b) (4) carton and containers. OPDP has no comments on either of these cartons or containers.

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARYBETH TOSCANO

06/01/2012

2. The Division would also prefer to revise the language in the appropriate sections of the label to follow the format proposed by the draft Physician's Pregnancy and Labor Labeling Rule (PLLR). We therefore request assistance from the Maternal Health Team in drafting the language for Sections 5.3 (Warnings), 8.1 (Use in Specific Populations: Pregnancy) and 13.2 (Animal Toxicology Data). Will the Maternal Health Team be able to provide assistance to the Division nonclinical review staff?

INTRODUCTION

PERJETA (pertuzumab) intravenous injection (BLA 125409) was submitted on December 6, 2011 and given a priority review with a PDUFA date of June 8, 2012. Genentech, Inc. is seeking approval of pertuzumab, a HER2/neu antagonist, to be used in combination with trastuzumab and docetaxel for the treatment of HER-2 positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease

The Division of Oncology Products 1(DOP1) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the pregnancy and nursing mothers sections in the PERJETA labeling.

The PMHS-MHT review provides suggested revisions and re-ordering of information related to pregnancy and nursing mothers in the PERJETA labeling to comply with current regulatory requirements.

BACKGROUND

Pertuzumab is an IgG1 (k) humanized monoclonal antibody (human-mouse monoclonal 2C4 heavy chain) with Fc framework identical to trastuzumab (HERCEPTIN). Pertuzumab differs from trastuzumab at certain complementarily determining regions (CDRs) – 12 Amino Acids (AA) on the light chain, and 29 AAs on the heavy chain. Pertuzumab is produced in Chinese Hamster Ovary cell cultures. Like trastuzumab, pertuzumab targets the Her2 receptor extracellular domain (ECD) but differs in binding sites of the HER2 receptor ECD. Pertuzumab inhibits ligand-dependent HER2 dimerization with other HER family members such as HER1(EGFR), HER3 (ERBB3) and HER4 as well as homodimerization with HER2. This inhibition of HER2 homo- and heterodimerization is thought to activate antibody dependent cell-mediated cytotoxicity (ADCC) and inhibit downstream signaling of pathways crucial to cancer cell proliferation and survival such as PI3K and MAPK.

DISCUSSION AND CONCLUSION

Teratogenic signal in cynomologus monkeys

Pertuzumab was administered to pregnant cynomologus monkeys by IV injection on GD 19 at doses of 0, 30, 100, and 150 mg/kg with subsequent, bi-weekly doses of 10, 33.3, and 100 mg/kg, respectively, until GD 50. No maternal toxicity was noted. Pertuzumab caused fetal lethality in pregnant monkeys treated with loading doses of ≥ 30 mg/kg followed by bi-weekly doses ≥ 10

mg/kg (approximately 0.2 to 2-fold greater than the exposure at the recommended human dose, by AUC). Decreased amniotic fluid volume and an increased incidence of oligohydramnios was noted at all doses. Fetal effects were also noted at doses $\geq 30/10$ mg/kg. Malformations were observed at doses $\geq 100/33.3$ mg/kg dose. Fetal effects included reduced fetal weight at $\geq 30/10$ mg/kg; head width, circumference, hindfoot length $\geq 100/33.3$ mg/kg, crown rump and tail length $\geq 100/33.3$ mg/kg, decreased lung and kidney weight $\geq 100/33.3$ mg/kg, and hypoplasia in the kidney $\geq 30/10$ mg/kg. Malformations and variations were observed at $\geq 100/33.3$ mg/kg and included paw hyperextension/hyperflexion, microtia, small lungs, thin walls in the ventricular, fused caudal and sacral vertebra, and supernumerary lumbar vertebra. Exposure was reported at delivery in offspring at levels of 30 - 86 % of the maternal blood levels. Due to fetal toxicities, a no-observed-adverse-effect-level, NOAEL, was not established.

Reviewer comment:

As noted by the Division, Herceptin (trastuzumab) has known human data with oligohydramnios and resulting deleterious effects on lung and renal development in exposed fetuses. Given similar findings in the embryo-fetal development study in cynomolgus monkeys with pertuzumab and the structural and functional similarity of pertuzumab and trastuzumab, PMHS-MHT concurs with Division that the label for pertuzumab should strongly convey these findings to inform patients and prescribing physicians of the risks of pertuzumab use in pregnant patients. PMHS-MHT agrees with the category D label and recommended label language as outlined below.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

PMHS-MHT LABELING RECOMMENDATIONS

The recommendations for labeling from PMHS-MHT are noted below and are based on the initial label draft provided by Dr. Anne Pilaro. The annotated label version from May 15, 2012 is found in Appendix A.

Highlights

Warnings and Precautions

- Embryofetal toxicity (5.3, 8.1)

Use in Specific Populations

- Nursing mothers: Discontinue nursing or discontinue drug taking into consideration importance of drug to mother (8.3)
- Females of Reproductive Potential: Counsel females on pregnancy prevention and planning. Encourage patient participation in the PERJETA pregnancy registry by contacting XXXXX. (5.3, 8.1, 8.6, 17)

Box Warning

Warning: Embryofetal toxicity

Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development and death. Advise patients of these risks and the need for effective contraception. [5.3, 8.1, 8.6]

5.3 Embryo-fetal Toxicity

PERJETA can cause fetal harm when administered to a pregnant woman. Treatment of pregnant cynomolgus monkeys with pertuzumab resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death. If PERJETA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations (8.1)*].

Verify pregnancy status prior to the initiation of PERJETA. Advise female patients of the risks of embryo-fetal death and birth defects and the need for contraception during and after treatment. Advise female patients to contact their healthcare provider immediately if they suspect they may be pregnant. If PERJETA is used during pregnancy or if a patient becomes pregnant while taking PERJETA, immediately report exposure to the Genentech Adverse Event Line at XXXXXX. Encourage women who may be exposed during pregnancy to enroll in the PERJETA pregnancy registry program. Patients or their physicians should call 1-800-XXX-XXXX to enroll [*see Patient Counseling Information (17)*].

Monitor patients who become pregnant during PERJETA therapy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of intravenous hydration in the management of oligohydramnios due to PERJETA exposure is not known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

There are no adequate and well-controlled studies of PERJETA in pregnant women. Based on findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. Pertuzumab administered to pregnant cynomolgus monkeys resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures of (b) (4) -fold greater than the recommended human dose, based on (b) (4). If PERJETA is used during pregnancy, or if a patient becomes pregnant while receiving PERJETA, the patient should be apprised of the potential hazard to the fetus.

If PERJETA is used during pregnancy or if a patient becomes pregnant while (b) (4) PERJETA, immediately report exposure to the Genentech Adverse Event Line at XXXXXX. Encourage women who may be exposed during pregnancy to enroll in the PERJETA pregnancy registry program. Patients or their physicians should call 1-XXX-XXX-XXXX to enroll [*see Patient Counseling Information (17)*].

Clinical Considerations

The effects of PERJETA are likely to be greater during the second and third trimesters of pregnancy. The ability of monoclonal antibodies, such as pertuzumab, to be transported across the placenta increases in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data

Reproductive toxicology studies have been conducted in cynomolgus monkeys. Pregnant monkeys were treated on Gestational Day (GD) 19 with loading doses of 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of (b) (4) fold greater than the recommended human dose, based on (b) (4). Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively. At Caesarean section on GD100, oligohydramnios was (b) (4). Decreased (b) (4) lung and kidney weights and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in (b) (4) dose groups (b) (4). Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29 to 40% of maternal serum levels at GD100.

8.3 Nursing Mothers

It is not known whether PERJETA is excreted in human milk, but human IgG is excreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from PERJETA, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of PERJETA and the importance of the drug to the mother [See *Warnings and Precautions* (b)(4), *Clinical Pharmacology* (12.3)].

8.6 Females of Reproductive Potential

PERJETA may cause embryo-fetal harm when administered to during pregnancy. Counsel patients regarding pregnancy prevention and planning. Advise females of reproductive potential to use effective contraception while receiving PERJETA and for 6 months following the last dose of PERJETA.

If PERJETA is (b)(4) during pregnancy or if a patient becomes pregnant while taking PERJETA, immediately report exposure to the Genentech Adverse Event Line at XXXXXX. Encourage women who may be exposed during pregnancy to enroll in the PERJETA pregnancy registry program. Patients or their physicians should call 1-800-XXX-XXXX to enroll [see *Patient Counseling Information* (17)].

17 PATIENT COUNSELING INFORMATION

- Advise pregnant women and females of reproductive potential that PERJETA exposure can result in fetal harm, including embryo-fetal death or birth defects [see *Warnings and Precautions* (5.3) and *Use in Specific Populations* (8.1)]
- Advise females of reproductive potential to use effective contraception while receiving PERJETA and for 6 months following the last dose of PERJETA [see *Warnings and Precautions* (5.3) and *Use in Special Populations* (8.6)]
- Advise nursing mothers treated with PERJETA to discontinue nursing or discontinue PERJETA, taking into account the importance of the drug to the mother [see *Use in Specific Populations* (8.3)]
- Encourage women who are exposed to PERJETA during pregnancy to enroll in the PERJETA pregnancy registry program (1-800-XXX-XXXX) [see *Warnings and Precautions* (5.3) and *Use in Specific Populations* (8.1)]

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/s/

MELISSA S TASSINARI
05/22/2012

LISA L MATHIS
05/24/2012



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

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

FINAL LABEL AND LABELING REVIEW-Amendment

Date: May 22, 2012

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

Through: Kathryn King, Ph.D.
Division of Monoclonal Antibodies

Division Deputy Director: Patrick Swann, Ph.D.
Division of Monoclonal Antibodies

Application Number: STN 125409/0 amendment

Name of Drug: TRADENAME™ (pertuzumab)

Applicant: Genetech USA, Inc.

Material Reviewed: TRADENAME™ (pertuzumab)
Carton and Container Labels

Submission Dates: December 6, 2011, March 16, 2012, May 17, 2012

EXECUTIVE SUMMARY

The carton and container labels for TRADENAME™ (pertuzumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 5/1/12-8/1/12, USP 35/NF 30. Labeling deficiencies were identified, mitigated and resolved. The revised labels submitted May 17, 2012 are acceptable. Please see comments in the conclusions section.

Background

STN 125409/0 for pertuzumab is an original Biologic License Application (BLA) indicated in combination with Herceptin® (trastuzumab) and docetaxel for patients with HER2-positive metastatic (b)(4) breast cancer, who have not received previous treatment (b)(4). The product is supplied as a 420 mg/ 14 mL solution in a single-use glass vial.

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/s/

KIMBERLY M RAINS
05/22/2012

KATHRYN E KING
05/25/2012

PATRICK G SWANN
05/31/2012

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

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

Memorandum

Date: May 17, 2012

To: Amy Tilley – Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

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

Subject: OPDP comments on draft product labeling for Perjeta (pertuzumab) injection
(Perjeta)
BLA 125409

As requested in your consult dated February 3, 2012, OPDP has reviewed the draft labeling, Package Insert (PI) for Perjeta.

OPDP's comments are based on the proposed, marked-up, substantially complete version of the PI following the May 15, 2012 labeling meeting. OPDP's comments on the draft PI and Med Guide are provided directly in the attached, marked-up copy of the labeling.

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/s/

MARYBETH TOSCANO
05/17/2012



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

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

FINAL LABEL AND LABELING REVIEW

Date: May 10, 2012

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

Through: Kathryn King, Ph.D.
Division of Monoclonal Antibodies

Division Deputy Director: Patrick Swann, Ph.D.
Division of Monoclonal Antibodies

Application Number: STN 125409/0

Name of Drug: TRADENAME™ (pertuzumab)

Applicant: Genetech USA, Inc.

Material Reviewed: TRADENAME™ (pertuzumab)
Carton and Container Labels

Submission Dates: December 6, 2011, March 16, 2012

EXECUTIVE SUMMARY

The carton and container labels for TRADENAME™ (pertuzumab) were reviewed and found to comply with most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 5/1/12-8/1/12, USP 35/NF 30. Labeling deficiencies were identified. Please see comments in the conclusions section.

Background

STN 125409/0 for pertuzumab is an original Biologic License Application (BLA) indicated in combination with Herceptin® (trastuzumab) and docetaxel for patients with HER2-positive metastatic (b)(4) breast cancer, who have not received previous treatment (b)(4). The product is supplied as a 420 mg/ 14 mL solution in a single-use glass vial.

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/s/

KIMBERLY M RAINS
05/11/2012

KATHRYN E KING
05/11/2012

PATRICK G SWANN
05/16/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: May 16, 2012

TO: Gideon Blumenthal
Nancy Scher
Amy Tilley
DOP1

FROM: Robert Young
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125409

APPLICANT: Genentech
South San Francisco, CA 94080

DRUG: Perjeta (pertuzumab)
NME: Original BLA
THERAPEUTIC CLASSIFICATION: Priority

INDICATION: In combination with Herceptin® (trastuzumab) and docetaxel for patients with HER-2-positive metastatic (b) (4),

(b) (4) breast cancer, who have not received previous treatment (b) (4)

CONSULTATION REQUEST DATE: 2/7/2012
 INSPECTION SUMMARY GOAL DATE: 5/8/2012
 DIVISION ACTION GOAL DATE: 5/25/2012
 PDUFA DATE: 6/8/2012

- I. **BACKGROUND:** In support of this application, protocol study WO20698/TOC4129g was submitted. The trial was conducted in subjects with HER2-positive metastatic breast cancer. Subjects were randomized 1:1 to either the active arm of trastuzumab and docetaxel with iv pertuzumab 840 mg/kg loading dose followed by 420 mg/kg every third week or the comparator arm of trastuzumab and docetaxel with “pertuzumab placebo” until disease progression. The primary objective was a comparison of progression free survival based on tumor assessments by an independent review facility every nine weeks from randomization. The secondary objective was a comparison of overall survival. The study randomized 808 subjects in 204 sites in 25 countries.

II. **RESULTS (by Site):**

Name of CI	Site # # of Subjects	Inspection Date	Final Classification
Roberto Hegg Hospital Perola Bygton Av. Brigadeiro Luis Antonio 683 Sao Paulo, 01317-000 Brazil	Site 121228 22 subjects	April 16-20, 2012	Pending NAI
Sung-bae Kim ASAN Medical Center 388-1 Pungnap-dong Seoul, 138-736 Korea	Site 121117 30 subjects	April 9-13, 2012	Pending VAI
Seock Ah Im Seoul National Hospital 28 Yongon-dong, Chongro-gu Seoul, 110-744 Korea	Site 12116 23 subjects	April 2-6, 2012	Pending VAI
Genentech South San Francisco, CA 94080	N/A	April 23-30, 2012	Pending NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

Note: EIRs for the Kim and Im sites have been received, but are not yet finally reviewed. Information provided in this Summary was obtained from written correspondence with the inspecting FDA field investigators.

1. Roberto Hegg
Sao Paulo, Brazil

- a. What was inspected: Informed consent documents for all subjects were reviewed. Subject case histories were also reviewed.
- b. General observations/commentary: Study site records were neat and well organized and no data issues were identified. No Form FDA 483 was issued.
- c. Assessment of data integrity: The data from this clinical site may be used in the assessment of the submitted application.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Sung-bae Kim
Seoul, Korea

- a. What was inspected: At this site 30 subjects were entered into the study. Informed consents, HER-2 test results, dosing and tumor assessments were reviewed for all subjects and 10 case histories were reviewed in depth.
- b. General observations/commentary: The study was properly conducted and case histories were in order except for two issues which were discussed with the clinical investigator and reported on a Form FDA 483. The hospital's electronic medical system calculated doses of study drug trastuzumab based on a patient's current weight and not on a subject's baseline weight as directed by the protocol. For example there were three instances related to three subjects who gained weight and each received a 10 mg increase in study drug over the average 350 mg they should have received. This 3% increase in dose administered most likely had no measurable effect on the drug's actions – therapeutic effectiveness or toxicity. Study monitors identified and corrected this problem early in the study. A confirmatory CT was missed for subject 7151.

- c. Assessment of data integrity: The data from this clinical site may be used in the assessment of the submitted application. The issues identified by the inspection were relatively small and limited in number and would not have much effect on the overall evaluation of the study.

Note: Observations noted above are based on the Form FDA 483, communications with the field investigator, and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

3. Seock Ah Im
Seoul, Korea

- a. What was inspected: At this site 23 subjects were entered into the study. Informed consents, HER-2 test results, dosing and tumor assessments were reviewed for all subjects and 13 case histories were reviewed in depth.
- b. General observations/commentary: The case histories were in good order, but several issues recorded on an issued Form FDA 483 were discussed with the clinical investigator. For example, subjects 7139 and 7504 did not meet the 12 month disease free exclusion entry criterion, but were continued in the study under a waiver granted by the sponsor. Subject 7135's medication order was misentered so that the subject received a first infusion dose of 130 mg of docetaxel instead of the correct dose of 108 mg docetaxel. Additionally, subject 7138 missed a week 9 tumor assessment and concomitant medications used by Subjects 7135 and 7148 were not timely reported.
- c. Assessment of data integrity: The data from this clinical site may be used in the assessment of the submitted application. The issues identified by the inspection were random and limited in number and would not have much effect on the overall evaluation of the study.

Note: Observations noted above are based on the Form FDA 483, communications with the field investigator, and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

4. Genentech

- a. What was inspected: Sponsor's selection of clinical investigators, and monitors, monitoring procedures, adverse event reporting, quality assurance, data review and test article accountability.
- b. General observations/commentary: Records were in order and no Form FDA 483 was issued.
- c. Assessment of data integrity: The study appears to have been adequately conducted and the data appears to be reliable.

Note: Observations noted above are based on written correspondence from the field investigator, an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Data from the three clinical sites inspected appear to be reliable and may be used in assessment of the present application.

Note: Observations noted above are based on the Form FDA 483 for the Sung-bae Kim and Seock Ah Im sites and communications with the field investigator for all three CI and sponsor sites; an inspection summary addendum will be generated if conclusions change upon review of the EIRs.

{ See appended electronic signature page }

Robert Young
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE:

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Lauren Iacono-Connors, Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
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/s/

ROBERT S K YOUNG
05/16/2012

JANICE K POHLMAN
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LAUREN C IACONO-CONNORS
05/16/2012

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

Label and Labeling Review

Date: May 8, 2012

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

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

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

Drug Name and Strength: Perjeta
(Pertuzumab)
Injection
420 mg/14 mL

Application Type/Number: BLA 125409

Applicant: Genentech

OSE RCM #: 2012-130

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Perjeta (Pertuzumab) BLA 125409 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted the original labels and labeling on December 6, 2011. The Applicant submitted updated insert labeling on March 9, 2012 and container labels and carton labeling on March 19, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 6, 2011 submission.

- Active Ingredient: Pertuzumab
- Indication of Use: is a HER2 dimerization inhibitor indicated in combination with Herceptin (trastuzumab) and docetaxel for patients with HER2-positive metastatic ^{(b) (4)} breast cancer, who have not received previous treatment ^{(b) (4)}
- Route of Administration: Intravenous
- Dosage Form: Injection
- Strength: 420 mg/14 mL
- Dose and Frequency: 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 to 60 minutes

When administered with Perjeta, the recommendation is to follow a 3 weekly schedule for Herceptin (trastuzumab) administered as an IV infusion with an initial dose of 8 mg/kg followed every 3 weeks thereafter by a dose of 6 mg/kg.

When administered with Perjeta, the recommended initial dose of docetaxel is 75 mg/m² administered as an intravenous infusion. The dose may be escalated to 100 mg/m² every 3 weeks if the initial dose is well tolerated.

- How Supplied: 420 mg/14 mL (30 mg/mL) single-dose vial
- Storage: Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep vial in the outer carton in order to protect from light
- Container and Closure System: 20 mL glass vial, sealed with a rubber stopper, and crimped with an aluminum seal fitted with a flip-off plastic cap

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Perjeta label and labeling submitted by the Applicant.

2.1 LABELS AND LABELING

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

- Container Label submitted March 19, 2012 (Appendix A)
- Carton Labeling submitted March 19, 2012 (Appendix B)
- Insert Labeling submitted March 9, 2012

3 MEDICATION ERROR RISK ASSESSMENT

The following section describes the results of our risk assessment of the Perjeta product design as well as the associated label and labeling. Our evaluation identified deficiencies with the labels and labeling. These deficiencies are described in section 4.1 - *Comments to the Division* and section 4.2 - *Comments to the Applicant*. We also identified potential confusion between the established names pertuzumab and trastuzumab.

Healthcare practitioners are likely to be confused with the established names (Pertuzumab and Trastuzumab) due to their similarity, similar strength vials (420 mg vs. 440 mg), colors of the container label and carton labeling, storage in the refrigerator, and likelihood these products will be prepared in the pharmacy at the same time. See Appendix C for Herceptin (trastuzumab) container label and carton labeling and Appendix D for characteristics of products in treatment regimen).

This product treatment regimen design is unique in that two products from the same pharmacologic class (humanized monoclonal antibody) are being administered concomitantly in a treatment regimen. Generally, drug products from different pharmacologic classes with different mechanisms of action are used to treat disease and minimize toxicity. However, the Applicant proposes pertuzumab and trastuzumab bind to distinct epitopes on the human epidermal growth factor receptor 2 protein (HER2) receptor without competing with each other, and have distinct mechanisms for disrupting HER2 signaling. This results in significant clinical benefit to patients with HER2-positive metastatic breast cancer with no increase in cardiac toxicity and no detriment in quality of life.

Improved differentiation of Perjeta container label and carton labeling from Herceptin (trastuzumab) may minimize confusion during product selection from the refrigerator and during preparation in the pharmacy.

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

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling are unacceptable as they are not well differentiated from Herceptin (trastuzumab). The following recommendations should be implemented prior to approval of this BLA.

If you have further questions or need clarifications, please contact Frances Fahnbulleh, project manager, at 301-796-0942.

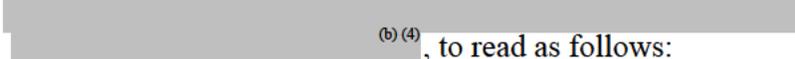
4.1 COMMENTS TO THE DIVISION

Based on this review, DMEPA recommends the following revisions to the insert labeling:

A. General Comments for the Insert Labeling

1.  (b) (4)
2. Replace  (b) (4) with the word, *to*.

B. Highlights – Dosage and Administration

1. Delete the statement, *Do not administer as an intravenous push or bolus*. The preceding statement clearly states, *For intravenous infusion only*.
2. Revise the statement,  (b) (4)
 (b) (4), to read as follows:

Initial dose of 840 mg administered as an intravenous infusion over 60 minutes, followed every 3 weeks thereafter by 420 mg administered over 30 to 60 minutes

C. Section 2.2 - Dose Modification

Revise the statement regarding LVEF of 40% - 45% to read as follows:

- a LVEF of 40% to 45% with a 10% or greater decrease below pretreatment values.

D. Section 2.3 - Preparation for Administration

1. Revise the statement, *Do not administer as an intravenous push or bolus*. *Do not mix [Tradename] with other drugs*, to read as follows:

Administer as an intravenous infusion only.

² ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations.
<http://www.ismp.org/tools/errorproneabbreviations.pdf>. Last accessed April 13, 2012

2. State how long the diluted infusion solution is stable for after it has been prepared.

3. Revise the statement, [redacted] (b) (4)
[Tradename], to read as follows:

Dilute with 0.9% sodium chloride only. Do not use Dextrose 5%.

E. Section 3 - Dosage Forms and Strengths

Revise the strength statement to include the concentration. The statement should appear as follows:

420 mg/14 mL (30 mg/mL)

F. Section 10 – Overdosage

Provide general treatment procedures and specific measures for management of overdose of pertuzumab.

G. Section 16 - How Supplied

Revise the first paragraph to read as follows:

Perjeta is supplied as a 420 mg/14 mL (30 mg/mL) single-use vial containing preservative free liquid concentrate. NDC 50242-145-01.

4.2 COMMENTS TO THE APPLICANT

DMEPA recommends the following be implemented prior to approval of your BLA:

A. General Comments for the Container Label and Carton Labeling

1. Revise the color scheme to differentiate from Trastuzumab packaging.
2. Revise the proprietary name to appear in Title Case and revise the established name, (Pertuzumab) Injection, to have the same font size and weight as the proprietary name. For example:

Tradename
(Pertuzumab)
Injection

3. Revise the concentration portion of the strength statement, 30 mg/mL, by slightly increasing the font size and relocating so that it appears within the colored background bar with the total drug content (420 mg/14 mL).
4. Revise the listing of important information on the label in the following order:

Dilute Prior To Use
For Intravenous Infusion Only
Single-Use Vial
Discard Unused Portion

5. Relocate the statement, *No preservative*, to the side panel to provide space for the preceding recommendation in A4.

6. Revise the storage and handling statements on the side panel to read as follows:

Storage: Refrigerate at 2°C to 8°C (36°F to 46°F). Store in original carton to protect from light

Do Not Freeze. Do Not Shake.

Additionally, note the change in case to sentence case and Title case in both statements, respectively.

3 Pages of Draft Labeling
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Appendix D: Treatment Regimen Product Characteristics

Drug	Perjeta (Pertuzumab)	Herceptin (Trastuzumab)	Taxotere (Docetaxel)
Strength	420 mg/14 mL injection	440 mg per vial for injection	20 mg, 80 mg, 160 mg vials (various concentrations)
Dose	840 mg iv over 60 minutes (loading dose), 420 mg iv over 30 to 60 minutes every 3 weeks (maintenance dose)	8 mg/kg iv over 90 minutes (loading dose), then 6 mg/kg iv over 30 to 90 minutes every weeks	75 mg/m ² to 100 mg/m ² every 3 weeks
Storage	Refrigerator 2°C to 8°C (36°F to 46°F)	Refrigerator 2°C to 8°C (36°F to 46°F)	(undiluted) between 2° and 25°C (36° and 77°F).

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/s/

JIBRIL ABDUS-SAMAD
05/08/2012

CAROL A HOLQUIST
05/09/2012

**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Epidemiology Review

Date: May 4, 2012

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Office of Surveillance and Epidemiology

Drug Name(s): Pertuzumab, Trastuzumab (Herceptin®)

Application Type/Number: BLA 125409, BLA 103792

Applicant/sponsor: Genentech, Inc.

OSE RCM #: 2012-347

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EXECUTIVE SUMMARY

The Division of Oncology Products I (DOP1) is evaluating a Therapeutic Biologic License Application (BLA) submitted by the sponsor of **pertuzumab** to be used for a new indication as first-line treatment in metastatic breast cancer in combination with docetaxel and **trastuzumab**. Drug utilization data were requested to determine the extent to which trastuzumab is currently used and to determine the estimates of the number of patients with evidence of metastatic breast cancer with one or more claims for the selected diagnoses. This review provides an analysis of trastuzumab use among pediatric and adult patients from years 2009 through 2011, cumulative. Proprietary drug use databases licensed by FDA were used to conduct this analysis. In addition, DOP1 also consulted DEPI to find the incidence of HER2+ breast cancer in the U.S., as well as the HER2+ incidence rates by racial categories, stage distribution, and 5-year survival by stage distribution.

Summary of Findings:

- During the cumulative study period from years 2009 through 2011, there were (b) (4) unique patients with primary breast cancer who received trastuzumab and were enrolled for at least one month in the year of the claim.
- Patients aged 55-64 years and 45-54 years accounted for the largest proportions of patients accounting for 35% and 30.5% of total patients, respectively, for years 2009-2011, aggregated. There was only one pediatric patient aged 0 to 17 years captured in the sample during this study period.
- There was a greater proportion of female patients (over 99% or 6,994 patients) compared to male patients (0.6% or 41 patients).
- Approximately 96% of trastuzumab users had a diagnosis of primary breast cancer in the same calendar year for each year 2009 through 2011, over the cumulative study period. Of these, approximately 22% of trastuzumab users also had a diagnosis for a secondary neoplasm.
- Limited research has evaluated the stage distribution, 5-year survival, and racial differences in patients with HER2+ breast cancer. The majority of the research presented in this review is from two patient populations and the results may not be generalizable. Therefore the results should be considered in the context of this limitation.
- The incidence rate of HER2+ breast cancer in the United States is estimated between 22.3 and 31.0 per 100,000 in 2011.
- At diagnosis, about 40% of HER2+ breast cancers are AJCC Stage I, 44% are Stage II and about 15% are Stage III. The distribution varies by ER/PR subtype; ER+/PR+ tumors have the lowest proportion of Stage III diagnoses (~13%) while ER-/PR- tumors have the highest (~20%).
- Five-year survival by stage of HER2+ breast cancer diagnosis varies greatly by stage and is largely influenced by ER subtype. Survival among patients with AJCC Stage I tumors ranges from about 97% to 94% for ER+ and ER- subtypes, respectively. Among Stage II cases, ER+ subtypes had the best survival ranging

- from 97% to 92%. ER- subtype case survival was around 83%. Survival of Stage III cases diminishes even further; ER+ subtypes had about 80% survival while ER- subtypes had 63% and 51% survival for PR- and PR+ tumors, respectively. Statistical differences were not provided for the reported survival rates and the variation of each rate is unknown. For example, it cannot be determined if the variation among survival of Stage II HER2+ breast cancer patients (97% to 92%) truly exists or if the 95% confidence intervals overlap, suggesting similar rates.
- Based on data from limited patients population at a metropolitan area, Breast cancer incidence did not seem to differ significantly between Black and White females. However, Black women might have a higher proportion of Stage III and IV tumors at diagnosis and a higher proportion of ER-/PR- tumors compared to White women.

1 INTRODUCTION

The Division of Oncology Products I (DOP1) is evaluating a Therapeutic Biologic License Application (BLA) submitted by the sponsor of *pertuzumab* to be used for a new indication as first-line treatment in metastatic breast cancer in combination with docetaxel and *trastuzumab*. In support of this assessment, the Division of Epidemiology has been requested to provide drug utilization and epidemiologic data to assist DOP1 in assessing the application. Specifically, we will provide the estimated utilization of trastuzumab from the IMS Lifelink™ Health Plan Claims Database stratified by patient sex and age (0-17, 18-24, 25-34, 35-44, 45-54, 55-64, and 65 years and older) from years 2009 through 2011, cumulative. In addition, an estimate of the number of patients with evidence of metastatic breast cancer with one or more claims for the selected diagnoses was examined from years 2009 through 2011, cumulative. This review also describes the incidence of human epidermal growth factor receptor 2 positive (HER2+) breast cancers in the U.S., as well as the HER2+ incidence rates by racial categories, stage distribution, and 5-year survival by stage distribution.

1.1 BACKGROUND

1.1.1 Regulatory History¹

The FDA approved *trastuzumab*, [REDACTED]^{(b) (4)}, on September 25, 1998 for the treatment of patients with metastatic breast cancer whose tumors over express the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Trastuzumab in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors over express the HER2 protein and who have not received chemotherapy for their metastatic disease.

Pertuzumab, also an anti-HER2 humanized monoclonal antibody, has a complimentary mechanism of action to trastuzumab by binding to receptor dimerization but is currently not FDA approved.

1.1.2 Product Labeling^{2,3}

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2, in some patients with breast cancer and other malignancies (eg, ovarian, lung). The antibody is an IgG1 kappa that contains human framework regions with murine antibody (4D5) complementarily-

¹Labeling for trastuzumab. Drugs@FDA FDA Approved Drug Products, http://www.accessdata.fda.gov/drugsatfda_docs/label/1998/trasgen0925981b.pdf. accessed 3/29/2012.

²Labeling for trastuzumab. Drugs@FDA FDA Approved Drug Products, http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s52561b1.pdf. accessed 3/29/2012..

³Trastuzumab, Micromedex® 2.0: <https://www.thomsonhc.com/micromedex2/librarian>. Accessed March 23, 2012.

determining regions. Trastuzumab induces antibody-dependent cell- mediate cytotoxicity (ADCC) and lacks effects on cells not overexpressing HER2.

Trastuzumab is supplied in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile powder, under vacuum. Each carton contains one vial of trastuzumab and one vial (20mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative. Reconstitution with 20mL of the appropriate diluent yields a solution containing 21 mg/mL of trastuzumab.

Trastuzumab Indications and Dosages Approved by FDA:

Adjuvant Treatment of HER2-Overexpressing Breast Cancer
<ul style="list-style-type: none">• Administer at either: (1) 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 (2) Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks.
Metastatic HER2-Overexpressing Breast Cancer
<ul style="list-style-type: none">• 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.
Metastatic HER2-overexpressing Gastric Cancer
<ul style="list-style-type: none">• Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

2 METHODS AND MATERIALS

2.1 DRUG UTILIZATION

2.1.1 Determining Setting of Care

IMS Health, IMS National Sales Perspectives™ Sales Perspectives (see **Appendix 3** for full database description) was used to determine the various retail and non-retail channels of distribution for trastuzumab. Sales data for year 2011 indicated that approximately

(b) (4)

2.1.2 Data Sources Used

Based on the sales distribution analysis described in Section 2.1.1, the IMS Lifelink™ Health Plan Claims Database, a proprietary drug use database purchased by the FDA, was used to select patients because the medical claims captured by IMS Lifelink™

⁴ IMS Health, IMS National Sales Perspectives™ Database. Year 2011. Extracted 2/2012. File: NSPC 2012-347 Trastuzumab 2-29-12.

include non-retail settings, such as doctor's offices and specialists. The IMS Lifelink™ Health Plan Claims Database is a commercially insured health care claims database with a subset of Medicare and Medicaid patients that are enrolled in commercially administered plans. The data are not nationally projected.

2.1.3 Claims Data Analysis

The dataset analysis of trastuzumab claims and diagnosis claims from the IMS Lifelink™ Health Plan Claims Database was conducted by (b) (4). For the first analysis (Tables 1 and 2 in Appendix 1), patients selected from the IMS Lifelink™ Health Plan Claims Database consisted of those who had a diagnosis for primary breast cancer with one or more claims for trastuzumab (prescription claims or procedure claims) within the same calendar year for each year from 2009 through 2011. All selected patients had at least one month of health plan enrollment in the calendar year of the trastuzumab claim. Patients had a prescription for trastuzumab if they had one of the following codes:

- Health Care Common Procedure Coding System (HCPCS Code): J9355
- National Drug Codes (NDC): 50242-0056-56, 50242-0134-60, 50242-0134-68

Patients with a diagnosis of primary breast cancer had to have at least one of the selected International Classification of Diseases (ICD-9-CM) Codes 174.xx “Malignant Neoplasm of Male Breast” and 175.xx “Malignant Neoplasm of Female Breast”. The first analysis was further stratified by patient sex and age.

For the second analysis (Table 3 in Appendix 1), patients were selected if they had at least one claim for trastuzumab at any time during years 2009 through 2011. All selected patients had at least one month of health plan enrollment for each calendar year with a trastuzumab claim from 2009 through 2011. These patients were then stratified by the presence of a primary breast cancer diagnosis in the same calendar year as the trastuzumab claim **and** did not have a claim for trastuzumab alone in the year or years prior to the calendar year with both claims, versus those with primary breast cancer diagnosis **and** evidence of metastatic breast cancer as identified by at least one selected diagnosis for secondary neoplasm, ICD-9 CM Codes 197.xx “Secondary malignant neoplasm of respiratory and digestive systems” or 198.xx “Secondary malignant neoplasm of other specified sites” within the 90 days prior or 120 days after a trastuzumab claim, even if the 90 days before or 120 days after extended into a different calendar year. Patients who had claims for trastuzumab in a year prior to having claims for trastuzumab **and** a primary breast cancer diagnosis in a subsequent year were not counted as having breast cancer. These four diagnoses for breast cancer and secondary neoplasms were not considered if they were on an ancillary or auxiliary claim-type because of possible inclusion of diagnoses that might be associated with rule-out tests for the condition.

Because IMS LifeLink™ Health Plan Claims Database receives data from a differing number of health plans over each year and has a data lag of 6-months, we only examined the cumulative patient counts for the entire study period in this analysis.

2.2 LITERATURE REVIEW

2.2.1 Determining HER2-Positive Breast Cancer Incidence

Information related to the incidence of HER2+ breast cancer was identified through a search of PubMed@FDA and Cochran Database using search terms “HER2”, “breast cancer”, and “incidence”. Additionally, cancer organization websites were searched for breast cancer epidemiology information (e.g. National Cancer Institute, North American Association of Central Cancer Registries).

3 RESULTS

3.1 DRUG UTILIZATION

3.1.1 Trastuzumab Patient Data

Table 1 in Appendix 1 provides the total number of patients stratified by patient age (0-17, 18-24, 25-34, 35-44, 45-54, 55-64, and 65 years and older) with selected diagnoses for primary breast cancer (refer to **Appendix 4** for list of selected ICD-9-CM Codes) and a claim for trastuzumab in the same calendar year for each year from 2009 through 2011 in the IMS Lifelink™ Health Plan Claims Database. During the cumulative study period, (b) (4) patients had selected diagnoses for primary breast cancer and a claim for trastuzumab and were enrolled for at least one month in the year of the claim. Patients aged 55-64 years accounted for the (b) (4) of patients at approximately (b) (4) of the total (b) (4), followed by patients aged 45-54 years accounting for approximately (b) (4) (b) (4)). Patients aged 35-44 years accounted for approximately (b) (4) (b) (4) of the total number of patients with selected diagnoses for primary breast cancer and a claim for trastuzumab. (b) (4) pediatric patient aged 0 to 17 years captured in the study period.

We also examined the total number of patients stratified by patient sex with selected diagnoses for primary breast cancer and a claim for trastuzumab in the IMS Lifelink™ Health Plan Claims Database for the cumulative study period, 2009 through 2011 (**Table 2 in Appendix 1**). Of the (b) (4) patients with a claim for trastuzumab, the (b) (4) of patients were female (over (b) (4) or (b) (4) patients) compared to male patients (b) (4) or (b) (4) patients).

Table 3 in Appendix 1 shows the distribution of patients with a claim for trastuzumab stratified by diagnosis codes in the IMS Lifelink™ Health Plan Claims Database from years 2009 through 2011. For the cumulative study period, there was an aggregate number of (b) (4) patients with a claim for trastuzumab for years 2009-2011. Due to the methodology used for this part of the analysis, there were (b) (4) patients, or (b) (4) of all patients with a trastuzumab claim, who also had a diagnosis claim for primary breast cancer **and** did not have a claim for trastuzumab alone in the year or years prior to the calendar year with both claims. Of those patients, approximately (b) (4) had a diagnosis code for secondary neoplasms in the 90 days prior or 120 days after a trastuzumab claim, even if the 90 days before or 120 days after extended into a different calendar year. A total of (b) (4) patients had claims for trastuzumab in the year prior to having claims for trastuzumab **and** a primary breast cancer diagnosis in a subsequent year (Table 3 in Appendix 1) and therefore were not counted as having breast cancer in the aggregate total patient count.

3.2 LITERATURE REVIEW

3.2.1 U.S. Incidence of HER2+ Breast Cancer

The incidence of HER2+ breast cancer was not reported by any of the National Cancer Institutes' data sources. Studies published in the literature have estimated HER2+ cancers to occur in 18% to 25% of all breast cancer cases.^{5,6} The age-adjusted rate of breast cancer reported by SEER in 2011 (124.0 per 100,000).⁷ Although the populations reported in the literature may be different than that used by SEER to estimate national incidence rate, we could expect the HER2+ breast cancer incidence rate is between 22.3 and 31.0 per 100,000 in 2011.

3.2.2 Stage Distribution and 5-Year HER2+ Breast Cancer Survival

Parise and colleagues have conducted two analyses focusing on cancer staging and survival utilizing data from the California Cancer Registry, a population-based registry composed of eight regional registries collecting cancer incidence and mortality data for the entire population of California. The registry was implemented state wide in 1988. The registry requires the collection of tumor marker information including the status of estrogen receptor (ER) and progesterone receptor (PR) since January 1, 1990 and HER2 status since January 1, 1999. The details of breast cancer status identification are described elsewhere.⁸ Cases with complete tumor marker data are categorized into one of eight distinct subtypes based on biomarker status of the tumor. Stage at diagnosis is collected from the patient's medical record.

The first study by Praise et al.⁹, evaluating 55,188 females with incident breast cancer between 1999 and 2004, identified an increasing proportion of HER2+ tumors with increasing breast cancer stage; 18.2% of all Stage I breast cancer patients were HER2+, 24.9% of Stage II patients were HER2+, 32.7% and 36.0% of Stage III and Stage IV breast cancer patients were HER2+ (Table 4). The authors also reported a 50%

⁵ Slamon DJ, Clark GM, Wong SG, et al. Human Breast Cancer: Correlation of relapse and survival with amplification of the HER2/neu oncogene. *Science* 1987; 235:177-82.

⁶ Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med* 2007; 131:18-43.

⁷ Surveillance Epidemiology and End Results. SEER 17 Registries Research. US National Institutes of Health, National Cancer Institute. [updated 2011 Nov 10; cited 2012 Feb 21] Available from: <http://seer.cancer.gov/>.

⁸ Parise CA, Bauer KR, Brown MM, Caggiano V. Breast Cancer Subtypes as Defined by the Estrogen Receptor (ER), Progesterone Receptor (PR), and the Human Epidermal Growth Factor Receptor 2 (HER2) among women with invasive breast cancer in California, 1999-2004. *Breast J* 2009; 15(6):593-602.

⁹ Parise CA, Bauer KR, Brown MM, Caggiano V. Breast Cancer Subtypes as Defined by the Estrogen Receptor (ER), Progesterone Receptor (PR), and the Human Epidermal Growth Factor Receptor 2 (HER2) among women with invasive breast cancer in California, 1999-2004. *Breast J* 2009; 15(6):593-602.

increased odds of ER+/PR+/HER2+ AJCC Stage IV tumors compared to Stage I [Odds ratio (OR) = 1.47, 95% Confidence Interval (CI) (1.21 to 1.79)] and ER-/PR-/HER2+ tumors had a 25% increased odds of being Stage III [OR= 1.25 (1.08 to 1.44)] and a 58% increased odds of being Stage IV compared to Stage I [OR=1.58 (1.27 to 1.98)].

Figure 1: Proportion of HER2+ and HER2- Tumors Reported by Parise et al. (N=55,188)



This pattern is consistent with another study evaluating 1.22 million female members of Kaiser Permanente Northern California females age 20 years and older where HER2+ cases were present in 11% of local cancers, 18% of regional cancers, and 25% of distant cancers.¹⁰

The second study by Parise et al., utilizing California Cancer Registry data from 2001-2008, estimated 5-year survival of 87,652 Stage I-III first primary female invasive breast cancer cases with complete stage and ER/PR/HER2 status. (Table 5)^{11,12} The most common subtype among all HER2+ tumors was ER+/PR+, comprising almost 50% of the HER2+ patients. ER-/PR- tumors were present in about 32% of patients, followed by ER+/PR- (16%), and finally ER-/PR+ tumors comprising only 2% of the HER2+ patients. Among all diagnoses of HER2+ tumors, Stage II was the most common

¹⁰ Fehrenbacher L, Habel L, Capra A, Anthony A, Li X, Quesenberry C, & Fulton R. Incidence and demographic and tumor characteristics of HER2-positive invasive breast cancer in a large, unselected population, 2000-2006. *Cancer Research* 2009; 69(24 Suppl):Abstract nr 3058.

¹¹ Cagginao V, Bauer KR, Parise CA. Survival of triple-negative and HER2-positive breast cancer by AJCC stage. Poster presentation. ASCO Annual Meeting. 2011; Abstract *J Clin Oncol* 2011; 29 (suppl; abstr 1078).

¹² This study was presented at the June 2011 American Society of Clinical Oncology (ASCO) meeting (see Figure 7 for poster). The authors were unwilling to provide additional information in light of the upcoming manuscript publication.

(44.5%), followed by Stage I (39.8%) then Stage III (15.7%). This is consistent with a previous analysis conducted by this research group.¹³ This pattern is consistent across all tumor subtypes except ER+/PR+ tumors which have almost equal proportion of Stage I and Stage II tumors. ER-/PR- tumors had the lowest proportion of Stage I diagnoses and highest proportion of Stage III diagnoses (Figure 2).

Figure 2: Proportion of HER2+ Breast Cancer Cases by Hormone Subtype Stratified by AJCC Stage I-III



Five-year survival was similar among all Stage I breast cancer patients ranging from 97% among ER+ tumors to about 94% among ER-/PR+ tumors. Among Stage II tumors, 5-year survival became more differentiated. All ER+ tumors had better 5-year survival compared to ER- tumors. Among HER2+ subtypes, ER+/PR- had the best survival among all subtypes (97%) while ER-/PR+ and ER-/PR- had the worst (both ~83%). Patients with ER+/PR+/HER2+ Stage II tumors had approximately 92% five-year survival. Survival among Stage III tumors was further differentiated. Patients with HER2+ subtypes ER+/PR- and ER+/PR+ tumors continued to have the highest survival rate (both around 80%). HER2+ patients with ER-/PR- tumors had <65% five-year survival and patients with ER-/PR+ tumors has almost 50% 5-year survival rate.

The same research group also described 5-year breast cancer survival using the 2007 St. Gallen Consensus statement (Table 6). The St. Gallen Consensus is derived from an international group brought together to provide guidance for the therapy of early breast cancer outside clinical trials. The committee also provides a breast cancer risk

¹³ Parise CA, Bauer KR, Brown MM, Caggiano V. Breast Cancer Subtypes as Defined by the Estrogen Receptor (ER), Progesterone Receptor (PR), and the Human Epidermal Growth Factor Receptor 2 (HER2) among women with invasive breast cancer in California, 1999-2004. *Breast J* 2009; 15(6):593-602

categorization based on patient and tumor characteristics and node involvement. The categorization includes five groups: Low Risk, Intermediate Risk 2, Intermediate Risk 3, High Risk 4, and High Risk 5 (See Table 9 for full description). Patients with HER2+ tumors are considered Intermediate Risk 2, High Risk 4 or High Risk 5 and severity increases as the number of nodes increases. Among all HER2+ tumors, over half were categorized as Intermediate Risk 2, followed by High Risk 4 then High Risk 5.

Using the St. Gallen Consensus patients with ER+ tumors had good 5-year survival regardless of HER2 status. ER+/PR+/HER2+ patients had an estimated 5-year relative survival of 91.3% in contrast to ER-/PR-/HER2+ patients who had a 75.9% relative 5-year survival.¹⁴ Like the 5-year survival distribution in AJCC classification, all cancer subtypes in the Low Risk group had a close to 100% 5-year survival. Intermediate groups 1 and 2 did not statistically differ from each other. However, when tumor subtypes were evaluated among the Intermediate group, the subtypes significantly differed (Figure 5). Similar to the pattern in the AJCC classification, patients with ER- tumors had worse 5-year survival compared to patients with ER+ tumors. Among HER2+ subtypes, ER+/PR+ and ER+/PR- tumors had close to 100% 5-year survival, while ER-/PR+ and ER-/PR- tumors had about 92% 5-year survival. Among the collective High Risk groups, ER+/PR+ and ER+/PR- tumors had around 87% 5-year survival (Figure 6). Patients with ER-/PR- and ER-/PR+ tumors had a 5-year survival of 73% and 70%, respectively.

Neither analysis used analytic techniques to determine statistical differences between the survival rates of each group. Additionally, 95% confidence intervals for the survival rates were not reported. Therefore the variation of each rate is unknown. For example, it cannot be determined if the variation among survival of AJCC Stage II HER2+ breast cancer patients, ranging from 97% to 92%, truly exists or if the 95% confidence intervals overlap, suggesting similar rates.

3.2.3 Racial Distribution of HER2+ Breast Cancer

A population-based study using data from the Atlanta SEER registry in conjunction with the Georgia Comprehensive Cancer Registry identified cases of primary invasive breast cancer from 2003 to 2004. HER2 information was abstracted from medical records and registry abstracts. The study focused on age and race differences among incident breast cancer patients. The final study population consisted of 1,842 women, of which 12.6% were HER2+. The Incidence of HER2+ breast cancer was similar among Whites and Blacks and was reported at rates of 21.1 per 100,000.¹⁵ This finding is consistent with an earlier study using similar data.¹⁶

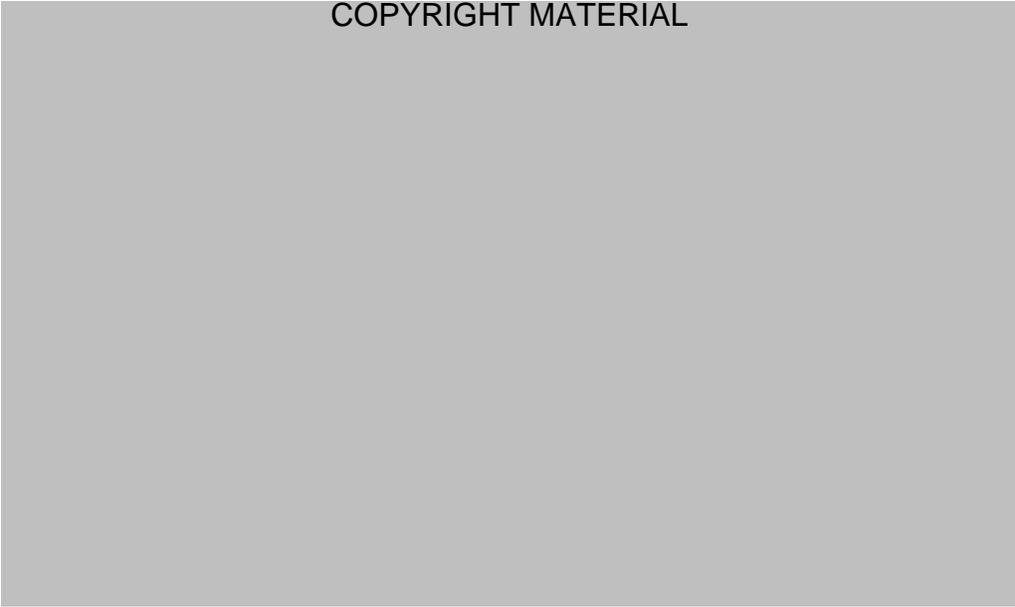
¹⁴ Bauer K, Parise C, Caggiano V. Use of ER/PR/HER2 subtypes in conjunction with the 2007 St. Gallen consensus statement for early breast cancer. *BMC Cancer* 2010; 10:228

¹⁵ Lund MJ, Butler EN, Hair BY, et al. Age/race differences in HER2 testing and in incidence rates for breast cancer triple subtypes. *Cancer* 2010;116:2549-59.

¹⁶ Lund MJ, Trivers KF, Porter PL et al. Race and triple negative treats to breast cancer survival: a population-based study in Atlanta, GA. *Breast Cancer Res Treat* 2009;113:357-70.

Although the proportion of HER2+ cases was similar between Blacks and Whites, stage distribution differed; Blacks had higher stage tumors at diagnosis compared to Whites (Figure 3).¹⁷ The distribution of HER2+ subtypes also differed between Blacks and Whites. White women had a higher proportion of ER+/PR+ tumors and Black women had a higher proportion of ER-/PR- tumors (Figure 4).

Figure 3: Proportion of HER2+ Breast Cancer Cases per AJCC Stage Stratified by Race



¹⁷ Lund MJ, Butler EN, Hair BY, et al. Age/race differences in HER2 testing and in incidence rates for breast cancer triple subtypes. *Cancer* 2010;116:2549-59.

Figure 4: Proportion of HER2+ Breast Cancer Cases per Hormone Receptor Status Stratified by Race



This finding is also described in a population based study of 950 women aged 20-54 in Atlanta, Georgia diagnosed with incident breast cancer between 1990 and 1992. This analysis suggested Black women had a 90% increased odds of ER-/PR-/HER2+ subtype compared to White women while no difference was seen with the odds of ER+/PR+/HER2+ tumors between Black and White women.¹⁸

4 DISCUSSION

Based on our analysis of the IMS LifeLink™ Health Plan Claims Database data, the (b) (4) trastuzumab use was in adult patients aged 45-64 years of age. Female patients accounted for (b) (4) (b) (4) patients) of use compared to male patients with around (b) (4) (b) (4) patients). (b) (4) pediatric patient aged 0 to 17 years captured during the study period. Approximately (b) (4) of trastuzumab users had a diagnosis of primary breast cancer in the same calendar year for each year over the study period. Of these, approximately (b) (4) of trastuzumab users also had a diagnosis for a secondary neoplasm.

Because of the slight variance in the methodology of patient selection for the stratification of trastuzumab patients by diagnoses (Table 3 in Appendix 1), there is an (b) (4) patient difference in the number of patients with trastuzumab and a primary breast cancer diagnosis as reported in Table 3 and the trastuzumab count as reported in Tables 1 and 2. There were (b) (4) patients with a claim for trastuzumab and a diagnosis claim for primary

¹⁸ Trivers KF, Lund MJ, Porter PL, et al. The epidemiology of triple-negative breast cancer, including race. *Cancer Cause Control* 2009;20:1071-82

breast cancer **and** did not have a claim for trastuzumab alone in the year or years prior to the calendar year with both claims. A total of (b) (4) patients had claims for trastuzumab in a year prior to having claims for trastuzumab **and** a primary breast cancer diagnosis in a subsequent year.

The IMS LifeLink Health Plan Claims Database is comprised of commercially insured patients, with a subset of managed Medicare and Medicaid patients, including medical services and prescription drug information across the entire continuum of care. The health plan database is representative of the U.S. Commercially Insured population by age and gender. The data are also longitudinal with average member enrollment duration of two to three years. Only health plans that submit data for all members are included in the database, ensuring complete data capture and representative samples.

The data presented in this review were obtained from a sample of healthcare claims from commercially insured patients, with a subset of managed Medicare and Medicaid patients, and were **not** nationally projected. Additionally, the IMS LifeLink™ Health Plan Claims Database receives data from a number of different health plans and currently has some data through the end of 2011; not all health plans are fully up to date due to a data lag of 6-months. Therefore, only cumulative data for year 2009 through 2011 were presented for this analysis.

Data on uninsured patients or cash-paying patients are not available from the IMS, LifeLink™ Health Plan Claims Database. Although, due to the nature of the drugs and conditions they are used to treat it is less likely that un-insured patients use them. The database includes both inpatient and outpatient diagnoses (in ICD-9-CM format) and procedures (in CPT-4 and HCPCS formats) as well as both retail and mail order prescription records. It should be noted that there is no validation method available to confirm the diagnosis using IMS LifeLink™ and diagnosis is limited to the reporting year of the prescription.

The rate of HER2+ breast cancer tumors occur in approximately 18% to 25% of all breast cancer cases.^{19,20} However, no studies have reported the incidence of HER2+ breast cancer in the United States. Using the SEER breast cancer incidence rate in 2011 we estimate the incidence of HER2+ breast cancer is between 22.3 and 31.0 per 100,000 in 2011.

Both the AJCC Staging and 2007 St. Gallen Consensus suggest that estimated survival among HER2+ patients decreases as stage at diagnosis worsens and survival may be worse in patients with ER- subtypes. Survival estimates were lower using the AJCC staging criteria; ER-/HER2+ AJCC Stage III cases had 60% to 51% survival while patients identified as High Risk using the St. Gallen Consensus were estimated to have 73% to 70% 5-year survival. Differences in staging criteria should be taken into

¹⁹ Slamon DJ, Clark GM, Wong SG, et al. Human Breast Cancer: Correlation of relapse and survival with amplification of the HER2/neu oncogene. *Science* 1987; 235:177-82.

²⁰ Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med* 2007; 131:18-43.

consideration when interpreting the results of each study. Also, the use of trastuzumab was not available in either study and its effect on survival is unknown in the study populations. Furthermore, the population utilized for the analyses was from California only and may not be representative of all areas of the United States. However, the incidence of breast cancer in California has historically been similar to the national incidence rate of breast cancer.²¹

The results of two studies, each conducted during different time periods, indicated that incidence rates of all HER2+ breast cancers do not differ between Black and White females but suggested that Black women are more likely to have ER- tumors compared to White women. However, all data presented in this section was conducted in a limited population from the Atlanta, Georgia metropolitan area. The incidence rate of women diagnosed with breast cancer reported by Lund et al. was 176 per 100,000. This rate is higher than reported by the CDC for the state of Georgia in 2004 (120 per 100,000)²² and the generalizability of these results to other populations may be limited.

5 CONCLUSION

- Based on our analysis of the IMS LifeLink™ Health Plan Claims Database data, (b) (4) trastuzumab use was in adult patients aged 45-64 years. Female patients accounted for (b) (4) (b) (4) patients) of use compared to male patients with around (b) (4) (b) (4) patients). (b) (4) pediatric patient aged 0 to 17 years captured during the study period.
- Of those patients with selected diagnoses for primary breast cancer and one selected secondary neoplasm, nearly a quarter had evidence of secondary neoplasm exposure during the cumulative study period, respectively.
- Limited research has evaluated the stage distribution, 5-year survival, and racial differences in patients with HER2+ breast cancer. The majority of the research presented in this review is from two patient populations and the results may not be generalizable. Therefore the results should be considered in the context of this limitation.
- The incidence rate of HER2+ breast cancer in the United States is estimated between 22.3 and 31.0 per 100,000 in 2011.
- At diagnosis, about 40% of HER2+ breast cancers are AJCC Stage I, 44% are Stage II and about 15% are Stage III. The distribution varies by ER/PR subtype; ER+/PR+ tumors have the lowest proportion of Stage III diagnoses (~13%) while ER-/PR- tumors have the highest (~20%).
- Five-year survival by stage of HER2+ breast cancer diagnosis varies greatly by stage and is largely influenced by ER subtype. Survival among patients with AJCC Stage I tumors ranges from about 97% to 94% for ER+ and ER- subtypes, respectively. Among Stage II cases, ER+ subtypes had the best survival ranging from 97% to 92%. ER- subtype case survival was around 83%. Survival of Stage

²¹ Centers for Disease Control and Prevention. U.S. Cancer Statistics: An Interactive Atlas [Online]. Accessed March 14, 2012 at http://apps.nccd.cdc.gov/DCPC_INCA/DCPC_INCA.aspx

²² Centers for Disease Control and Prevention. U.S. Cancer Statistics: An Interactive Atlas [Online]. Accessed March 14, 2012 at http://apps.nccd.cdc.gov/DCPC_INCA/DCPC_INCA.aspx

III cases diminishes even further; ER+ subtypes had about 80% survival while ER- subtypes had 63% and 51% survival for PR- and PR+ tumors, respectively. Statistical differences were not provided for the reported survival rates and the variation of each rate is unknown. For example, it cannot be determined if the variation among survival of Stage II HER2+ breast cancer patients, ranging from 97% to 92%, truly exists or if the 95% confidence intervals overlap, suggesting similar rates.

- Based on data from limited patients population at a metropolitan area, Breast cancer incidence did not seem to differ significantly between Black and White females. However, Black women may have a higher proportion of Stage III and IV tumors at diagnosis and a higher proportion of ER-/PR- tumors compared to White women.

6 APPENDIX 1: DRUG UTILIZATION TABLES

(b) (4)



7 APPENDIX 2: LITERATURE REVIEW TABLES

Table 4: Proportion of HER2-Positive and HER2-Negative Tumors Reported by Parise et al. (N=55,188)

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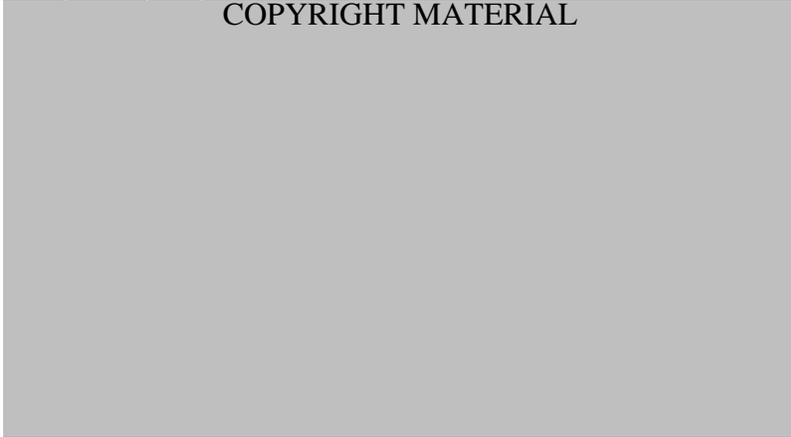


Table 5: Proportion of HER2+ Breast Cancer Cases by Hormone Subtype Stratified by AJCC Stage I-III

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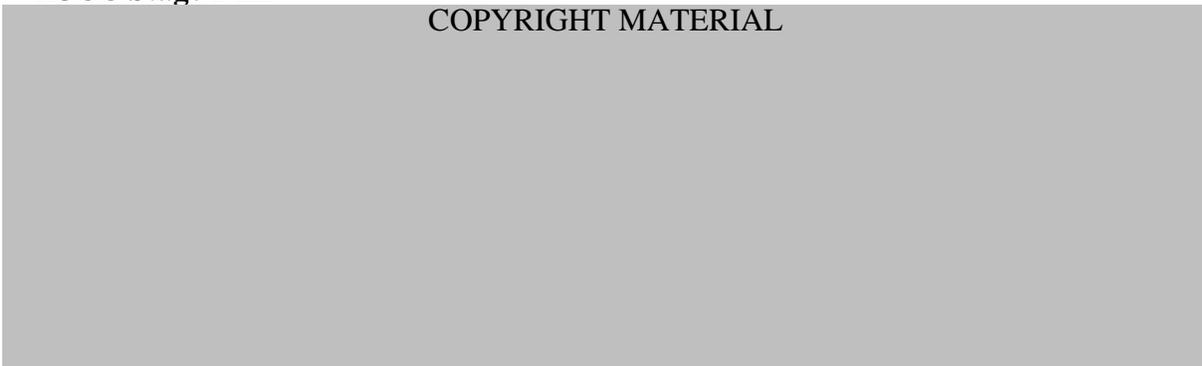


Table 6: St. Gallen Distribution of HER2+ Tumors

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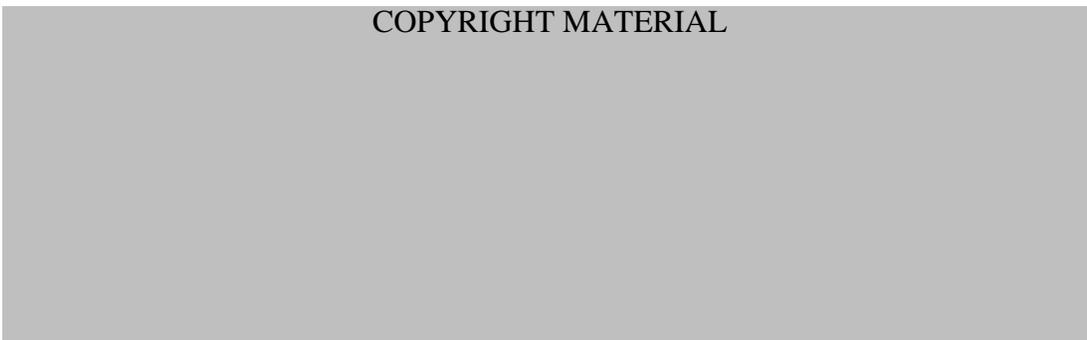
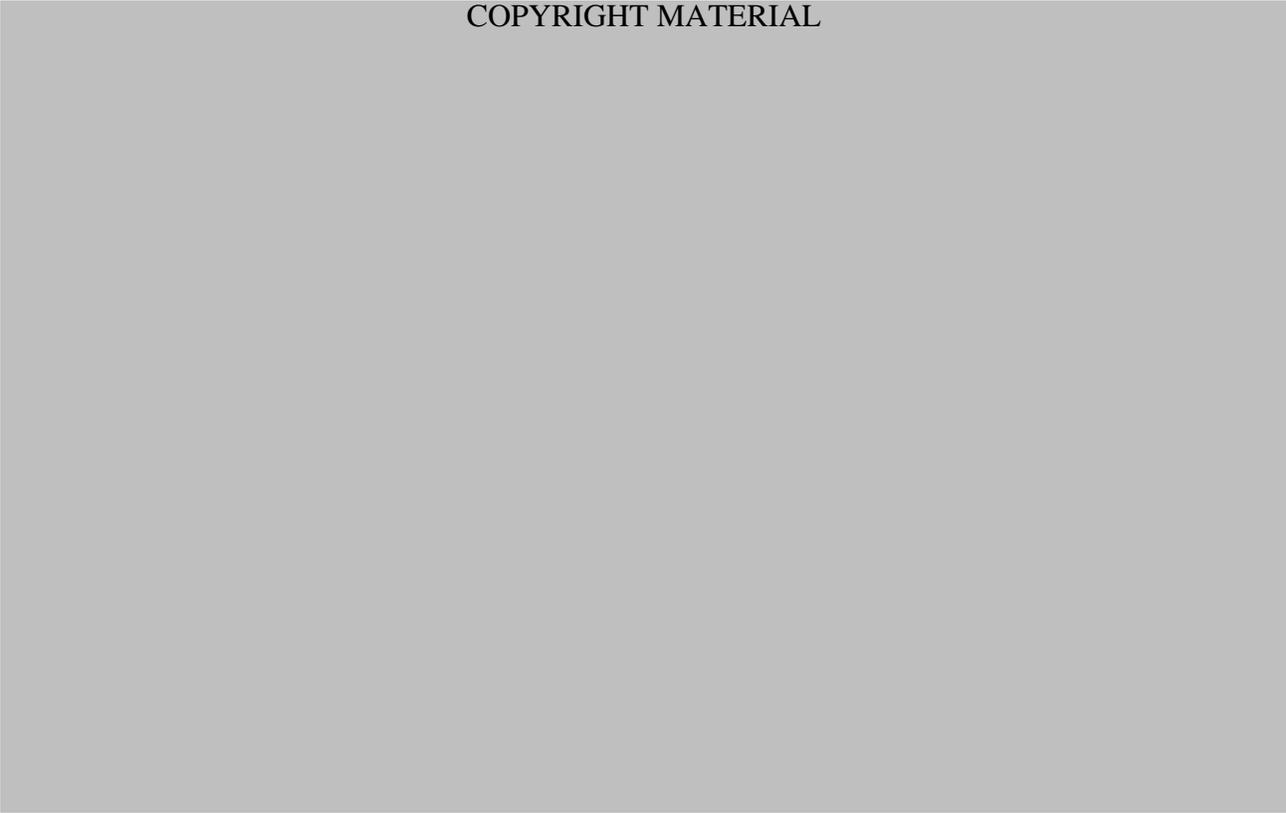


Figure 5: Five-year relative survival for all cases within the St. Gallen Intermediate risk group by ER/PR/HER2 subtype²³

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²³ Bauer K, Parise C, Caggiano V. Use of ER/PR/HER2 subtypes in conjunction with the 2007 St. Gallen consensus statement for early breast cancer. *BMC Cancer* 2010; 10:228

Figure 6: Five-year relative survival for all cases within the St. Gallen high risk group by ER/PR/HER2 subtype²³

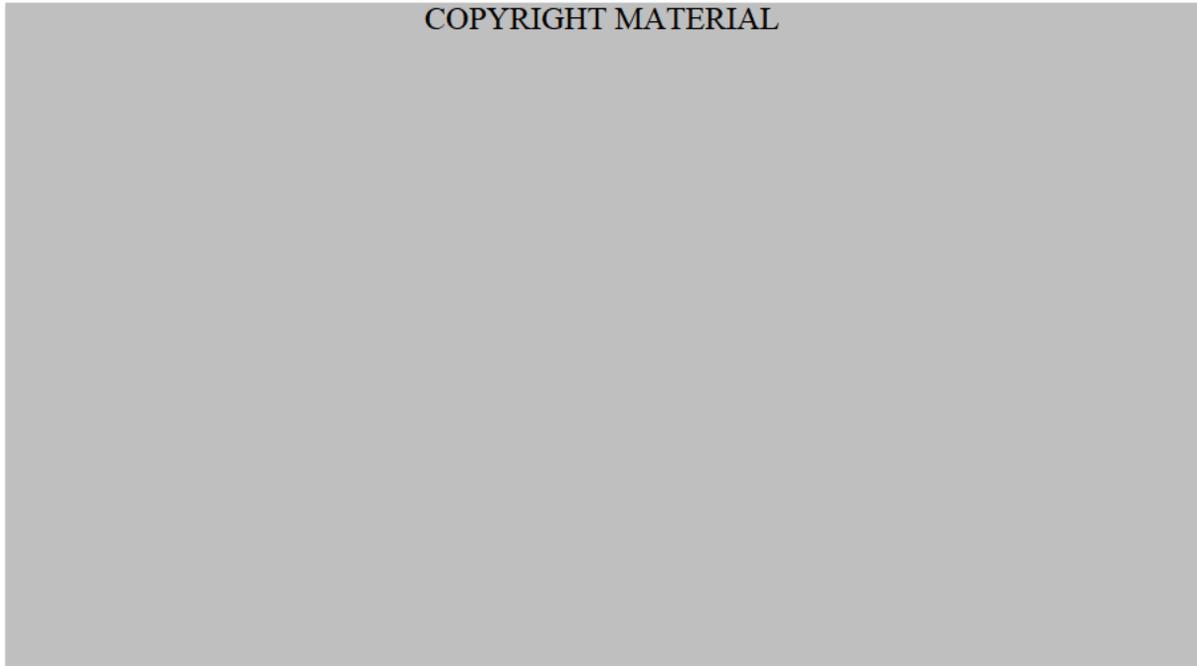


Table 7: CC Stage Distribution Among All Breast Cancer Patients (Lund et al, 2010)

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Table 8: Definition of risk categories for patients with operated breast cancer (From Goldhirsch et al. Table 2)

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^aSome Panel members view pT1a and pT1b (i.e. pT <1 cm) tumors with node-negative disease as representing low risk even if higher grade and/or younger age.

^bExtensive peritumoral vascular invasion (i.e. neoplastic emboli seen in two or more blocks of the tumor) was recognized as a discriminatory feature of increased risk; its presence defined intermediate risk for node-negative disease, but did not influence risk category for node-positive disease [74].

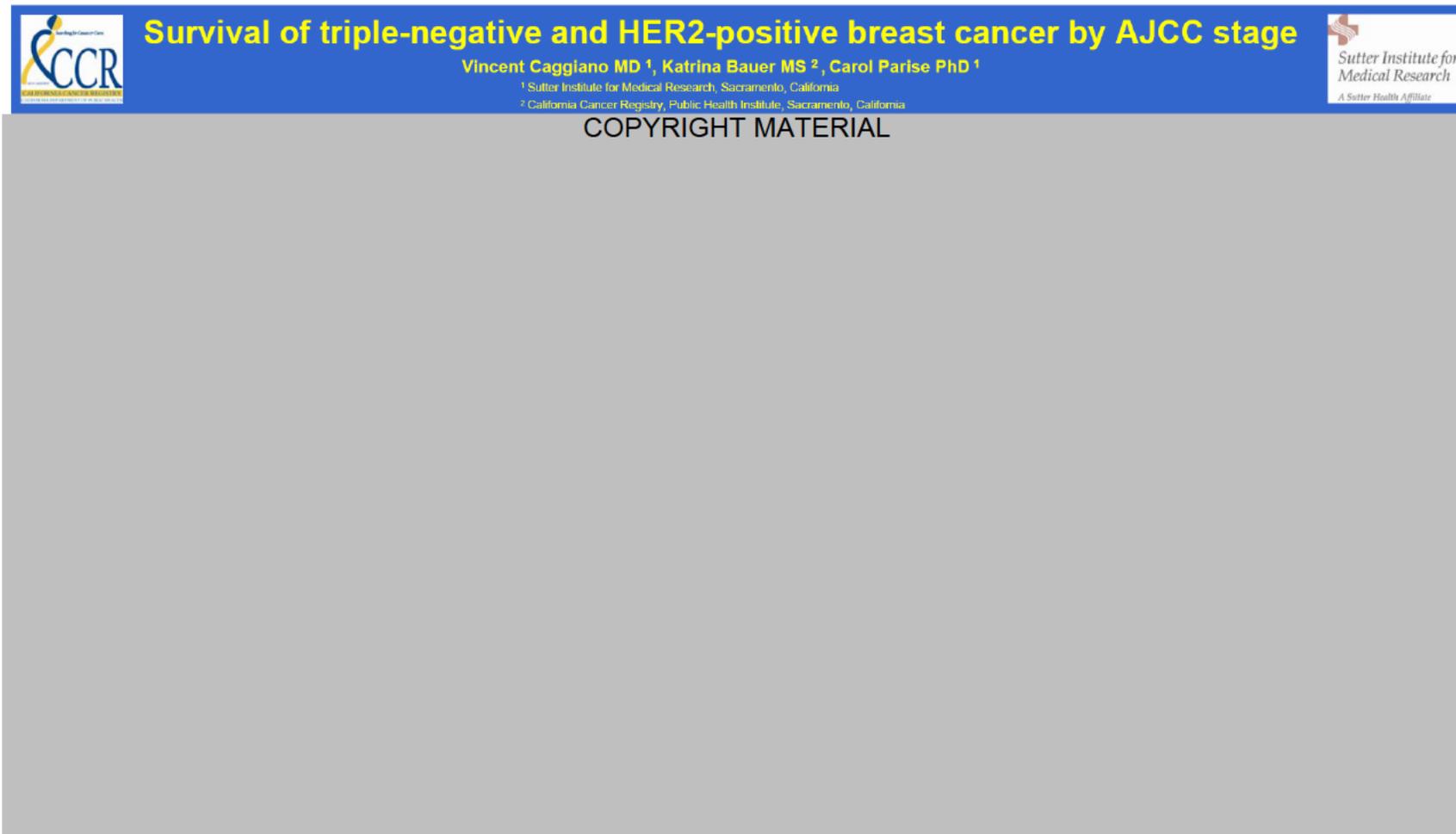
^cSome cases such as medullary carcinoma and apocrine carcinoma may be regarded as low risk despite the absence of steroid hormone receptor expression.

^dHER2/*neu* gene overexpression or amplification must be determined by quality-controlled assays using immunohistochemistry or FISH analysis.

^eNote that the intermediate risk category includes both node-negative and node-positive 1–3 disease.

*pT, pathological tumor size (i.e. size of the invasive component); **histologic and/or nuclear grade; ***ER, estrogen receptor; PgR, progesterone receptor.

Figure 7: Data From Caggiano et al. American Society of Clinical Oncology Annual Meeting, June 2011



10 APPENDIX 3: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS LifeLink™ Health Plan Claims Database

The IMS Health Plan Claims Database is a health plan claims database representing approximately 101 managed care plans and covering approximately 65.8 million de-identified patients. The medical claims are captured from doctor's offices, retail and mail order pharmacies, patient visits to specialists and hospitalizations including diagnoses, ER visits, office visits, home care, diagnostic tests, procedures and injections. The data are not nationally projected; however, it represents approximately 9 percent of the U.S. commercially insured population based on year 2007 U.S. Census.

The IMS, LifeLink™ Health Plan Claims Database is comprised of commercial health plan information obtained from health plans and other related sources throughout the United States. It is largely a commercially insured database with a subset of Medicare and Medicaid patients that are enrolled in commercially administered plans. The data are paid claims data, which are fully adjudicated and paid for covered services on behalf of an enrollee by their health plan. The database consists of medical and pharmaceutical claims for over 70 million unique patients from over 75 health plans across the U.S. (approximately 15 million covered lives per year).

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**Interdisciplinary Review Team for QT Studies Consultation:
QT Sub-Study Review**

IND or NDA	BLA 125409
Generic Name	Pertuzumab
Sponsor	Genentech, Inc.
Indication	For the treatment of patients with 1st Line HER2-positive metastatic breast cancer
Dosage Form	Intravenous infusion
Drug Class	HER2 blocker
Therapeutic Dosing Regimen	840 mg loading dose by i.v. infusion followed by 420 mg every 3 weeks (q3wk)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	15 mg/kg q3wk
Submission Number and Date	8 Dec 2011
Review Division	DOP1

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes in mean QTc intervals (i.e., >20 ms) were detected at the proposed pertuzumab therapeutic dose in this QTc substudy. Although the largest upper bound of the 2-sided 90% CI for the mean difference between pertuzumab (pertuzumab + trastuzumab + docetaxel) and placebo arm (placebo + trastuzumab + docetaxel) was 17.5 ms, the point estimate was 6.0 ms. Due to study design limitations (e.g. lack of positive control, confounding of effects of concomitant treatments on the QT interval, underlying disease in patient population, and slightly higher QTcF baseline in the placebo group compared to that in the pertuzumab treatment group), precise effect of pertuzumab on QT interval cannot be estimated. Because of the lack of demonstrated assay sensitivity, the results should be interpreted as having ruled out an effect of about 20 ms.

This is a randomized, double-blind, placebo-controlled QTc substudy of the pivotal Phase III trial TOC4129g/WO20698. The pertuzumab dose studied is the proposed therapeutic dose (840 mg loading dose by i.v. infusion followed by 420 mg q3wk). The substudy included total 37 patients with HER2 positive, previously untreated metastatic breast cancer (17 in the placebo+trastuzumab+docetaxel group, 20 in the pertuzumab+trastuzumab+docetaxel group). Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Pertuzumab (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
Pertuzumab	C3POST15*	6.0	17.5

* Cycle 3, Day 1, 15 min post infusion

QT evaluation of pertuzumab was performed at the proposed therapeutic dose. Pertuzumab is eliminated via intracellular lysosomal degradation. There is no effect of intrinsic factors on the exposure of pertuzumab and drug interactions are not expected. Hence QT evaluation at the therapeutic dose is reasonable. At the concentrations observed in this QT substudy, there are no detectable prolongations of the QT interval. Furthermore, exposure-response relationship was not evident within the range of concentrations observed in the study.

2 BACKGROUND

2.1 PRODUCT INFORMATION

Pertuzumab (rhuMAb 2C4), a fully humanized monoclonal antibody, acts by blocking the association of human epidermal growth factor receptor-2 (HER2) with other HER family members, including epidermal growth factor receptor (EGFR, also known as HER1), HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, MAP kinase and PI3K.

Pertuzumab is being developed for the treatment of patients with solid tumors.

2.2 MARKET APPROVAL STATUS

Pertuzumab is not approved for marketing in any country

2.3 PRECLINICAL INFORMATION

Dedicated cardiovascular safety pharmacology studies were not conducted.

2.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

“A summary of ECG abnormalities is provided in Table 113. This summary is based on Investigator assessments of ECG abnormalities, which were collected as free text in the eCRF. Measurements of ECG parameters such as QT interval duration were not requested and are only available if the Investigator reported them. These Investigator assessments were based on routine ECGs recorded at the study site. For details of ECG findings based on Holter monitoring of patients in the QT Substudy, refer to the separate report and to Section 2.1.5.2.

“Most abnormalities emerging during treatment were seen on one or two ECGs only and previous and/or subsequent ECGs were unremarkable. Some of the patients also had abnormalities on their baseline ECG. All except six patients (3 in each arm) with post-baseline ECG abnormalities were reviewed by the CRC at some time during the study.

Table 2: Summary of ECG abnormalities not present at baseline (other than isolated sinus tachycardia, sinus arrhythmia or sinus bradycardia; or single/occasional ventricular extrasystoles)

Main Post-baseline ECG abnormality (based on Investigator comment for abnormal ECGs)	No. of patients	
	Pla+T+D n=397	Ptz+T+D n=407
QT prolongation	4	4
First degree AV block	3	5
Bundle branch & fascicular blocks	3	4
Atrial fibrillation	5	1
Atrial enlargement	2	0
Myocardial infarction & ischemia*	3	7
Repolarization abnormalities	3	3
Axis deviation	1	0
Non-specific ST, T wave and other abnormalities	3	7
Pericarditis, pericardial effusions & low voltage complexes	3	0
Left ventricular hypertrophy	1	2
Ventricular arrhythmias	1	2
Miscellaneous & multiple abnormalities	2	5
No clear information	1	3
Total	35	43

Derived from summary of ECG abnormalities

*Including old or indeterminate changes

Where more than one post-baseline abnormality is described, patients were categorized according to the most dominant or most clinically significant (prolonged QTc considered of high importance).

Source: eCTD 2.7.4., Table 113, page 227

-QT Prolongation Events by SMQ in Study WO20698/TOC4129g

“The frequency of occurrence of QT prolongation (SMQ) AEs reported in the main study, WO20698/TOC4129g (N= 804) was comparable in the two treatment arms: five patients (1.3%) in the Pla+T+D arm and eight patients (2.0%) patients in the Ptz+T+D arms experienced these events (Table 61). A balanced proportion of patients in each arm (four patients) had syncope and a review of individual cases of syncope did not suggest that these were due to significant cardiac (or infusion-related) events. Two patients in the Ptz+T+D arm had AEs of ventricular fibrillation and ventricular arrhythmia. Of the 13 QT prolongation events reported, two were SAEs; one case of syncope and one case of ventricular fibrillation which led to discontinuation of study treatment.

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Table 3: Summary of QT Prolongation (SMQ) AEs by Trial Treatment: Pivotal Study (WO20698/TOC4129g)

t aell qt Summary of QT Prolongation (SMQ) Adverse Events by Trial Treatment
 PProtocol(s): WO20698
 Analysis: SAFETY (BY TREATMENT RECEIVED) Center: ALL CENTERS
 Snapshot Date: 06JUL2011 Clinical Cut-Off Date: 13MAY2011

Body System/ Adverse Event	Placebo + Trastuzumab + Docetaxel N = 397 No. (%)	Pertuzumab + Trastuzumab + Docetaxel N = 407 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	5 (1.3)	8 (2.0)
Total Number of AEs	5	8
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	4 (1.0)	4 (1.0)
SYNCOPE	4 (1.0)	4 (1.0)
Total Number of AEs	4	4
INVESTIGATIONS		
Total Pts With at Least one AE	1 (0.3)	2 (0.5)
ELECTROCARDIOGRAM QT PROLONGED	1 (0.3)	2 (0.5)
Total Number of AEs	1	2
CARDIAC DISORDERS		
Total Pts With at Least one AE	-	2 (0.5)
VENTRICULAR ARRHYTHMIA	-	1 (0.2)
VENTRICULAR FIBRILLATION	-	1 (0.2)
Total Number of AEs	-	2

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Investigator text for Adverse Events encoded using MedDRA version 14.0.
 Percentages are based on N.
 Multiple occurrences of the same adverse event in one individual counted only once.
 QT prolongation AEs identified using the SMQ (wide) 'Torsade de pointes/QT prolongation' - see
 glossary L UD09_AEGT for more detailed
 description
 AEl1 08JUL2011:15:06:48 (1 of 1)

Source: eCTD 2.7.4, Table 61

From ISS, (Page 290)

Single-agent pertuzumab studies (ECG)

“In the single-agent studies, twelve-lead ECGs were performed at screening and final visit (or as clinically indicated).

“Two patients in study BO17004 developed ECG abnormalities that were reported as serious AEs and judged related to pertuzumab:

- Patient 37784/2001, who had a history of mitral valve insufficiency, had a protocol required ECG which showed asymptomatic tachyarrhythmia with Grade 2 atrial fibrillation, a LVEF of 40% and minor mitral- and tricuspid valve insufficiency (on Day 38). At his final visit (Day 65), he had a LVEF of 58%. Two weeks later, the patient died due to fulminant progression of prostate cancer and tumor cachexia. At the time of his death, the atrial fibrillation was persisting.
- Patient 38418/3102 had T-wave inversion in the antero-lateral ECG leads (V3-V6) with corresponding hypokinesia and slight elevation of troponin I (0.07 ng/mL; normal range: 0-0.05 ng/mL) which normalized 2h later (Day 33). The event was preceded by dyspnea and a LVEF of 40%. The LVEF value improved to 54% and a further ECG (Day 90) revealed no evidence of T-wave inversion.

“No other significant ECG abnormalities were reported as AEs in these or other pertuzumab studies. Individual patient listings of ECG abnormalities are provided in the clinical study reports.”

From ISS (page 105)

Single-agent pertuzumab studies (Adverse events)

“In the single-agent studies, AEs were most frequently reported in the SOC ‘Gastrointestinal disorders’ (80.8%; with diarrhea and nausea being the most common AEs in this category), followed by SOC ‘General disorders and administration site conditions’ (59.6%; with fatigue being the most common AE in this category. Most events were Grade 1-2 in severity.

The most frequently occurring AEs (> 25% of patients) were diarrhea, nausea, fatigue, alopecia, neutropenia and rash Table 4.

Table 4: Summary Of Adverse Events Occurring In $\geq 5\%$ Of Patients: All Pertuzumab-Treated Patients

t_ae13_pe Summary Of Adverse Events With An Incidence Rate Of At least 5%: All Pertuzumab-Treated Patients
 Protocol(s): ALL PERTUZUMAB TREATED PATIENTS
 Analysis: ALL PATIENTS Center: ALL CENTERS

Adverse Event	ALL PERTUZUMAB EXPOSED N = 1412 No. (%)
DIARRHOEA	821 (58.1)
NAUSEA	543 (38.5)
FATIGUE	492 (34.8)
ALOPECIA	421 (29.8)
NEUTROPENIA	399 (28.3)
RASH	360 (25.5)
DECREASED APPETITE	324 (22.9)
VOMITING	320 (22.7)
HEADACHE	241 (17.1)
ASTHENIA	234 (16.6)
MUCOSAL INFLAMMATION	221 (15.7)
ANAEMIA	218 (15.4)
ABDOMINAL PAIN	203 (14.4)
OEDEMA PERIPHERAL	196 (13.9)
MYALGIA	195 (13.8)
COUGH	192 (13.6)
PYREXIA	187 (13.2)
CONSTIPATION	186 (13.2)
STOMATITIS	184 (13.0)
DYSPNOEA	169 (12.0)
ARTHRALGIA	166 (11.8)
DYSGEUSIA	154 (10.9)
BACK PAIN	151 (10.7)
DYSPEPSIA	144 (10.2)
NAIL DISORDER	135 (9.6)
PRURITUS	135 (9.6)
INSOMNIA	131 (9.3)
NEUROPATHY PERIPHERAL	127 (9.0)
PAIN IN EXTREMITY	121 (8.6)
DIZZINESS	120 (8.5)
EPISTAXIS	117 (8.3)
UPPER RESPIRATORY TRACT INFECTION	117 (8.3)
LEUKOPENIA	116 (8.2)
ABDOMINAL PAIN UPPER	110 (7.8)
URINARY TRACT INFECTION	101 (7.2)
CHILLS	93 (6.6)
DRY SKIN	92 (6.5)
PERIPHERAL SENSORY NEUROPATHY	89 (6.3)
MUSCULOSKELETAL PAIN	85 (6.0)
HYPOGAEMIA	84 (5.9)
NASOPHARYNGITIS	84 (5.9)
LACRIMATION INCREASED	78 (5.5)
FEBRILE NEUTROPENIA	75 (5.3)
WEIGHT DECREASED	75 (5.3)
DYSURIA	74 (5.2)
PARAESTHESIA	74 (5.2)
OROPHARYNGEAL PAIN	73 (5.2)
BONE PAIN	72 (5.1)
PAIN	71 (5.0)

BEST
POSSIBLE
COPY

Investigator text for Adverse Events encoded using MedDRA version 14.0.
 Percentages are based on N.
 Multiple occurrences of the same adverse event in one individual counted only once.
 Adverse events are ordered by largest overall incidence
 AE13 18JUL2011:21:01:41
 Spacing modified by PDRD (Source: t_ae13_pe)

Source: ISS, Table 36

From ISS (page 114).

-Single-agent pertuzumab studies (Grade 3-4, Adverse events)

“The incidence of Grade 3-4 AEs in the single agent studies (39.9%) was lower than that observed in the pivotal study, with Grade 3-4 neutropenia occurring in <1% of the

population, once again indicating that neutropenia was driven by treatment with docetaxel.

“Apart from gastrointestinal disorders, the incidence of Grade 3-4 events in the single-agent pertuzumab studies was < 10% in all SOCs, with diarrhea (6.5%) being the most commonly reported Grade 3-4 AE.”

From eCTD 2.7.4 (page 97)

Pivotal study (Deaths)

“In the pivotal study WO20698/TOC4129g, 22 deaths (12 in the Pla+T+D arm and 10 in the Ptz+T+D arm), were reported during or within 42 days of the last treatment (Table 37). The incidence of death due to febrile neutropenia or an infectious etiology was balanced between treatment arms (3 patients in the Pla+T+D arm and 5 patients in the Ptz+T+D arm). There were three cardiovascular-related deaths, all in the Pla+T+D arm.”

Reviewer’s Comments: The main cardiovascular AE in all studies (pivotal study WO20698/TOC4129g, key supporting studies and single-agent study) was decline of LVEF. The incidence of this AE ranged between 4.5 to 7 %. In the pivotal study there was a report of ventricular arrhythmia and another of ventricular fibrillation, both in the pertuzumab+trastuzumab+docetaxel arm. It seems unlikely that events were linked to pertuzumab (i.e., event took place >100 days after starting treatment, the events were confounded by comorbidities). No sudden cardiac death occurred when under pertuzumab.

2.5 CLINICAL PHARMACOLOGY

Appendix 5.1 summarizes the key features of *pertuzumab*’s clinical pharmacology.

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under BB IND 9900. The sponsor submitted the study report WO20698-pkpd-qtc-substudy for pertuzumab, including electronic datasets and waveforms to the ECG warehouse.

3.2 TQT STUDY

3.2.1 Title

A Substudy in Association with Pertuzumab Protocol TOC4129g/W020698 to Evaluate Corrected QT Interval, Pharmacokinetics, and Drug-Drug Interaction.

3.2.2 Protocol Number

TOC4129g/W020698 (Substudy 2)

3.2.3 Study Dates

The pivotal Phase III trial TOC4129g/W020698 is still ongoing. First patient enrolled on 12 February 2008, primary analysis data cut on 13 May 2011.

3.2.4 Objectives

- To describe of the potential effects of pertuzumab on the QTc interval.
- To evaluate the pharmacokinetic profile of pertuzumab in the presence of trastuzumab and docetaxel and to describe any drug-drug interactions that might be observed when all three drugs are co-administered.

3.2.5 Study Description

3.2.5.1 Design

Study TOC4129g/WO20698 is a randomized, double-blind, placebo-controlled study. The substudy was designed to enroll a total of 50 electrocardiogram (ECG)-evaluable patients and at least 40 pharmacokinetic (PK)-evaluable patients. The main study will enroll 800 patients from approximately 250 sites worldwide.

3.2.5.2 Controls

The Sponsor used placebo control.

3.2.5.3 Blinding

All treatment arms were administered blinded.

3.2.6 Treatment Regimen

3.2.6.1 Treatment Arms

Treatment Arm A: placebo + trastuzumab + docetaxel every 3 weeks

Treatment Arm B: pertuzumab + trastuzumab + docetaxel every 3 weeks

3.2.6.2 Sponsor's Justification for Doses

The dose to be studied is the proposed therapeutic dose (840 mg loading dose by i.v. infusion followed by 420 mg q3wk).

Reviewer's Comments: QT evaluation of pertuzumab was performed at the proposed therapeutic dose. Pertuzumab is (b) (4).

There is no effect of intrinsic factors on the exposure of pertuzumab and drug interactions are not expected. Hence QT evaluation at the therapeutic dose is reasonable.

3.2.6.3 Instructions with Regard to Meals

Pertuzumab is administered via i.v. infusion, hence food affects are not anticipated.

3.2.6.4 ECG and PK Assessments

On Cycle 1 Day 1 and Cycle 3 Day 1, ECGs were assessed at the following time points: 30 min prior to pertuzumab/placebo infusion, 15 min prior to pertuzumab/placebo infusion, immediately postinfusion (0-15 min post-pertuzumab/placebo infusion), and 60-75 min post-pertuzumab/placebo infusion. ECGs were also assessed at Cycle 1 Day 3 (approximately 72 h post-infusion), post-docetaxel infusion and coincident with the 23-h PK sample. Study treatment cycles were three weeks (21 days) in length.

Blood samples for PK evaluations were plan at the following timepoints: Pre-dose: within 15 min before the infusion; post-dose: within 15 min after the end of infusion. At Cycles 1 and 3, the post-pertuzumab PK sample will be drawn 60–75 min after the end of the pertuzumab/placebo infusion (prior to administration of trastuzumab).

Reviewer's Comments: There is no real consensus on the best approach to evaluate the QT effects of monoclonal antibodies. The classic mechanism of directly inhibiting the hERG channel is not probable due to the large size of monoclonal antibodies. We do recognize the monoclonal antibodies can have off-target cardiac effects but to date QT prolongation has not been observed. The design of the proposed substudy is reasonable to capture large effects on the QT interval.

3.2.6.5 Baseline

Baseline ECG was defined as the average of pre-dose observations at Cycle 1 Day 1 (15 minutes and 30 minutes prior to infusion). This definition of baseline is carried forward throughout the substudy.

3.2.7 ECG Collection

ECG data were obtained through 12-lead electrocardiogram (ECG) measurements which were extracted in triplicate. These measurements were sent to a central core cardiology laboratory which produced a single data set which was forwarded to (b) (4) by the Sponsor following unblinding of the main study.

3.2.8 Sponsor's Results

3.2.8.1 Study Subjects

Descriptive statistics of demographic data and other baseline characteristics of the female breast cancer patients enrolled in the substudy are presented in Table 5.

Table 5: Summary of Demographic Data

	Total N = 37	Placebo + Trastuzumab + Docetaxel N = 17	Pertuzumab + Trastuzumab + Docetaxel N = 20
Sex			
Female	37 (100%)	17 (100%)	20 (100%)
n	37	17	20
Race			
Asian	8 (21.6%)	4 (23.5%)	4 (20.0%)
Other	4 (10.8%)	2 (11.8%)	2 (10.0%)
White	25 (67.6%)	11 (64.7%)	14 (70.0%)
n	37	17	20
Age (years)			
Mean	53.1	55.3	51.2
Median	56	58	53.5
Min-Max	22 - 67	36 - 67	22 - 66
n	37	17	20
Age groups (years)			
<65	33 (89.2%)	14 (82.4%)	19 (95.0%)
>=65	4 (10.8%)	3 (17.6%)	1 (5.0%)
n	37	17	20
Age groups (years)			
<75	37 (100%)	17 (100%)	20 (100%)
n	37	17	20
Weight at baseline (kg)			
Mean	70.9	71	70.9
Median	71	72	68.5
Min-Max	48 - 98	48 - 98	52 - 98
n	37	17	20
Height at screening (cm)			
Mean	160.3	161.8	159
Median	160	162	159
Min-Max	141 - 176	152 - 176	141 - 171
n	37	17	20
Ethnicity			
Hispanic	4 (10.8%)	3 (17.6%)	1 (5.0%)
NK ¹	1 (2.7%)	-	1 (5.0%)
Non-hispanic	32 (86.5%)	14 (82.4%)	18 (90.0%)
n	37	17	20
Female Reproductive Status			
Postmenopausal	26 (70.3%)	11 (64.7%)	15 (75.0%)
Surgically sterilized	5 (13.5%)	3 (17.6%)	2 (10.0%)
With Contraceptive Protection ²	6 (16.2%)	3 (17.6%)	3 (15.0%)
n	37	17	20
Male Reproductive Status			
n	0	0	0

¹ Not known

² Childbearing potential with contraceptive protection

Source: t_dm11_db_pk Summary of History of Breast Cancer and HER2 Status by Trial Treatment - PK/QTc Substudy Patients Protocol(s): WO20698

Source: CSR, Table 1

3.2.8.2 Statistical Analyses

3.2.8.2.1 Primary Analysis

All ECG analyses will be exploratory, and fixed hypotheses will not be tested. The nominal times were used in the analysis. Treatment group comparisons were performed between means of baseline-adjusted measurements. The Δ QTcF upper ranges for the pertuzumab –treated group were less than 30 ms. Point estimates of $\Delta\Delta$ QTcF in Cycle 1 were all lower than 5 ms, with corresponding upper 90% CIs values lower than 10 ms. Point estimates of Δ QTcF for the placebo treatment in Cycle 3 were generally lower than

those observed for the Δ QTcF of pertuzumab. As a result, $\Delta\Delta$ QTcF values may have been inflated due to the over-correction associated to the Δ QTcF of placebo. The baseline QTcF in the placebo group was slightly higher compared to that in the pertuzumab group. Overall, the above effects on QTcF interval in patients were not deemed clinically relevant.

Table 6: Summary Statistics of Δ QTcF (ms) and $\Delta\Delta$ QTcF (ms) in Cycle 1

Treatment	Summary Statistic	Time Points		
		Immediately post-infusion	60-75 mins post-infusion	Day 3
Δ QTcF Pertuzumab	N	18	17	17
	Mean	2.36	0.34	-3.54
	SD	9.81	12.93	12.83
	Median	2.92	-2.17	-2.83
	Range	-16.67 : 20.17	-16.00 : 29.83	-26.83 : 16.33
Δ QTcF Placebo	N	15	15	15
	Mean	9.32	6.69	0.54
	SD	12.99	10.87	15.69
	Median	12	8.67	-1
	Range	-21.92 : 34.83	-20.58 : 18.83	-25.58 : 29.50
$\Delta\Delta$ QTcF	Mean	-6.96	-6.35	-4.08
	90% CI	-13.69 : -0.23	-13.57 : 0.88	-12.64 : 4.48

(Source: Sponsor's Study Report wo20698-pkpd-qtc-substudy, Table 7. on Page 25)

Table 7: Summary Statistics of Δ QTcF (ms) and $\Delta\Delta$ QTcF (ms) in Cycle 3

Treatment	Summary Statistic	Time Points			
		30 mins pre-infusion	15 mins pre-infusion	Immediately post-infusion	60-75 mins post-infusion
Δ QTcF Pertuzumab	N	17	17	17	17
	Mean	-3.80	-5.51	2.02	-4.45
	SD	15.29	14.31	13.17	15.19
	Median	-1.33	-8.17	-1	-7.5
	Range	-28.67 : 27.50	-24.83 : 25.50	-15.17 : 23.33	-28.83 : 25.83
Δ QTcF Placebo	N	15	15	15	15
	Mean	-8.88	-9.46	-6.39	-4.41
	SD	21.86	17.94	21.5	21.55
	Median	-7.67	-8.83	-5.92	-6.92
	Range	-48.00 : 33.67	-40.33 : 18.00	-38.67 : 44.67	-38.00 : 46.33
$\Delta\Delta$ QTcF	Mean	5.07	3.95	8.41	-0.04
	90% CI	-6.14 : 16.29	-5.74 : 13.63	-2.58 : 19.39	-11.12 : 11.04

(Source: Sponsor's Study Report wo20698-pkpd-qtc-substudy, Table 8. on Page 25)

Reviewer's Comments: The sponsor's exploratory analyses are reasonable. The reviewer performed independent analyses in section 5.2.

3.2.8.2.2 Categorical Analysis

The categorical evaluation of the maximum absolute QTcF intervals indicated that none of the subjects had values >450 ms with the pertuzumab treatment. Similarly, the

maximum QTcF change from baseline did not exceed the clinically significant category of 30 ms for subjects with the pertuzumab treatment and 60 ms for any subject across all treatments.

3.2.8.3 Safety Analysis

Table 8: Incidence of Adverse Events That Could be Associated with Prolongation of Cardiac Repolarization or Proarrhythmia

Adverse Event	Treatment Arm	Patient ID	Number and Percentage
QT Prolongation on ECG	Pertuzumab (n=20)	None	0/20 =0.00%
	Placebo (n=17)	8850, 9250, 9578	3/17 =17.65%
Tachycardia	Pertuzumab (n=20)	9572	1/20 =5.00%
	Placebo (n=17)	9870	1/17 =5.88%
Palpitations	Pertuzumab (n=20)	None	0/20 =0.00%
	Placebo (n=17)	9870	1/17 =5.88%
Syncope	Pertuzumab (n=20)	None	0/20 =0.00%
	Placebo (n=17)	9962	1/17 =5.88%

Source: CSR, Appendix F, Table 12

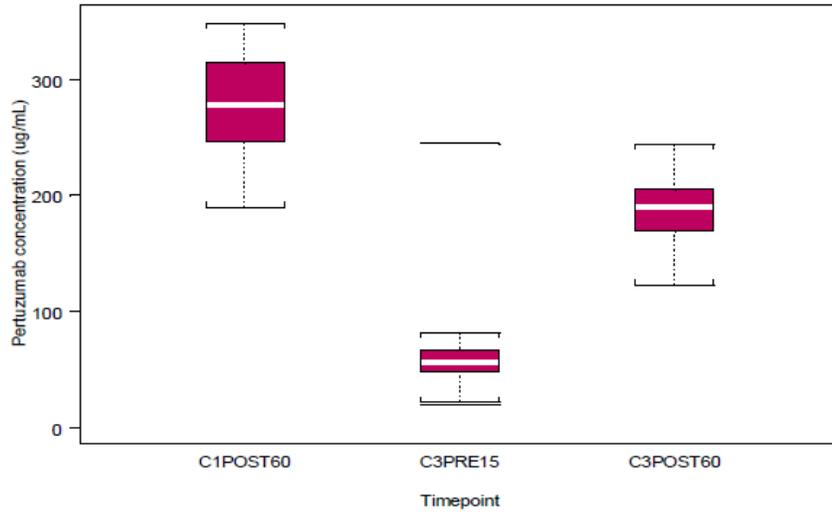
Reviewer's Comments: No relevant differences between treatment arms were reported in AEs presented in Table 8.

3.2.8.4 Clinical Pharmacology

3.2.8.4.1 Pharmacokinetic Analysis

Serum pertuzumab concentrations are presented in Figure 1.

Figure 1: Boxplots of Serum Pertuzumab Concentrations



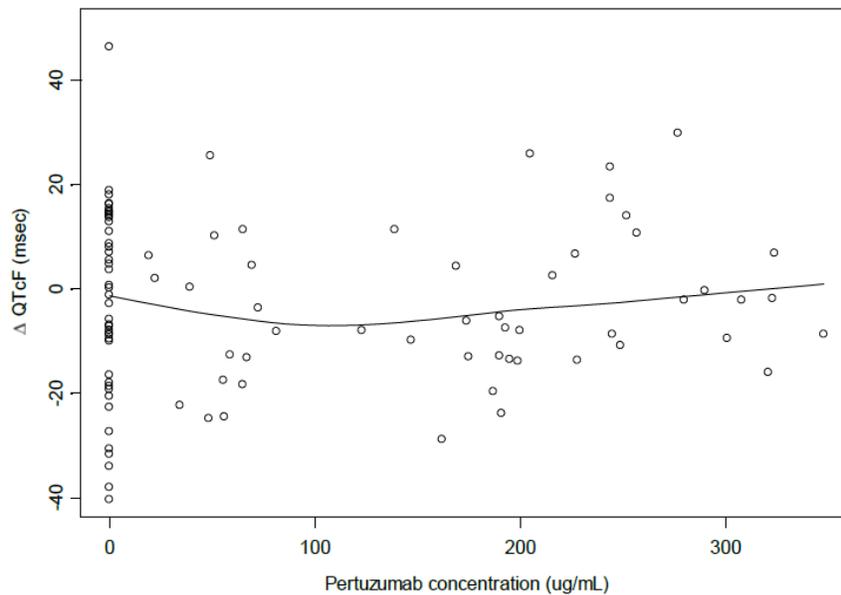
C1POST60: Cycle 1 Day 1 60 minutes post infusion; C3PRE15: Cycle 3 Day 1 15 minutes pre infusion; C3POST60: Cycle 3 Day 1 60 minutes post infusion;

(Source: Sponsor's Study Report wo20698-pkpd-qtc-substudy, Figure 12. on Page 32)

3.2.8.4.2 Exposure-Response Analysis

The concentration- Δ QTcF plot shows the lack of any apparent relationship between serum pertuzumab concentrations and Δ QTcF (Figure 2).

Figure 2: Scatter-Smooth of Concentration versus Δ QTcF, Both Cycles



(Source: Sponsor's Study Report wo20698-pkpd-qtc-substudy, Figure 16. on Page 35)

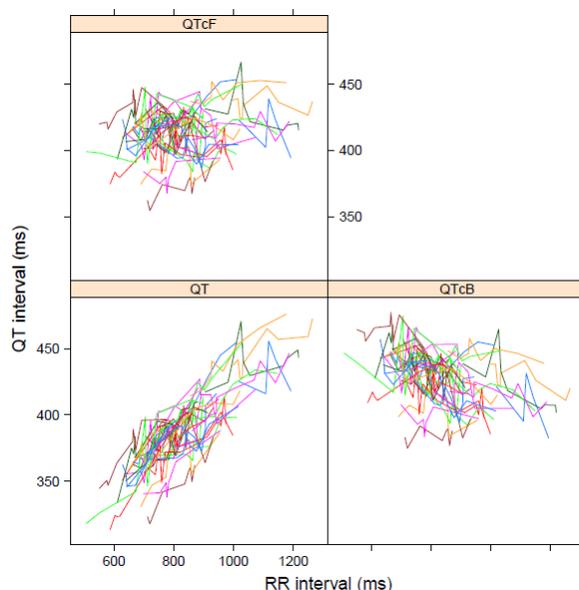
Reviewer's Comments: The reviewer performed independent analyses to explore the relationship between pertuzumab concentration and $\Delta QTcF$ or $\Delta\Delta QTcF$ (see section 5.3). Consistent with the sponsor's results, the slope of the concentration-response relationship is relatively flat and non-significant from zero.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Ideally, a good correction QTc would result in no relationship of QTc and RR intervals. The relationship between different correction methods and RR is presented in Figure 3. QTcF was used for further analysis.

Figure 3: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



4.2 STATISTICAL ASSESSMENTS

4.2.1 QTc Analysis

4.2.1.1 The Primary Analysis for Pertuzumab

The reviewer used mixed model to analyze the $\Delta\Delta QTcF$ effect. The analysis results are listed in Table 9. There was no moxifloxacin arm in the study so the assay sensitivity can not be established.

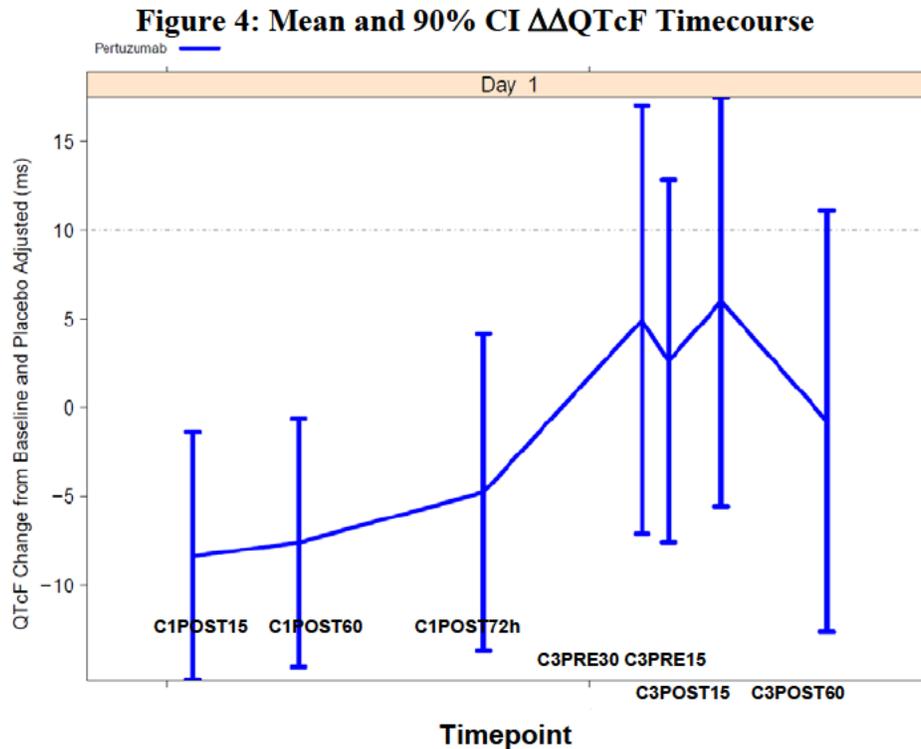
Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = Pertuzumab

Time	Δ QTcF: pertuzumab			Δ QTcF: placebo			$\Delta\Delta$ QTcF		
	N	LS Mean	SD	N	LS Mean	SD	LS Mean	SD	90% CI
C1POST15	19	2.0	2.2	14	10.3	3.4	-8.4	4.1	(-15.4, -1.4)
C1POST60	18	0	3.0	14	7.6	2.9	-7.6	4.1	(-14.6, -0.6)
C1POST72h	18	-3.7	3.0	14	1.1	4.3	-4.8	5.2	(-13.7, 4.2)
C3PRE30	18	-4.0	3.5	14	-9.0	6.1	4.9	7.0	(-7.1, 17.0)
C3PRE15	18	-6.2	3.3	14	-8.8	4.9	2.6	6.0	(-7.6, 12.8)
C3POST15	18	0.7	3.3	14	-5.3	5.8	6.0	6.7	(-5.5, 17.5)
C3POST60	18	-4.8	3.5	14	-4.0	6.0	-0.7	6.9	(-12.6, 11.1)

C1POST15, C1POST60, C1POST72h represents samples collected in cycle 1 at 15 min, 60 min and 2 h post-dose respectively. C3PRE30 and C3PRE15 represents samples collected in cycle 3 at 15 min and 30 min pre-dose, respectively. C3POST15 and C3POST60 represents samples collected in cycle 3 at 15 min and 60 min post-dose respectively

4.2.1.2 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for pertuzumab treatment groups.



4.2.1.3 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 10: Categorical Analysis for QTcF

Treatment Group	Total N		Value \leq 450 ms		450 ms<Value \leq 480 ms	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
Pertuzumab	21	175	21 (100%)	175 (100%)	0 (0%)	0 (0%)
Placebo	16	136	13 (81.2%)	129 (94.9%)	3 (18.8%)	7 (5.1%)

Table 11 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 11: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Pertuzumab	19	127	19 (100%)	127 (100%)	0 (0%)	0 (0%)
Placebo	14	98	12 (85.7%)	94 (95.9%)	2 (14.3%)	4 (4.1%)

4.2.2 PR analysis

The outlier analysis results for PR are presented in Table 12.

Table 12: Categorical Analysis of PR

Treatment Group	Total N		Value > 200ms	
	# Subj.	# Obs.	# Subj.	# Obs.
Pertuzumab	21	175	4 (19%)	7 (4%)
Placebo	16	132	2 (12.5%)	4 (3%)

4.2.3 QRS analysis

The outlier analysis results for QRS are presented in Table 13.

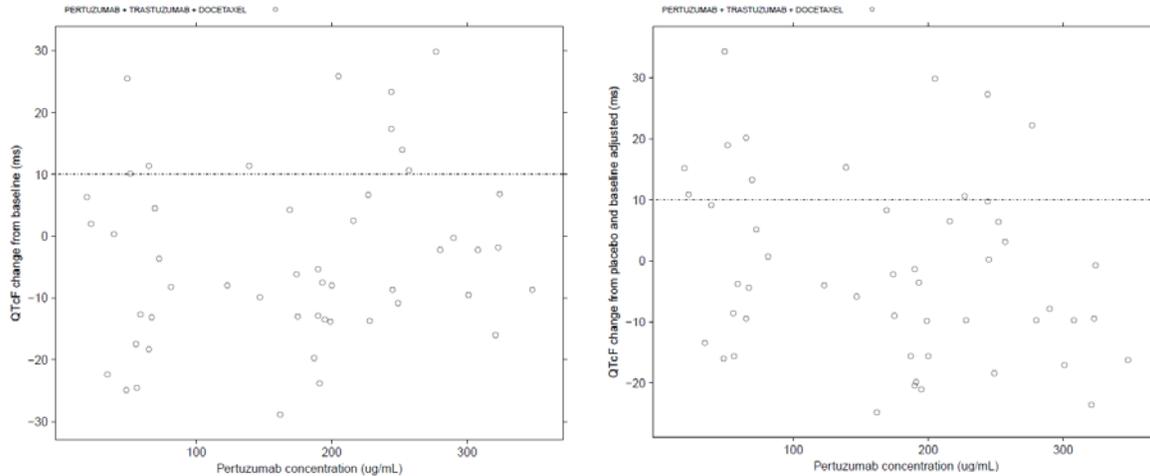
Table 13: Categorical Analysis of QRS

Treatment Group	Total N		Value > 110ms	
	# Subj.	# Obs.	# Subj.	# Obs.
Pertuzumab	21	175	0 (0%)	0 (0%)
Placebo	16	136	1 (6.2%)	9 (6.6%)

4.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between Δ QTcF (or $\Delta\Delta$ QTcF) and pertuzumab concentrations is visualized in Figure 5 with no evident positive exposure-response relationship.

Figure 5: Δ QTcF (left) and $\Delta\Delta$ QTcF (right) vs. Pertuzumab Concentration



4.4 CLINICAL ASSESSMENTS

4.4.1 Safety assessments

No seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

4.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 19 % of the ECGs were annotated in the primary lead II and rest in multiple leads, with less than 0.5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

4.4.3 PR and QRS Interval

Four subjects in the pertuzumab arm had a PR greater than 200 ms. In two subjects the effect was observed before starting the infusion in cycle 3 day 1. None of the post-pertuzumab values were > 40 % of baseline values.

None of the subjects under pertuzumab had a QRS > 110 ms at baseline.

5 APPENDIX

5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

ABSORPTION	Absolute/Relative Bioavailability	NA; administered as an IV infusion
	T _{max}	NA; administered as an IV infusion
DISTRIBUTION	V _d	The mean value for V _d is 2.9 L (1.9 % RSE)
	% Bound	NA
ELIMINATION	Route	Intercellular lysosomal degradation via the FcRn-IgG recycling pathway
	Terminal t _{1/2}	The terminal t _{1/2β} is ~16.9 days
	CL	Systemic serum CL is 0.224 L/day (2.9% RSE)
INTRINSIC FACTORS	Age	Based on the interim PPK model, age was not a significant covariate to explain interpatient variability in pertuzumab for V _d or CL, suggesting that there is no correlation between pertuzumab exposure and age. Age: Median = 57 years (32–83 years)
	Gender	The interim PPK model did not include gender as a covariate because the current indications of interest are breast and ovarian cancers (TOC2689g, BO16934). However, concentration–time profiles do suggest that there is a gender effect on V _d and CL, with males having lower exposure at similar doses (TOC2682g, TOC2572g).
	Race	Based on the interim PPK model, race is not a significant covariate to explain interindividual variability in pertuzumab V _d or CL, suggesting that there is no correlation between pertuzumab exposure and race.
	Hepatic and Renal Impairment	The safety, efficacy, and pharmacokinetics of pertuzumab have not been studied in patients with renal or hepatic impairment.
	Other Factors	Based on the interim PPK model, body weight was the most significant covariate to explain interpatient variability for V _d . Serum albumin, alkaline phosphatase, and body weight were the most significant covariates to explain interpatient variability for CL.

CL = total clearance of drug; IV = intravenous; NA = not applicable; PPK = population PK; RSE = relative standard error; t_{1/2} = half-life; V_d = volume of distribution of the central compartment.

EXTRINSIC FACTORS	Drug Interactions	<ul style="list-style-type: none"> • Gemcitabine (TOC3258g) No clinically relevant pharmacokinetic interaction between pertuzumab and gemcitabine has been observed with concurrent administration. • Docetaxel (BO17021) Pertuzumab did not appear to alter the PK of docetaxel. Pertuzumab PK was similar to the PK obtained from single-agent pertuzumab studies. • Capecitabine (BO17003) Pertuzumab did not appear to alter the PK of capecitabine. Pertuzumab PK was similar to the PK obtained in single-agent pertuzumab studies.
	Food Effects	NA; pertuzumab is administered as an IV infusion
EXPECTED HIGH-CLINICAL-EXPOSURE SCENARIO	There has been no dose-limiting toxicity observed for pertuzumab up to doses of 1050 mg. At steady state, a dose of 1050 mg has a 2.5-fold greater exposure than the therapeutic dose of 420 mg.	

IV=intravenous; NA=not applicable.

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/s/

JIANG LIU
03/20/2012

NITIN MEHROTRA
03/20/2012

MONICA L FISZMAN
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03/20/2012