CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125409Orig1s113

Trade Name:	PERJETA
Generic or Proper Name:	pertuzumab
Sponsor:	Genentech, Inc.
Approval Date:	December 20, 2017

Indication:	Perjeta is a HER2/neu receptor antagonist indicated for:
	• Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
	• Use in combination with trastuzumab and chemotherapy as
	  ○ neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.
	  ○ adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s113

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125409/S-113
BLA 125409/S-118

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
REQUIREMENT and COMMITMENT

Genentech, Inc.
Attention: Ardelle (Jia) Ying, MD, PhD
Program Director, Global Regulatory Affair (PDR-PM)
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Ying:

Please refer to your Supplemental Biologics License Applications (sBLAs), dated February 28, 2017 (S-113), and July 28, 2017 (S-118), and your amendments, submitted under section 351(a) of the Public Health Service Act for Perjeta® (pertuzumab), 20 ml vial containing 420 mg, intravenous injection.

Prior Approval Supplemental Biologics Application 113 (S-113) provides for the fulfillment of Postmarketing Requirement (PMR) #2446-2 and Postmarketing Commitment (PMC) #2446-4, as listed in the Accelerated Approval letter for BLA 125409/S-051 dated September 30, 2013.

Prior Approval Supplemental Biologics Application 118 (S-118) provides for a new indication for Perjeta® for the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence. This prior approval supplement also provides for fulfillment of PMR #2446-1, as listed in the Accelerated Approval letter for BLA 125409/S-051 dated September 30, 2013.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the prescribing information, text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on November 14, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125409/ S-113 and S-118**." Approval of this submission by FDA is not required before the labeling is used.

SUBPART E FULFILLED

We approved this BLA under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 601.41 for the following postmarketing requirement:

2446-1 Submit the final efficacy (disease-free survival) and safety results from Trial BO25126 (APHINITY) as defined in your protocol and Statistical Analysis Plan (SAP).

REQUIRED PEDIATRIC ASSESSMENTS

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

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated February 28, 2017, containing the final reports for the following postmarketing requirement and commitment listed in the September 30, 2013, approval letter for BLA 125409/S-051.

2446-2 Conduct a clinical trial to further assess the cardiac safety of neoadjuvant anthracycline/taxane-based chemotherapy regimens when administered in combination with neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early stage HER2-positive breast cancer.

2446-4 Conduct a study of pre-treatment molecular sub-typing of tumors from patients treated in the post-marketing cardiac safety trial (PMR 2) and submit an exploratory analysis of the relationship of pathological complete response with the different tumor sub-types.

We have reviewed your submission and conclude that the above requirement and commitment were fulfilled.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our September 30, 2013, supplemental approval letter.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3312-1 Submit the overall survival (OS) data and analysis with a final report from the clinical trial APHINITY BIG 4-11/BO25126/TOC4939g clinical trial entitled “A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer.”

The timetable you submitted on December 6, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2011
Final Protocol Submission:	02/2015
Trial Completion:	12/2023
Final Report Submission:	06/2024

Submit clinical protocols to your IND 9900 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

JULIA A BEAVER
12/20/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s113

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PERJETA® (pertuzumab) injection, for intravenous use
Initial U.S. Approval: 2012

WARNING: LEFT VENTRICULAR DYSFUNCTION and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Left Ventricular Dysfunction: PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function. (2.3, 5.1, 6.1)**
- **Embryo-fetal Toxicity: Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception. (5.2, 8.1, 8.3)**

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

Indications and Usage (1.2)	12/2017
Dosage and Administration (2.1, 2.2, 2.3)	12/2017
Warnings and Precautions (5.1, 5.3, 5.4)	12/2017

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

PERJETA is a HER2/neu receptor antagonist indicated for:

- Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. (1.1)
- Use in combination with trastuzumab and chemotherapy as
  - neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. (1.2, 2.2, 14.2)
  - adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence (1.2, 2.2, 14.3)

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

- **For intravenous infusion only.** Do not administer as an intravenous push or bolus. (2.4)
- HER2 testing: Perform using FDA-approved tests by laboratories with demonstrated proficiency. (2.1)
- The initial PERJETA dose is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion. (2.2)
- MBC: Administer PERJETA, trastuzumab, and docetaxel by intravenous infusion every 3 weeks. (2.2)
- Neoadjuvant: Administer PERJETA, trastuzumab, and chemotherapy by intravenous infusion preoperatively every 3 weeks for 3 to 6 cycles. (2.2)
- Adjuvant: Administer PERJETA, trastuzumab, and chemotherapy by intravenous infusion postoperatively every 3 weeks for a total of 1 year (up to 18 cycles). (2.2)

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

- Injection: 420 mg/14 mL single-dose vial. (3)

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

PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients. (4)

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

- Infusion-Related Reactions: Monitor for signs and symptoms. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. (5.3)
- Hypersensitivity Reactions/Anaphylaxis: Monitor for signs and symptoms. If a severe hypersensitivity reaction/anaphylaxis occurs, discontinue the infusion immediately and administer appropriate medical therapies. (5.4)

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

Metastatic Breast Cancer

- The most common adverse reactions (> 30%) with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. (6.1)

Neoadjuvant Treatment of Breast Cancer

- The most common adverse reactions (> 30%) with PERJETA in combination with trastuzumab and docetaxel were alopecia, diarrhea, nausea, and neutropenia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and docetaxel when given for 3 cycles following 3 cycles of FEC were fatigue, alopecia, diarrhea, nausea, vomiting, and neutropenia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with docetaxel, carboplatin, and trastuzumab (TCH) were fatigue, alopecia, diarrhea, nausea, vomiting, neutropenia, thrombocytopenia, and anemia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and paclitaxel when given for 4 cycles following 4 cycles of ddAC were nausea, diarrhea, alopecia, fatigue, constipation and headache. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and docetaxel when given for 4 cycles following 4 cycles of FEC were diarrhea, nausea, alopecia, asthenia, constipation, fatigue, mucosal inflammation, vomiting, myalgia, and anemia. (6.1)

Adjuvant Treatment of Breast Cancer

- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and chemotherapy were diarrhea, nausea, alopecia, fatigue, peripheral neuropathy and vomiting. (6.1)

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

---------- USE IN SPECIFIC POPULATIONS ----------

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of PERJETA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: LEFT VENTRICULAR DYSFUNCTION and EMBRYO-FETAL TOXICITY

- **Left Ventricular Dysfunction: PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function *[see Dosage and Administration (2.3), Warnings and Precautions (5.1) and Adverse Reactions (6.1)].***
- **Embryo-fetal Toxicity: Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1) (8.3)].***

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer (MBC)

PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease *[see Dosage and Administration (2.2) and Clinical Studies (14.1)]*.

1.2 Early Breast Cancer (EBC)

PERJETA is indicated for use in combination with trastuzumab and chemotherapy for

- the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer *[see Dosage and Administration (2.2) and Clinical Studies (14.2)]*.
- the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence *[see Dosage and Administration (2.2) and Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens *[see Indications and Usage (1) and Clinical Studies (14)]*. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast cancer by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Recommended Doses and Schedules

The initial dose of PERJETA is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks by a dose of 420 mg administered as an intravenous infusion over 30 to 60 minutes.

When administered with PERJETA, the recommended initial dose of trastuzumab is 8 mg/kg administered as a 90-minute intravenous infusion, followed every 3 weeks by a dose of 6 mg/kg administered as an intravenous infusion over 30 to 90 minutes.

PERJETA, trastuzumab, and taxane should be administered sequentially. PERJETA and trastuzumab can be given in any order. Taxane should be administered after PERJETA and trastuzumab. An observation period of 30 to 60 minutes is recommended after each PERJETA infusion and before commencement of any subsequent infusion of trastuzumab or taxane *[see Warnings and Precautions (5.3)]*.

In patients receiving an anthracycline-based regimen, PERJETA and trastuzumab should be administered following completion of the anthracycline.

Metastatic Breast Cancer (MBC)

When administered with PERJETA, the recommended initial dose of docetaxel is 75 mg/m^2 administered as an intravenous infusion. The dose may be escalated to 100 mg/m^2 administered every 3 weeks if the initial dose is well tolerated.

Neoadjuvant Treatment of Breast Cancer

PERJETA should be administered every 3 weeks for 3 to 6 cycles as part of one of the following treatment regimens for early breast cancer *[see Clinical Studies (14.2)]*:

- Four preoperative cycles of PERJETA in combination with trastuzumab and docetaxel followed by 3 postoperative cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) as given in NeoSphere
- Three or four preoperative cycles of FEC alone followed by 3 or 4 preoperative cycles of PERJETA in combination with docetaxel and trastuzumab as given in TRYPHAENA and BERENICE, respectively
- Six preoperative cycles of PERJETA in combination with docetaxel, carboplatin, and trastuzumab (TCH) (escalation of docetaxel above 75 mg/m^2 is not recommended) as given in TRYPHAENA
- Four preoperative cycles of dose-dense doxorubicin and cyclophosphamide (ddAC) alone followed by 4 preoperative cycles of PERJETA in combination with paclitaxel and trastuzumab as given in BERENICE

Following surgery, patients should continue to receive PERJETA and trastuzumab to complete 1 year of treatment (up to 18 cycles).

Adjuvant Treatment of Breast Cancer

PERJETA should be administered in combination with trastuzumab every 3 weeks for a total of 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy as given in APHINITY. PERJETA and trastuzumab should start on Day 1 of the first taxane-containing cycle *[see Clinical Studies (14.3)]*.

2.3 Dose Modification

For delayed or missed doses, if the time between two sequential infusions is less than 6 weeks, the 420 mg dose of PERJETA should be administered. Do not wait until the next planned dose. If the time between two sequential infusions is 6 weeks or more, the initial dose of 840 mg PERJETA should be re-administered as a 60-minute intravenous infusion followed every 3 weeks thereafter by a dose of 420 mg administered as an intravenous infusion over 30 to 60 minutes.

PERJETA should be discontinued if trastuzumab treatment is discontinued.

Dose reductions are not recommended for PERJETA.

For chemotherapy dose modifications, see relevant prescribing information.

Left Ventricular Ejection Fraction (LVEF):

Assess left ventricular ejection fraction (LVEF) prior to initiation of PERJETA and at regular intervals during treatment as indicated in Table 1. The recommendations on dose modifications in the event of LVEF dysfunction are also indicated in Table 1 *[see Warnings and Precautions (5.1)]*.

Table 1 Dose Modifications for Left Ventricular Dysfunction

<table>
<tr><th></th><th>Pre-treatment LVEF:</th><th>Monitor LVEF every:</th><th colspan="2">Withhold PERJETA and trastuzumab for at least 3 weeks for an LVEF decrease to:</th><th colspan="2">Resume PERJETA and trastuzumab after 3 weeks if LVEF has recovered to:</th></tr>
<tr><td rowspan="2">Metastatic Breast Cancer</td><td rowspan="2">≥ 50%</td><td rowspan="2">~12 weeks</td><td colspan="2">Either</td><td colspan="2">Either</td></tr>
<tr><td><40%</td><td>40%-45% with a fall of ≥10%-points below pre-treatment value</td><td>>45%</td><td>40%-45% with a fall of <10%-points below pre-treatment value</td></tr>
<tr><td rowspan="2">Early Breast Cancer</td><td rowspan="2">≥ 55%*</td><td rowspan="2">~12 weeks (once during neoadjuvant therapy)</td><td colspan="2" rowspan="2"><50% with a fall of ≥10%-points below pre-treatment value</td><td colspan="2">Either</td></tr>
<tr><td>≥50%</td><td><10% points below pre-treatment value</td></tr>
</table>

*For patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines, before starting PERJETA and trastuzumab

Infusion-Related Reactions

The infusion rate of PERJETA may be slowed or interrupted if the patient develops an infusion-related reaction *[see Warnings and Precautions (5.3)]*.

Hypersensitivity Reactions/Anaphylaxis

The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction *[see Warnings and Precautions (5.4)]*.

2.4 Preparation for Administration

Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus. Do not mix PERJETA with other drugs.

Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.
- Withdraw the appropriate volume of PERJETA solution from the vial(s).

- Dilute into a 250 mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag.
- Mix diluted solution by gentle inversion. Do not shake.
- Administer immediately once prepared.
- If the diluted infusion solution is not used immediately, it can be stored at 2ºC to 8ºC for up to 24 hours.
- Dilute with 0.9% Sodium Chloride injection only. Do not use dextrose (5%) solution.

3 DOSAGE FORMS AND STRENGTHS

Injection: 420 mg/14 mL (30 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Left Ventricular Dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within normal limits. If the LVEF declines and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and trastuzumab should be strongly considered *[Dosage and Administration (2.3)*].

In CLEOPATRA, for patients with MBC, PERJETA in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel *[see Clinical Studies (14.1)]*. Left ventricular dysfunction occurred in 4% of patients in the PERJETA-treated group and 8% of patients in the placebo-treated group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in 1% of patients in the PERJETA-treated group and 2% of patients in the placebo-treated group *[see Adverse Reactions (6.1)]*. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

In patients receiving neoadjuvant treatment in NeoSphere, the incidence of LVSD was higher in the PERJETA-treated groups compared to the trastuzumab- and docetaxel-treated group. An increased incidence of LVEF declines was observed in patients treated with PERJETA in combination with trastuzumab and docetaxel. In the overall treatment period, LVEF decline > 10% and a drop to less than 50% occurred in 2% of patients treated with neoadjuvant trastuzumab and docetaxel as compared to 8% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and docetaxel. Left ventricular dysfunction occurred in 0.9% of patients treated with neoadjuvant trastuzumab and docetaxel as compared to 3% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and docetaxel. Symptomatic LVSD occurred in 0.9% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and no patients in the other 3 arms. LVEF recovered to ≥ 50% in all patients.

In patients receiving neoadjuvant PERJETA in TRYPHAENA, in the overall treatment period, LVEF decline > 10% and a drop to less than 50% occurred in 7% of patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 16% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 11%

of patients treated with PERJETA in combination with TCH. Left ventricular dysfunction occurred in 6% of patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 4% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 3% of patients treated with PERJETA in combination with TCH. Symptomatic LVSD occurred in 4% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, 1% of patients treated with PERJETA in combination with TCH, and none of the patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel. LVEF recovered to ≥ 50% in all but one patient.

In patients receiving neoadjuvant PERJETA in BERENICE, in the neoadjuvant period, LVEF decline ≥ 10% and a drop to less than 50% as measured by ECHO/MUGA assessment occurred in 7% of patients treated with PERJETA plus trastuzumab and paclitaxel following ddAC, and 2% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC. Ejection fraction decreased (asymptomatic LVD) occurred in 7% of patients treated with PERJETA plus trastuzumab and paclitaxel following ddAC and 4% of the patients treated with PERJETA plus trastuzumab and docetaxel following FEC in the neoadjuvant period. Symptomatic LVSD (NYHA Class III/IV Congestive Heart Failure) occurred in 2% of patients treated with PERJETA plus trastuzumab and paclitaxel following ddAC and none of the patients treated with PERJETA plus trastuzumab and docetaxel following FEC in the neoadjuvant period.

In patients receiving adjuvant PERJETA in APHINITY, the incidence of symptomatic heart failure (NYHA Class III/IV) with a LVEF decline ≥ 10% and a drop to less than 50% was <1% (0.6% of PERJETA-treated patients vs. 0.2% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 47% of PERJETA-treated patients and 67% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. The majority of the events (86%) were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA Class II) declines in LVEF ≥ 10% and a drop to less than 50% were reported in 3% of PERJETA-treated patients and 3% of placebo-treated patients, of whom 80% of PERJETA-treated patients and 81% of placebo-treated patients recovered at the data cutoff.

PERJETA has not been studied in patients with a pretreatment LVEF value of ≤ 50%, a prior history of CHF, decreases in LVEF to < 50% during prior trastuzumab therapy, or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360 mg/m^2 of doxorubicin or its equivalent.

5.2 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. PERJETA is a HER2/neu receptor antagonist. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy. In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at exposures 2.5 to 20 times the exposure in humans at the recommended dose, based on C_{max}.

Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA. Advise pregnant women and females of reproductive potential that exposure to

PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception can result in fetal harm, including embryo-fetal death or birth defects. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab *[see Use in Specific Populations (8.1, 8.3)]*.

5.3 Infusion-Related Reactions

PERJETA has been associated with infusion reactions *[see Adverse Reactions (6.1)]*. An infusion reaction was defined in CLEOPATRA as any event described as hypersensitivity, anaphylactic reaction, acute infusion reaction, or cytokine release syndrome occurring during an infusion or on the same day as the infusion. The initial dose of PERJETA was given the day before trastuzumab and docetaxel to allow for the examination of PERJETA-associated reactions. On the first day, when only PERJETA was administered, the overall frequency of infusion reactions was 13% in the PERJETA-treated group and 10% in the placebo-treated group. Less than 1% were Grade 3 or 4. The most common infusion reactions (≥ 1.0%) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting.

During the second cycle when all drugs were administered on the same day, the most common infusion reactions in the PERJETA-treated group (≥ 1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting.

In NeoSphere, TRYPHAENA, and APHINITY, PERJETA was administered on the same day as the other study treatment drugs. For APHINITY, infusion-related reactions occurred in 21% of patients on the first day of PERJETA administration (in combination with trastuzumab and chemotherapy) and in 18% of patients in the placebo arm. The incidence of Grade 3-4 National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI - CTCAE v4.0) reactions was 1% for the PERJETA arm and 0.7% for the placebo arm.

Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of PERJETA. If a significant infusion-related reaction occurs, slow or interrupt the infusion, and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions *[see Dosage and Administration (2.2)]*.

5.4 Hypersensitivity Reactions/Anaphylaxis

In CLEOPATRA, the overall frequency of hypersensitivity/anaphylaxis reactions was 11% in the PERJETA-treated group and 9% in the placebo-treated group. The incidence of Grade 3 – 4 hypersensitivity/anaphylaxis reactions was 2% in the PERJETA-treated group and 3% in the placebo-treated group according to NCI - CTCAE v3.0. Overall, 4 patients in the PERJETA-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

In NeoSphere, TRYPHAENA, BERENICE, and APHINITY, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NeoSphere, two patients in the PERJETA- and docetaxel-treated group experienced anaphylaxis. In APHINITY, the overall frequency of hypersensitivity/anaphylaxis was 5% in the PERJETA treated group vs. 4% in the placebo-treated group. The incidence was highest in the PERJETA plus TCH treated group (8%) of which 1% were NCI-CTCAE (v4.0) Grade 3 – 4.

Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis, has been observed in clinical trials with treatment of PERJETA *[see Clinical Trials Experience (6.1)]*. Medications to treat such reactions, as well as emergency

equipment, should be available for immediate use. PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

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

- Left Ventricular Dysfunction *[see Warnings and Precautions (5.1)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.2)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions/Anaphylaxis *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

Metastatic Breast Cancer (MBC)

The adverse reactions described in Table 2 were identified in 804 patients with HER2-positive metastatic breast cancer treated in CLEOPATRA. Patients were randomized to receive either PERJETA in combination with trastuzumab and docetaxel or placebo in combination with trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for patients in the PERJETA-treated group and 11.8 months for patients in the placebo-treated group. No dose adjustment was permitted for PERJETA or trastuzumab. Adverse reactions resulting in permanent discontinuation of all study therapy were 6% in the PERJETA-treated group and 5% for patients in the placebo-treated group. The most common adverse reactions (>1%) that led to discontinuation of all study therapy was left ventricular dysfunction (1% for patients in the PERJETA-treated group and 2% for patients in the placebo-treated group). The most common adverse reactions that led to discontinuation of docetaxel alone were edema, fatigue, edema peripheral, neuropathy peripheral, neutropenia, nail disorder and pleural effusion. Table 2 reports the adverse reactions that occurred in at least 10% of patients in the PERJETA-treated group. The safety profile of PERJETA remained unchanged with an additional 2.75 years of follow-up (median total follow-up of 50 months) in CLEOPATRA.

The most common adverse reactions (> 30%) seen with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. The most common NCI - CTCAE v3.0 Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue. An increased incidence of febrile neutropenia was observed for Asian patients in both treatment arms compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (26%) compared with the placebo-treated group (12%).

Table 2 Summary of Adverse Reactions Occurring in ≥ 10% of Patients on the PERJETA Treatment Arm in CLEOPATRA

Body System/ Adverse Reactions	PERJETA + trastuzumab + docetaxel n=407 Frequency rate %		Placebo + trastuzumab + docetaxel n=397 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions				
Fatigue	37	2	37	3
Mucosal inflammation	28	1	20	1
Asthenia	26	2	30	2
Edema peripheral	23	0.5	30	0.8
Pyrexia	19	1	18	0.5
Skin and subcutaneous tissue disorders				
Alopecia	61	0	60	0.3
Rash	34	0.7	24	0.8
Nail disorder	23	1	23	0.3
Pruritus	14	0	10	0
Dry skin	11	0	4	0
Gastrointestinal disorders				
Diarrhea	67	8	46	5
Nausea	42	1	42	0.5
Vomiting	24	1	24	2
Stomatitis	19	0.5	15	0.3
Constipation	15	0	25	1
Blood and lymphatic system disorders				
Neutropenia	53	49	50	46
Anemia	23	2	19	4
Leukopenia	18	12	20	15
Febrile neutropenia*	14	13	8	7
Nervous system disorders				
Neuropathy peripheral	32	3	34	2
Headache	21	1	17	0.5

Dysgeusia	18	0	16	0
Dizziness	13	0.5	12	0
Musculoskeletal and connective tissue disorders				
Myalgia	23	1	24	0.8
Arthralgia	15	0.2	16	0.8
Infections and infestations				
Upper respiratory tract infection	17	0.7	13	0
Nasopharyngitis	12	0	13	0.3
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	14	1	16	2
Metabolism and nutrition disorders				
Decreased appetite	29	2	26	2
Eye disorders				
Lacrimation increased	14	0	14	0
Psychiatric disorders				
Insomnia	13	0	13	0

* In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

The following clinically relevant adverse reactions were reported in < 10% of patients in the PERJETA-treated group in CLEOPATRA:

Infections and infestations: Paronychia (7% in the PERJETA-treated group vs. 4% in the placebo-treated group)

Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab After Discontinuation of Docetaxel

In CLEOPATRA, adverse reactions were reported less frequently after discontinuation of docetaxel treatment. All adverse reactions in the PERJETA and trastuzumab treatment group occurred in < 10% of patients with the exception of diarrhea (19%), upper respiratory tract infection (13%), rash (12%), headache (11%), and fatigue (11%).

Neoadjuvant Treatment of Breast Cancer (NeoSphere)

In NeoSphere, the most common adverse reactions seen with PERJETA in combination with trastuzumab and docetaxel administered for 4 cycles were similar to those seen in the PERJETA-treated group in CLEOPATRA. The most common adverse reactions (> 30%) were alopecia, neutropenia, diarrhea, and nausea. The most common NCI – CTCAE v3.0 Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, and diarrhea. In this group, one patient permanently discontinued neoadjuvant treatment due to an adverse event. Table 3 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in NeoSphere.

Table 3 Summary of Adverse Reactions Occurring in ≥ 10% in the Neoadjuvant Setting for Patients Receiving PERJETA in NeoSphere

Body System/ Adverse Reactions	Trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab n=108 Frequency rate %		PERJETA + docetaxel n=108 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions								
Fatigue	27	0	26	0.9	12	0	26	1
Mucosal inflammation	21	0	26	2	3	0	26	0
Asthenia	18	0	21	2	3	0	16	2
Pyrexia	10	0	17	0	8	0	9	0
Edema peripheral	10	0	3	0	0.9	0	5	0
Skin and subcutaneous tissue disorders								
Alopecia	66	0	65	0	3	0	67	0
Rash	21	2	26	0.9	11	0	29	1
Gastrointestinal disorders								
Diarrhea	34	4	46	6	28	0	54	4
Nausea	36	0	39	0	14	0	36	1
Stomatitis	7	0	18	0	5	0	10	0
Vomiting	12	0	13	0	5	0	16	2
Blood and lymphatic system disorders								
Neutropenia	64	59	50	45	0.9	0.9	65	57
Leukopenia	21	11	9	5	0	0	14	9
Nervous system disorders								
Dysgeusia	10	0	15	0	5	0	7	0
Headache	11	0	11	0	14	0	13	0
Peripheral Sensory Neuropathy	12	0.9	8	0.9	2	0	11	0
Musculoskeletal and connective tissue disorders								
Myalgia	22	0	22	0	9	0	21	0
Arthralgia	8	0	10	0	5	0	10	0
Metabolism and nutrition disorders								
Decreased appetite	7	0	14	0	2	0	15	0

Psychiatric disorders								
Insomnia	11	0	8	0	4	0	9	0

The following adverse reactions were reported in < 10% of patients receiving neoadjuvant treatment and occurred more frequently in PERJETA-treated groups in NeoSphere: (Ptz=pertuzumab; H=trastuzumab; D=docetaxel)

Blood and lymphatic system disorders: Anemia (7% in the H+D arm, 3% in the Ptz+H+D arm, 5% in the Ptz+H arm and 9% in the Ptz+D arm), Febrile neutropenia (7% in the H+D arm, 8% in the Ptz+H+D arm, 0% in the Ptz+H arm and 7% in the Ptz+D arm)

Nervous system disorders: Dizziness (4% in the H+D arm, 3% in the Ptz+H+D arm, 6% in the Ptz+H arm and 3% in the Ptz+D arm)

Infections and infestations: Upper respiratory tract infection (3% in the H+D arm, 5% in the Ptz+H+D arm, 2% in the Ptz+H arm and 7% in the Ptz+D arm)

Eye disorders: Lacrimation increased (2% in the H+D arm, 4% in the Ptz+H+D arm, 0.9% in the Ptz+H arm, and 4% in the Ptz+D arm)

Neoadjuvant Treatment of Breast Cancer (TRYPHAENA)

In TRYPHAENA, when PERJETA was administered in combination with trastuzumab and docetaxel for 3 cycles following 3 cycles of FEC, the most common adverse reactions (> 30%) were diarrhea, nausea, alopecia, neutropenia, vomiting, and fatigue. The most common NCI-CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, leukopenia, febrile neutropenia, diarrhea, left ventricular dysfunction, anemia, dyspnea, nausea, and vomiting.

Similarly, when PERJETA was administered in combination with docetaxel, carboplatin, and trastuzumab (TCH) for 6 cycles, the most common adverse reactions (> 30%) were diarrhea, alopecia, neutropenia, nausea, fatigue, vomiting, anemia, and thrombocytopenia. The most common NCI-CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, anemia, leukopenia, diarrhea, thrombocytopenia, vomiting, fatigue, ALT increased, hypokalemia, and hypersensitivity.

Adverse reactions resulting in permanent discontinuation of any component of neoadjuvant treatment occurred in 7% of patients receiving PERJETA in combination with trastuzumab and docetaxel following FEC, and 8% for patients receiving PERJETA in combination with TCH. The most common adverse reactions (>2%) resulting in permanent discontinuation of PERJETA were left ventricular dysfunction, drug hypersensitivity, and neutropenia. Table 4 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in TRYPHAENA.

Table 4 Summary of Adverse Reactions Occurring in ≥ 10% of Patients Receiving Neoadjuvant Treatment with PERJETA in TRYPHAENA

Body System/Adverse Reactions	PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel n=72 Frequency rate %		PERJETA + trastuzumab + docetaxel following FEC n=75 Frequency rate %		PERJETA + TCH n=76 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions						
Fatigue	36	0	36	0	42	4
Mucosal inflammation	24	0	20	0	17	1
Pyrexia	17	0	9	0	16	0
Asthenia	10	0	15	1	13	1
Edema peripheral	11	0	4	0	9	0
Skin and subcutaneous tissue disorders						
Alopecia	49	0	52	0	55	0
Rash	19	0	11	0	21	1
Palmar-Plantar Erythrodysaesthesia Syndrome	7	0	11	0	8	0
Dry skin	6	0	9	0	11	0
Gastrointestinal disorders						
Diarrhea	61	4	61	5	72	12
Nausea	53	0	53	3	45	0
Vomiting	40	0	36	3	39	5
Dyspepsia	25	1	8	0	22	0
Constipation	18	0	23	0	16	0
Stomatitis	14	0	17	0	12	0
Blood and lymphatic system disorders						
Neutropenia	51	47	47	43	49	46

Leukopenia	22	19	16	12	17	12
Anemia	19	1	9	4	38	17
Febrile neutropenia	18	18	9	9	17	17
Thrombocytopenia	7	0	1	0	30	12
Immune system disorders						
Hypersensitivity	10	3	1	0	12	3
Nervous system disorders						
Headache	22	0	15	0	17	0
Dysgeusia	11	0	13	0	21	0
Dizziness	8	0	8	1	16	0
Neuropathy peripheral	6	0	1	0	11	0
Musculoskeletal and connective tissue disorders						
Myalgia	17	0	11	1	11	0
Arthralgia	11	0	12	0	7	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	13	0	8	3	11	1
Epistaxis	11	0	11	0	16	1
Cough	10	0	5	0	12	0
Oropharyngeal pain	8	0	7	0	12	0
Metabolism and nutrition disorders						
Decreased appetite	21	0	11	0	21	0
Eye disorders						
Lacrimation increased	13	0	5	0	8	0
Psychiatric disorders						
Insomnia	11	0	13	0	21	0
Investigations						
ALT increased	7	0	3	0	11	4

FEC=5-fluorouracil, epirubicin, cyclophosphamide, TCH=docetaxel, carboplatin, trastuzumab

The following selected adverse reactions were reported in < 10% of patients receiving neoadjuvant treatment in TRYPHAENA: (Ptz=pertuzumab; H=trastuzumab; D=docetaxel; FEC= fluorouracil, epirubicin, and cyclophosphamide; TCH=docetaxel, carboplatin, and trastuzumab)

Skin and subcutaneous tissue disorders: Nail disorder (10% in the Ptz+H+FEC/Ptz+H+D arm, 7% in the FEC/Ptz+H+D arm, and 9% in the Ptz+TCH arm), Paronychia (0% in the Ptz+H+FEC/Ptz+H+D arm, and 1% in both the FEC/Ptz+H+D and Ptz+TCH arms), Pruritus

(3% in the Ptz+H+FEC/Ptz+H+D arm, 4% in the FEC/Ptz+H+D arm, and 4% in the Ptz+TCH arm)

Infections and infestations: Upper respiratory tract infection (8.3% in the Ptz+H+FEC/Ptz+H+D arm, 4.0% in the FEC/Ptz+H+D arm, and 2.6% in the Ptz+TCH arm), Nasopharyngitis (6.9% in the Ptz+H+FEC/Ptz+H+D arm, 6.7% in the FEC/Ptz+H+D arm, and 7.9% in the Ptz+TCH arm)

Neoadjuvant Treatment of Breast Cancer (BERENICE)

In BERENICE, when PERJETA was administered in combination with trastuzumab and paclitaxel for 4 cycles following 4 cycles of ddAC, the most common adverse reactions (> 30%) were nausea, diarrhea, alopecia, fatigue, constipation, peripheral neuropathy and headache. The most common Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, neutrophil count decreased, white blood cell count decreased, anemia, diarrhea, peripheral neuropathy, alanine aminotransferase increased and nausea.

When PERJETA was administered in combination with trastuzumab and docetaxel for 4 cycles following 4 cycles of FEC, the most common adverse reactions (> 30%) were diarrhea, nausea, alopecia, asthenia, constipation, fatigue, mucosal inflammation, vomiting, myalgia, and anemia. The most common Grade 3 – 4 adverse reactions (> 2%) were febrile neutropenia, diarrhea, neutropenia, neutrophil count decreased, stomatitis, fatigue, vomiting, mucosal inflammation, neutropenic sepsis and anemia.

Adverse reactions resulting in permanent discontinuation of any component of neoadjuvant treatment were 14% for patients receiving PERJETA in combination with trastuzumab and paclitaxel following ddAC and 8% for patients receiving PERJETA in combination with trastuzumab and docetaxel following FEC. The most common adverse reactions (>1%) resulting in permanent discontinuation of any component of neoadjuvant treatment were neuropathy peripheral, ejection fraction decreased, diarrhea, neutropenia and infusion related reaction. Table 5 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in BERENICE.

Table 5 Summary of Adverse Reactions Occurring in ≥ 10% of Patients Receiving Neoadjuvant Treatment with PERJETA in BERENICE

Body System/Adverse Reactions	PERJETA + trastuzumab + paclitaxel following ddAC n=199 Frequency rate %		PERJETA + trastuzumab + docetaxel following FEC n=198 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions				
Fatigue	58	1	38	5
Asthenia	19	2	41	0

Mucosal inflammation	22	1	37	4
Pyrexia	15	0	18	0
Edema peripheral	9	0	12	1
Skin and subcutaneous tissue disorders				
Alopecia	62	0	59	0
Rash	14	0	11	0
Dry skin	14	0	10	0
Nail discoloration	15	0	2	0
Palmar-Plantar Erythrodysaesthesia Syndrome	6	0	10	0.5
Gastrointestinal disorders				
Nausea	71	3	69	2
Diarrhea	67	3	69	10
Constipation	35	0.5	38	0.5
Vomiting	23	1	35	4
Stomatitis	25	0	27	5
Dyspepsia	19	0	16	0
Abdominal pain upper	6	0	13	0
Abdominal pain	5	0	10	0
Gastroesophageal reflux disease	12	0	2	0
Blood and lymphatic system disorders				
Anemia	27	3	30	3
Neutropenia	22	12	16	9
Febrile neutropenia	7	7	17	17
Nervous system disorders				
Headache	30	0.5	14	0.5
Dysgeusia	20	0	19	0.5
Neuropathy peripheral	42	3	26	0.5
Paresthesia	15	0	9	0
Dizziness	12	0	8	0
Musculoskeletal and connective tissue disorders				
Myalgia	20	0	33	1
Arthralgia	20	0	21	1
Back pain	10	0	9	0
Pain in extremity	10	0	8	0
Bone pain	12	0.5	5	0
Infections and infestations				
Urinary tract infection	11	1	2	0
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	25	0	19	0
Dyspnea	15	0.5	15	0.5
Cough	20	0.5	9	0
Oropharyngeal pain	10	0	8	0.5
Metabolism and nutrition disorders				
Decreased appetite	20	0	23	0

Eye disorders				
Lacrimation increased	9	0	18	0
Psychiatric disorders				
Insomnia	19	0	13	0
Vascular disorders				
Hot flush	19	0	13	0
Investigations				
White blood cell count decreased	11	4	3	2
Injury, poisoning and procedural complications				
Infusion related reaction	16	1	13	1

ddAC = dose-dense doxorubicin, cyclophosphamide, FEC=5-fluorouracil, epirubicin, cyclophosphamide

The following selected adverse reactions were reported in < 10% of patients receiving neoadjuvant treatment in BERENICE: (Ptz=pertuzumab; H=trastuzumab; P=paclitaxel; ddAC=dose-dense doxorubicin and cyclophosphamide; D=docetaxel; FEC= fluorouracil, epirubicin, and cyclophosphamide)

Skin and Subcutaneous tissue disorders: Pruritus (9% in the ddAC/Ptz+H+P arm, and 8% in the FEC/Ptz+H+D arm), Nail disorder (7% in the ddAC/Ptz+H+P arm, and 10% in the FEC/Ptz+H+D arm)

Infections and infestations: Upper respiratory tract infection (7% in the ddAC/Ptz+H+P arm, and 2% in the FEC/Ptz+H+D arm), nasopharyngitis (7% in the ddAC/Ptz+H+P arm, and 9% in the FEC/Ptz+H+D arm), paronychia (0.5% in the ddAC/Ptz+H+P arm, and 1% in the FEC/Ptz+H+D arm)

Adjuvant Treatment of Breast Cancer (APHINITY)

The adverse reactions described in Table 6 were identified in 4769 patients with HER2-positive early breast cancer treated in APHINITY. Patients were randomized to receive either PERJETA in combination with trastuzumab and chemotherapy or placebo in combination with trastuzumab and chemotherapy.

Adverse reactions resulting in permanent discontinuation of any study therapy were 13% for patients in the PERJETA-treated group and 12% for patients in the placebo-treated group. Adverse reactions resulting in permanent discontinuation of PERJETA or placebo was 7% and 6%, respectively. The most common adverse reactions (>0.5%) resulting in permanent discontinuation of any study treatment were ejection fraction decreased, neuropathy peripheral, diarrhea, and cardiac failure. . Table 6 reports the adverse reactions that occurred in at least 10% of patients in the PERJETA-treated group.

When PERJETA was administered in combination with trastuzumab and chemotherapy, the most common adverse reactions (> 30%) were diarrhea, nausea, alopecia, fatigue, peripheral neuropathy, and vomiting. The most common Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, diarrhea, neutrophil count decreased, anemia, white blood cell count decreased, leukopenia, fatigue, nausea, and stomatitis.

The incidence of diarrhea, all Grades, was higher when chemotherapy was administered with targeted therapy (61% in the PERJETA-treated group vs. 34% in the placebo-treated group), and was higher when administered with non-anthracycline based therapy (85% in the PERJETA-treated group vs. 62% in the placebo-treated group) than with anthracycline based therapy (67%

in the PERJETA-treated group vs. 41% in the placebo-treated group). The incidence of diarrhea during the period that targeted therapy was administered without chemotherapy was 18% in the PERJETA-treated group vs. 9% in the placebo-treated group. The median duration of all Grades diarrhea was 8 days for the PERJETA-treated group vs. 6 days for the placebo-treated group. The median duration of Grade ≥3 diarrhea was 20 days for the PERJETA-treated group vs. 8 days for the placebo-treated group. More patients required hospitalization for diarrhea as a serious adverse event in the PERJETA-treated group (2.4%) than in the placebo-treated group (0.7%).

Table 6 Summary of Adverse Reactions Occurring in ≥ 10% of Patients Receiving Adjuvant Treatment with PERJETA in APHINITY

Body System/ Adverse Reactions	PERJETA + trastuzumab + chemotherapy n=2364 Frequency rate %		Placebo + trastuzumab + chemotherapy n=2405 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions				
Fatigue	49	4	44	3
Mucosal inflammation	23	2	19	0.7
Asthenia	21	1	21	2
Pyrexia	20	0.6	20	0.7
Edema peripheral	17	0	20	0.2
Skin and subcutaneous tissue disorders				
Alopecia	67	<0.1	67	<0.1
Rash	26	0.4	20	0.2
Pruritus	14	0.1	9	<0.1
Dry skin	13	0.1	11	<0.1
Nail disorder	12	0.2	12	0.1
Gastrointestinal disorders				
Diarrhea	71	10	45	4
Nausea	69	2	65	2
Vomiting	32	2	30	2
Constipation	29	0.5	32	0.3
Stomatitis	28	2	24	1
Dyspepsia	14	0	14	0
Abdominal pain	12	0.5	11	0.6
Abdominal pain upper	10	0.3	9	0.2
Blood and lymphatic system disorders				
Anemia	28	7	23	5
Neutropenia	25	16	23	16
Febrile neutropenia*	12	12	11	11
Nervous system disorders				

Dysgeusia	26	0.1	22	<0.1
Neuropathy peripheral	33	1	32	1
Headache	22	0.3	23	0.4
Paresthesia	12	0.5	10	0.2
Dizziness	11	0	11	0.2
Musculoskeletal and connective tissue disorders				
Arthralgia	29	0.9	33	1
Myalgia	26	0.9	30	1
Pain in extremity	10	0.2	10	0.2
Infections and infestations				
Nasopharyngitis	13	<0.1	12	0.1
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	18	<0.1	14	0
Cough	16	<0.1	15	<0.1
Dyspnea	12	0.4	12	0.5
Metabolism and nutrition disorders				
Decreased appetite	24	0.8	20	0.4
Vascular disorders				
Hot flush	20	0.2	21	0.4
Eye disorders				
Lacrimation increased	13	0	13	<0.1
Psychiatric disorders				
Insomnia	17	0.3	17	<0.1
Investigations				
Neutrophil count decreased	14	10	14	10
Injury, poisoning and procedural complications				
Radiation skin injury	13	0.3	11	0.3

* In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

For the adverse reactions that were reported in ≥10% of patients with at least 5% difference between the PERJETA-treated group and the placebo-treated group in APHINITY, the breakdown per chemotherapy regimen is provided: (Ptz=pertuzumab; H=trastuzumab; AC=anthracyclines; TCH=docetaxel, carboplatin, and trastuzumab)

Gastrointestinal disorders: Diarrhea (67% in the Ptz+H+AC chemo arm, 85% in the Ptz+TCH arm, 41% in the Pla+H+AC chemo arm, 62% in the Pla+TCH arm)

Skin and subcutaneous disorders: Rash (26% in the Ptz+H+AC chemo arm, 25% in the Ptz+TCH arm, 21% in the Pla+H+AC chemo arm, 19% in the Pla+TCH arm), Pruritus (14% in the Ptz+H+AC chemo arm, 15% in the Ptz+TCH arm, 9% in the Pla+H+AC chemo arm, 9% in the Pla+TCH arm)

The following clinically relevant adverse reactions were reported in < 10% of patients in the PERJETA-treated group in APHINITY:

Blood and lymphatic system disorders: Leukopenia (9% in the PERJETA-treated group vs. 9% in the placebo-treated group)

Infections and infestations: Upper respiratory tract infection (8% in the PERJETA-treated group vs. 7% in the placebo-treated group), paronychia (4% in the PERJETA-treated group vs. 2% in the placebo-treated group)

Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab After Discontinuation of Chemotherapy

In the APHINITY study, during the targeted treatment alone phase, all adverse reactions in the PERJETA treatment group occurred in < 10% of patients with the exception of diarrhea (18%), arthralgia (15%), radiation skin injury (12%), and hot flush (12%).

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to pertuzumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Patients in CLEOPATRA were tested at multiple time-points for antibodies to PERJETA. 3% (13/389) of patients in the PERJETA-treated group and 7% (25/372) of patients in the placebo-treated group tested positive for anti-PERJETA antibodies. Of these 38 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to the anti-drug antibodies (ADA). The presence of pertuzumab in patient serum at the levels expected at the time of ADA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-pertuzumab antibody development.

In the neoadjuvant period of BERENICE, 0.3% (1/383) of patients treated with PERJETA tested positive for anti-PERJETA antibodies. This patient did not experience any anaphylactic/hypersensitivity reactions.

7 DRUG INTERACTIONS

No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel, paclitaxel, or carboplatin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry and Pharmacovigilance Program

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PERJETA during pregnancy. Encourage women who receive PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception, to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720 or visiting http://www.motherpregnancyregistry.com/.

In addition, there is a pregnancy pharmacovigilance program for PERJETA. If PERJETA is administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA or within 7 months following the last dose of PERJETA in combination with trastuzumab, health

care providers and patients should immediately report PERJETA exposure to Genentech at 1-888-835-2555.

Risk Summary

Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of PERJETA in pregnant women. However, in post-marketing reports, use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures that were 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on C_{max} *[see Data]*. Apprise the patient of the potential risks to a fetus. There are clinical considerations if PERJETA in combination with trastuzumab is used during pregnancy or within 7 months prior to conception *[see Clinical Considerations]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Animal Data

Pregnant cynomolgus 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 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on C_{max}. 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 (2.5 to 20-fold greater than the recommended human dose, based on C_{max}). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights, and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pertuzumab in human milk, the effects on the breastfed infant or the effects on milk production. Published data suggest that human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial

amounts. Consider the developmental and health benefits of breast feeding along with the mother's clinical need for PERJETA treatment and any potential adverse effects on the breastfed child from PERJETA or from the underlying maternal condition. This consideration should also take into account the elimination half-life of pertuzumab and the trastuzumab wash out period of 7 months.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA.

Contraception

Females

Based on the mechanism of action and animal data, PERJETA can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

The safety and effectiveness of PERJETA have not been established in pediatric patients.

8.5 Geriatric Use

In studies in the indicated populations, CLEOPATRA, NeoSphere, TRYPHAENA, BERENICE, and APHINITY, 464 patients who received PERJETA were ≥65 years of age and 47 were ≥75 years of age. The most common (≥10%) Grade 3-4 adverse reactions in both age groups were neutropenia (22% ≥65 years, 23% ≥75 years), febrile neutropenia (12% ≥65 years, 13% ≥75 years), diarrhea (15% ≥65 years, 17% ≥75 years) and anemia (15% ≥75 years).

The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥65 years of age, compared to patients aged < 65 years of age: decreased appetite (13% higher), anemia (7% higher), weight decreased (7% higher), asthenia (7% higher), dysgeusia (7% higher), neuropathy peripheral and hypomagnesemia (both 5% higher).

No overall differences in efficacy of PERJETA were observed in patients aged ≥65 and <65 years of age. There are too few patients aged ≥75 years to draw conclusions on efficacy in this age group.

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of pertuzumab between patients < 65 years (n=306) and patients ≥ 65 years (n=175).

8.6 Renal Impairment

Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 90 mL/min) or moderate (CLcr 30 to 60 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited pharmacokinetic data available *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of pertuzumab.

11 DESCRIPTION

Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2). Pertuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture that may contain the antibiotic, gentamicin. Gentamicin is not detectable in the final product. Pertuzumab has an approximate molecular weight of 148 kDa.

PERJETA injection is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous infusion. Each single use vial contains 420 mg of pertuzumab at a concentration of 30 mg/mL in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pertuzumab targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab augmented anti-tumor activity in HER2-overexpressing xenograft models.

12.3 Pharmacokinetics

Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of pertuzumab was reached after the first maintenance dose.

The population PK analysis suggested no PK differences based on age, gender, ethnicity (Japanese vs. non-Japanese), or disease status (neoadjuvant or adjuvant vs. metastatic setting). Baseline serum albumin level and lean body weight as covariates only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are needed.

No dedicated renal impairment trial for PERJETA has been conducted. Based on the results of the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (CLcr 60 to 90 mL/min, n=200) and moderate renal impairment (CLcr 30 to 60 mL/min, n=71) were similar to those in patients with normal renal function (CLcr greater than 90 mL/min, n=200). No relationship between CLcr and pertuzumab exposure was observed over the range of observed CLcr (27 to 244 mL/min).

12.6 Cardiac Electrophysiology

The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with HER2-positive breast cancer in CLEOPATRA. No large changes in the mean QT interval (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in the

trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the limitations of the trial design.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of pertuzumab.

Studies have not been performed to evaluate the mutagenic potential of pertuzumab.

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six months duration in cynomolgus monkeys.

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

CLEOPATRA (NCT00567190) was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive metastatic breast cancer. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated 1:1 to receive placebo plus trastuzumab and docetaxel or PERJETA plus trastuzumab and docetaxel. Randomization was stratified by prior treatment (prior or no prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) and geographic region (Europe, North America, South America, and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of greater than 12 months before trial enrollment.

PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks thereafter. Patients were treated with PERJETA and trastuzumab until progression of disease, withdrawal of consent, or unacceptable toxicity. Docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for at least 6 cycles. The docetaxel dose could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. At the time of the primary analysis, the mean number of cycles of study treatment administered was 16.2 in the placebo-treated group and 19.9 in the PERJETA-treated group.

The primary endpoint of CLEOPATRA was progression-free survival (PFS) as assessed by an independent review facility (IRF). PFS was defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumor assessment. Additional endpoints included overall survival (OS), PFS (investigator-assessed), objective response rate (ORR), and duration of response.

Patient demographic and baseline characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumor prognostic characteristics, including hormone receptor status (positive 48%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone receptor positive tumors, 45% received prior adjuvant hormonal therapy and 11% received hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or

neoadjuvant trastuzumab.

CLEOPATRA demonstrated a statistically significant improvement in IRF-assessed PFS in the PERJETA-treated group compared with the placebo-treated group [hazard ratio (HR)=0.62 (95% CI: 0.51, 0.75), $p < 0.0001$] and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the PERJETA-treated group vs. 12.4 months in the placebo-treated group) (see Figure 1). The results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS.

Consistent results were observed across several patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52).

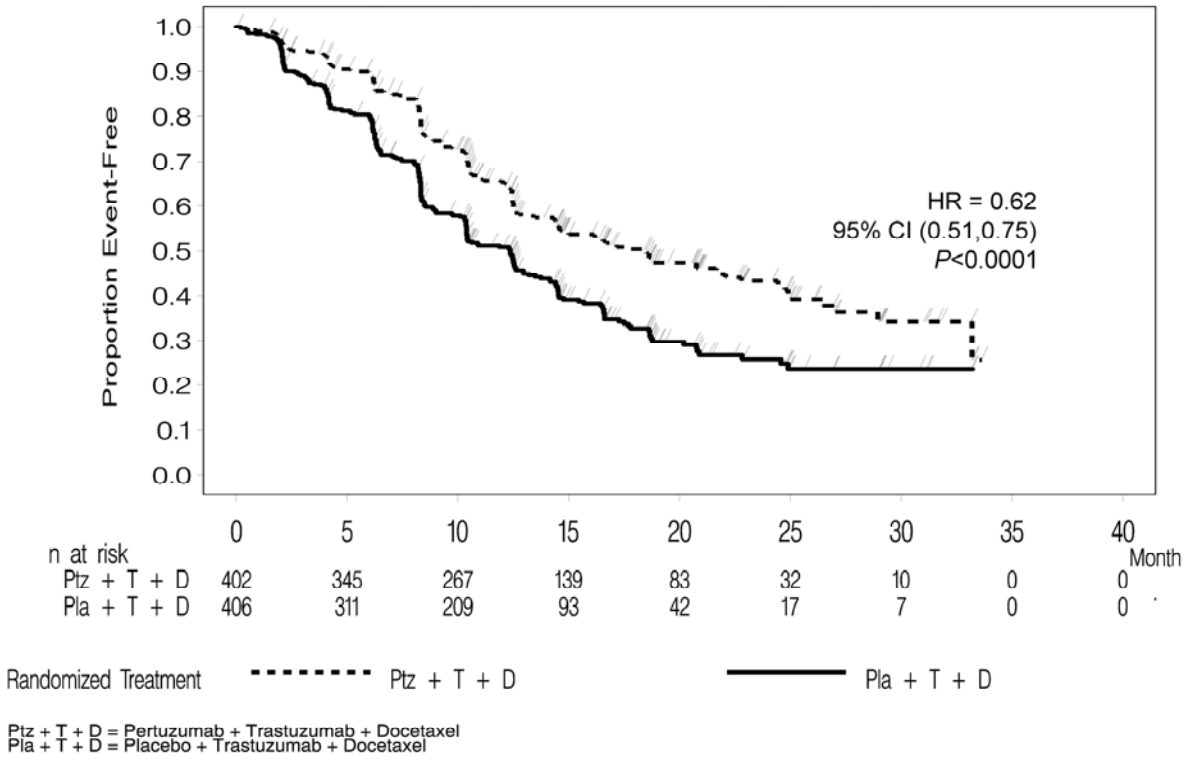
At the time of the final PFS analysis, 165 patients had died, and more deaths had occurred in the placebo-treated group (23.6%) compared with the PERJETA-treated group (17.2%); OS was not mature and interim OS analysis results did not meet the pre-specified stopping boundary for statistical significance. The final analysis of OS (Table 7, Figure 2) was performed when 389 patients had died (221 in the placebo-treated group and 168 in the PERJETA-treated group). A statistically significant OS improvement in favor of the PERJETA-treated group was demonstrated [HR=0.68 (95% CI; 0.56, 0.84), p=0.0002] with an increase in median OS of 15.7 months (median OS of 56.5 months in the PERJETA-treated group vs. 40.8 months in the placebo-treated group). OS results in patient subgroups were consistent with those observed for IRF-assessed PFS with the exception of the subgroup of patients with disease limited to non-visceral metastasis [HR=1.11 (95% CI: 0.66, 1.85)].

Table 7 Summary of Efficacy from CLEOPATRA

Parameter	PERJETA + trastuzumab + docetaxel n=402	Placebo + trastuzumab + docetaxel n=406	HR (95% CI)	p-value
Progression-Free Survival (independent review)				
No. of patients with an event	191 (47.5%)	242 (59.6%)	0.62	
Median months	18.5	12.4	(0.51, 0.75)	< 0.0001
Overall Survival* (final analysis)				
No. of patients who died	168 (41.8%)	221 (54.4%)	0.68	
Median months	56.5	40.8	(0.56, 0.84)	0.0002
Objective Response Rate (ORR, independent review)				
No. of patients analyzed	343	336		
Objective response (CR + PR)	275 (80.2%)	233 (69.3%)		
Complete response (CR)	19 (5.5%)	14 (4.2%)		
Partial Response (PR)	256 (74.6%)	219 (65.2%)		
Median Duration of Response (months)	20.2	12.5		
Difference in ORR	10.8%			
95% CI	(4.2%, 17.5%)			0.0011

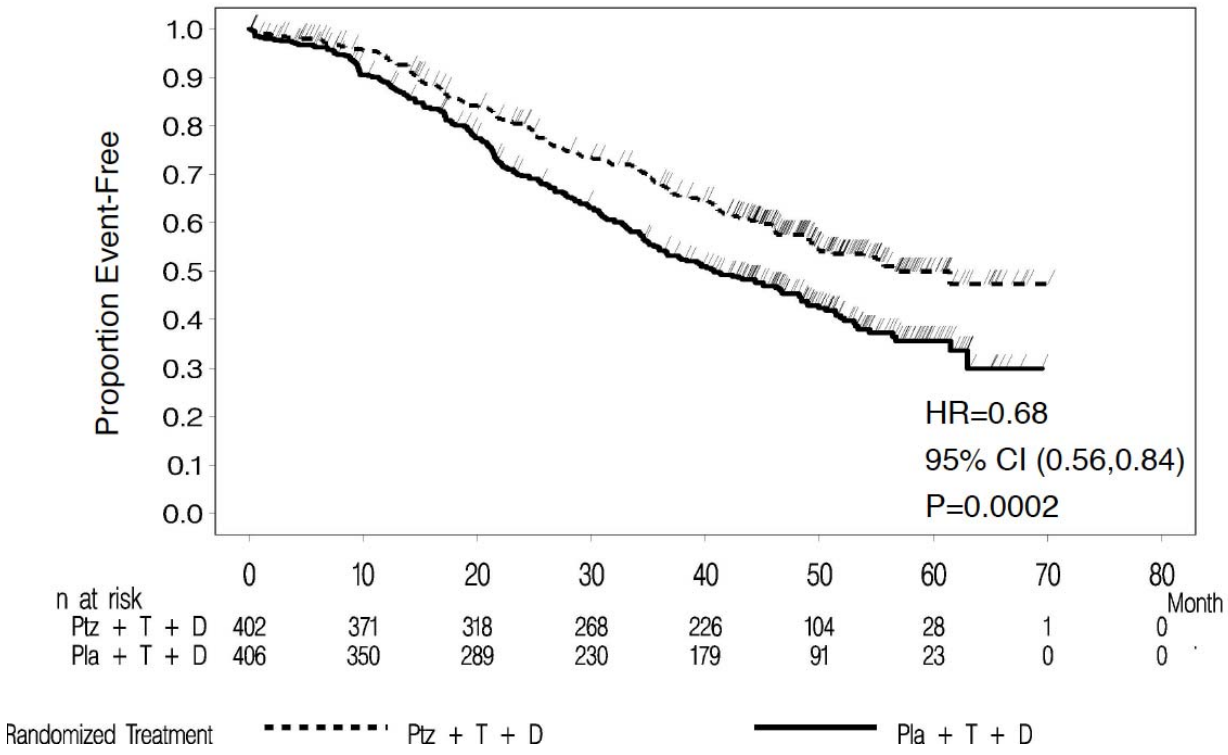
* Final analysis of overall survival, cutoff date Feb 2014
CI=Confidence Interval

Figure 1 Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival for CLEOPATRA



Ptz + T + D = Pertuzumab + Trastuzumab + Docetaxel
Pla + T + D = Placebo + Trastuzumab + Docetaxel

Figure 2 Kaplan-Meier Curve of Overall Survival for CLEOPATRA (Final Analysis)



14.2 Neoadjuvant Treatment of Breast Cancer

NeoSphere

NeoSphere (NCT00545688) was a multicenter, randomized trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel, PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab, or PERJETA plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity.

PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks for 4 cycles. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for 4 cycles. Docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 4 cycles. The docetaxel dose could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. Following surgery all patients received 3 cycles of 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2) (FEC) given intravenously every 3 weeks and trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy. After surgery, patients in the PERJETA plus trastuzumab arm received docetaxel every 3 weeks for 4 cycles prior to FEC.

The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). The FDA-preferred definition of pCR is the absence of invasive cancer in the breast and lymph nodes (ypT0/is ypN0).

Demographics were well balanced (median age was 49 – 50 years old, the majority were Caucasian (71%) and all were female. Overall, 7% of patients had inflammatory cancer, 32% had locally advanced cancer, and 61% had operable cancer. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR-positive).

The efficacy results are summarized in Table 8. Statistically significant improvements in pCR rates by both the study and FDA-preferred definitions were observed in patients receiving PERJETA plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel. The pCR rates and magnitude of improvement with PERJETA were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors.

Table 8 Summary of Efficacy from NeoSphere

Endpoint/Study Population	**H+T**	**Ptz+H+T**	**Ptz+H**	**Ptz+T**
Overall ITT	**N=107**	**N=107**	**N=107**	**N=96**
pCR[1], n **(%)** **[95% CI][2]**	23 (21.5%) [14.1, 30.5]	42 (39.3%) [30.0, 49.2]	12 (11.2%) [5.9, 18.8]	17 (17.7%) [10.7, 26.8]
p-value (with Simes correction for CMH test)[3]		0.0063 (vs. H+T)	0.0223 (vs. H+T)	0.0018 (vs. Ptz+H+T)

Hormone receptor-positive subgroup	N=50	N=50	N=51[4]	N=46
pCR[1], n **(%)** **[95% CI][2]**	6 (12.0%) [4.5, 24.3]	11 (22.0%) [11.5, 36.0]	1 (2.0%) [0.1, 10.5]	4 (8.7%) [2.4, 20.8]
Hormone receptor-negative subgroup	N=57	N=57	N=55[4]	N=50
pCR[1], n **(%)** **[95% CI][2]**	17 (29.8%) [18.4, 43.4]	31 (54.4%) [40.7, 67.6]	11 (20.0%) [10.4, 33.0]	13 (26.0%) [14.6, 40.3]

T=docetaxel, Ptz=PERJETA, H=trastuzumab
CI=Confidence Interval
[1] ypT0/is ypN0 (absence of invasive cancer in the breast and lymph nodes)
[2] 95% CI for one sample binomial using Pearson-Clopper method.
[3] p-value from Cochran-Mantel-Haenszel (CMH) test, with Simes multiplicity adjustment
[4] One patient had unknown hormone receptor status. The patient did not achieve a pCR.

TRYPHAENA
An additional neoadjuvant study (TRYPHAENA, NCT00976989) was conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess cardiac safety in which all arms included PERJETA. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory.

Patients were randomly allocated to receive 1 of 3 neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with PERJETA and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with PERJETA, or 6 cycles of docetaxel, carboplatin, and trastuzumab (TCH) in combination with PERJETA. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and/or PgR positivity.

PERJETA was given by intravenous infusion at an initial dose of 840 mg, followed by 420 mg every 3 weeks. Trastuzumab was given by intravenous infusion at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks. 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2) were given intravenously every 3 weeks for 3 cycles. In the PERJETA plus trastuzumab, docetaxel, and FEC arms, docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 3 cycles with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. However, in the PERJETA plus TCH arm, docetaxel was given intravenously at 75 mg/m^2 (no escalation was permitted) and carboplatin (AUC 6) was given intravenously every 3 weeks for 6 cycles. Following surgery all patients received trastuzumab to complete 1 year of therapy, which was administered intravenously every 3 weeks.

Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian [76%]) and all were female. Overall 6% of patients had inflammatory cancer, 25% had locally advanced cancer and 69% had operable cancer, with approximately half the patients in each treatment group having ER-positive and/or PgR-positive disease.

The pCR (ypT0/is ypN0) rates were 56.2% (95% CI: 44.1%, 67.8%), 54.7% (95% CI: 42.7%, 66.2%), and 63.6% (95% CI: 51.9%, 74.3%) for patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab and docetaxel following FEC, or PERJETA plus TCH, respectively. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 41.0% (95% CI: 25.6%, 57.9%), 45.7% (95% CI: 28.8%, 63.4%), and 47.5% (95% CI: 31.5%, 63.9%) than with hormone receptor-negative tumors: 73.5% (95% CI: 55.6%, 87.1%), 62.5% (95% CI: 45.8%, 77.3%), and 81.1% (95% CI: 64.8%, 92.0%), respectively.

BERENICE

A two-arm non-randomized study (BERENICE, NCT02132949) was conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage HER2-positive breast cancer. HER2 overexpression was defined as a score of 3+ IHC or ISH amplification ratio of 2.0 or greater as determined by a central laboratory.

Patients received 1 of 2 neoadjuvant regimens prior to surgery as follows: 4 cycles of dose dense doxorubicin and cyclophosphamide (ddAC) followed by 4 cycles of PERJETA in combination with trastuzumab and weekly paclitaxel for 12 weeksor 4 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by 4 cycles of PERJETA in combination with trastuzumab and docetaxel. The choice of neoadjuvant treatment regimen was made by the Investigator on a site-specific basis. Dosing for the regimens was as follows:

- PERJETA was given by intravenous infusion at an initial dose of 840 mg, followed by 420 mg every 3 weeks. Trastuzumab was given by intravenous infusion at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks.
- In the ddAC cohort, (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) were given intravenously every 2 weeks (ddAC) for 4 cycles with G-CSF (granulocyte colony stimulating factor) support at investigator discretion, followed by paclitaxel 80 mg/m^2 given intravenously weekly for 12 weeks, with PERJETA and trastuzumab every 3 weeks from the start of paclitaxel for 4 cycles.
- In the FEC cohort, 5-Fluorouracil (5-FU) (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2) were given intravenously every 3 weeks for 4 cycles, followed by docetaxel given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 4 cycles with PERJETA and trastuzumab, and with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated.

Following surgery, all patients received PERJETA and trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy.

The median age of the overall study population was 49 years old (range 21-78), 12% of patients were 65 or older, 83% were Caucasian, and all but one patient was female. Overall 3% of patients had inflammatory cancer, 23% had locally advanced cancer (Stage 3A or greater), 5% were not classified per TNM staging, with approximately two thirds of the patients in each treatment group having ER-positive and/or PgR-positive disease. All patients had an ECOG performance status of 0 or 1.

The pCR (ypT0/is ypN0) rates were 61.8% (95% CI: 54.7, 68.6) and 60.7% (95% CI: 53.6, 67.5) for patients treated with ddAC followed by PERJETA plus trastuzumab and paclitaxel, or FEC followed by PERJETA plus trastuzumab and docetaxel, respectively. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 51.6% (95% CI: 42.6,

60.5%) and 57.3% (95% CI: 48.1, 66.1%) than with hormone receptor-negative tumors: 81.5% (95% CI: 70.0, 90.1%) and 68.0% (95% CI: 56.2, 78.3%), respectively.

14.3 Adjuvant Treatment of Breast Cancer

APHINITY (NCT01358877) was a multicenter, randomized, double-blind, placebo-controlled study conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization. Patients were then randomized to receive PERJETA or placebo, in combination with adjuvant trastuzumab and chemotherapy. Randomization was stratified by the following factors: region, nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.

Investigators selected one of the following anthracycline-based or non-anthracycline-based chemotherapy regimens for individual patients:

- 3 or 4 cycles of FEC (5-FU 500-600 mg/m^2, epirubicin 90-120 mg/m^2, cyclophosphamide 500-600 mg/m^2) or FAC (5-FU 500-600 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500-600 mg/m^2), followed by 3 or 4 cycles of docetaxel (75 mg/m^2 which could be escalated to 100 mg/m^2 every 3 weeks) or 12 cycles of weekly paclitaxel (80 mg/m^2).
- 4 cycles of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 500-600 mg/m^2) or EC (epirubicin 90-120 mg/m^2 and cyclophosphamide 500-600 mg/m^2) either every 3 weeks or every 2 weeks with GCSF support, followed by docetaxel (100 mg/m^2 for 3 cycles or 75 mg/m^2 for first cycle and 100 mg/m^2 for subsequent three cycles, or 75 mg/m^2 for four cycles) or 12 cycles of weekly paclitaxel (80 mg/m^2).
- 6 cycles of docetaxel (75 mg/m^2) in combination with carboplatin (AUC 6)

PERJETA and trastuzumab were administered intravenously every 3 weeks starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (up to 18 cycles) or until recurrence, withdrawal of consent, or unmanageable toxicity.

After completion of chemotherapy, patients received radiotherapy and/or hormone therapy as per investigator's discretion.

The major efficacy outcome of the study was invasive disease-free survival (IDFS), defined as the time from randomization to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Additional efficacy endpoints were IDFS including second primary non-breast cancer, disease-free survival (DFS), and overall survival (OS).

Demographics were generally balanced between the two treatment arms. The median age was 51 years (range 18-86), 13% of patients were 65 or older, and over 99% of patients were female. Sixty-three percent of patients had node-positive disease, 64% had hormone receptor-positive disease, and 71% were Caucasian. All patients had an ECOG performance status of 0 or 1. Seventy-eight percent received an anthracycline containing regimen.

PERJETA-treated patients and placebo-treated patients both received a median number of 18 cycles of anti-HER2 therapy. After a median follow-up of 45.4 months, a statistically significant improvement in IDFS was demonstrated in patients randomized to receive PERJETA compared with patients randomized to receive placebo. The efficacy results from APHINITY are summarized in Tables 9 and 10 and in Figure 3.

Table 9 Efficacy Results from APHINITY

	PERJETA + trastuzumab + chemotherapy N=2400	Placebo + trastuzumab + chemotherapy N=2404
Invasive Disease Free Survival (IDFS)		
Number (%) of patients with event	171 (7.1%)	210 (8.7%)
HR [95% CI] [1]	0.82 [0.67, 1.00]	
p-value (Log-Rank test, stratified[1])	0.047	
3 year event-free rate[2], % [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
IDFS including second primary non-breast cancer		
Number (%) of patients with event	189 (7.9%)	230 (9.6%)
HR [95% CI] [1]	0.83 [0.68, 1.00]	
3 year event-free rate[2], % [95% CI]	93.5 [92.5, 94.5]	92.5 [91.4, 93.6]
Disease Free Survival (DFS)		
Number (%) of patients with event	192 (8.0%)	236 (9.8%)
HR [95% CI] [1]	0.82 [0.68, 0.99]	
3 year event-free rate[2], % [95% CI]	93.4 [92.4, 94.4]	92.3 [91.2, 93.4]
Overall Survival (OS)[3]		
Number (%) of patients with event	80 (3.3%)	89 (3.7%)
HR [95% CI] [1]	0.89 [0.66, 1.21]	
3 year event-free rate[2], % [95% CI]	97.7 [97.0, 98.3]	97.7 [97.1, 98.3]

HR=Hazard Ratio, CI=Confidence Interval

[1] All analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen. Stratification factors are defined according to the randomization data for IDFS.

[2] 3-year event-free rate derived from Kaplan-Meier estimates

[3] Data from first interim analysis

Figure 3 Kaplan-Meier Curve of Invasive Disease Free Survival from APHINITY (ITT Population)

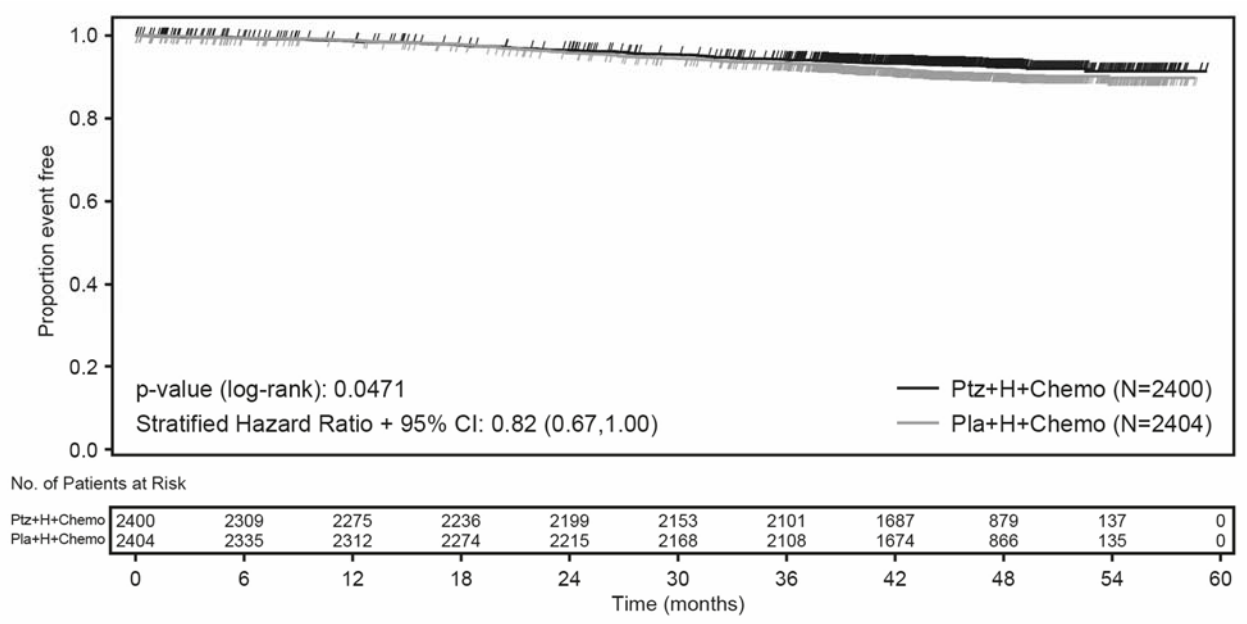


Table 10 Efficacy Results by Baseline Disease Characteristics and Adjuvant Chemotherapy from APHINITY[1]

Population	Number of events/Total N (%)		IDFS at 3 year (%, 95% CI)		Unstratified HR (95% CI)
	PERJETA + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	PERJETA + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	
Hormone Receptor Status					
Negative	71/864 (8.2%)	91/858 (10.6%)	92.8 (90.8, 94.3)	91.2 (89.0, 92.9)	0.76 (0.56, 1.04)
Positive	100/1536 (6.5%)	119/1546 (7.7%)	94.8 (93.5, 95.8)	94.4 (93.1, 95.4)	0.86 (0.66, 1.13)
Nodal Status					
Negative	32/897 (3.6%)	29/902 (3.2%)	97.5 (96.3, 98.4)	98.4 (97.3, 99.0)	1.13 (0.68, 1.86)
Positive	139/1503 (9.2%)	181/1502 (12.1%)	92.0 (90.5, 93.3)	90.2 (88.5, 91.6)	0.77 (0.62, 0.96)
Adjuvant Chemotherapy Regimen					
Anthracycline	139/1865 (7.4%)	171/1877 (9.1%)	93.8 (92.6, 94.8)	93.0 (91.8, 94.1)	0.82 (0.66, 1.03)
Non-Anthracycline	32/535 (6.0%)	39/527 (7.4%)	94.9 (92.6, 96.6)	94.0 (91.5, 95.8)	0.82 (0.51, 1.31)

[1]Exploratory analyses without adjusting multiple comparisons, therefore, results are considered descriptive.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PERJETA injection is supplied as a 420 mg/14 mL (30 mg/mL) single-dose vial containing preservative-free solution. NDC 50242-145-01.

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.

DO NOT FREEZE. DO NOT SHAKE.

17 PATIENT COUNSELING INFORMATION

Left Ventricular Dysfunction

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [*see Warnings and Precautions (5.1)*].

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that exposure to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise women who are exposed to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception that there is a pregnancy exposure registry and a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage these patients to enroll in the MotHER Pregnancy Registry and report their pregnancy to Genentech *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab *[see Use in Specific Populations (8.3)]*.

PERJETA® (pertuzumab)

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No. 1048

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s113

OFFICER/EMPLOYEE LIST

amiOfficer/Employee List

Application: sBLAs 125409/S-113 & S-118; PERJETA (PERTUZUMAB)

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s113

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	BLA 125409, supplements 113 and 118
Priority or Standard	Priority
Submit Date(s)	(supplement 113) 28 February 2017 (supplement 118) 28 July 2017
Received Date(s)	(supplement 113) 28 February 2017 (supplement 118) 28 July 2017
PDUFA Goal Date(s)	(supplement 113) 28 December 2017 (supplement 118) 28 January 2018
Division/Office	DOP1/OHOP/OND
Review Completion Date	Electronic Stamp Date
Established Name	Pertuzumab
Trade Name	PERJETA®
Pharmacologic Class	Monoclonal antibody
Code name	RO4368451, rhuMAb 2C4
Applicant	Genentech
Formulation(s)	Intravenous infusion
Dosing Regimen	The initial Perjeta dose is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion
Applicant Proposed Indication(s)/Population(s)	Use in combination with trastuzumab and chemotherapy as: • neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer • adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Use in combination with trastuzumab and chemotherapy as: • neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer • adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence

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Other	

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IxRS	Interactive Web/Voice Randomization System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Pertuzumab (PERJETA®) is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of human epidermal growth factor receptor 2 protein (HER2). This antibody binds to a different region than trastuzumab, another monoclonal HER2 antibody, and inhibits the ligand-dependent activation of the HER2 signaling pathway through blocking the dimerization of HER2 with other HER3 and other HER family receptors. Additionally, pertuzumab and trastuzumab both activate the immune system through the process of ADCC. Based on preclinical studies conducted by the applicant, the combination of trastuzumab and pertuzumab was shown to have greater antitumor effect when the two agents were combined as compared to either agent alone.

Pertuzumab (PERJETA®) was initially granted regular approval based on results from the CLEOPATRA study on June 8, 2012, for the treatment of patients with HER2-positive metastatic breast cancer (MBC) who had not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Pertuzumab was granted accelerated approval on September 30, 2013, for use in combination with docetaxel and trastuzumab as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm or lymph node positive) as part of a complete treatment regimen for early breast cancer (EBC). This approval was granted mainly based on the results of a phase 2 trial WO20697 (NEOSPHERE). At the time of sBLA125409/51 approval, Study BO25126 (APHINITY), "A Randomized Multicenter, Double-Blind, Placebo-Controlled Comparison of Chemotherapy Plus Trastuzumab Plus Placebo Versus Chemotherapy Plus Trastuzumab Plus Pertuzumab as Adjuvant Therapy in Patients with Operable HER2-Positive Primary Breast Cancer," was underway.

Multiple Post Marketing Requirements (PMR) and Commitments (PMC) were agreed upon with the Agency at the time of the sBLA125409/51 accelerated approval. PMRs and PMCs addressed in the review include:

PMR 2446-1 (PMR#1)

> "Submit the final efficacy (disease-free survival) and safety results from Trial BO25126 (APHINITY) as defined in your protocol and Statistical Analysis Plan (SAP)."

PMR 2446-2 (PMR#2)

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

PMC 2446-4 (PMC#4)

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

On February 28, 2017, the Applicant submitted the results of BERENICE trial (sBLA125409/113) to support the fulfillment of PMR#2 under 505(o) and PMC#4 under section 506B from the September 30, 2013, Accelerated Approval Letter for sBLA 125409/51.

On July 28, 2017, the applicant submitted the results of APHINITY trial (sBLA 125409/118) to support use of Pertuzumab in the adjuvant treatment of patients with HER2-positive early breast cancer (EBC) and to support the fulfillment of the PMR#1 under 21 CFR 601.41, Subpart E from the September 30, 2013 Accelerated Approval Letter for sBLA 125409/51.

The Applicant has proposed the following indications for the pertuzumab (PERJETA®) label (sBLA 125409/118):

> *"PERJETA is a HER2/neu receptor antagonist indicated for:*
>
> - *Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease*
> - *Use in combination with trastuzumab and chemotherapy as*
>   - *Neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm or node positive) as part of a complete treatment regimen for early breast cancer*
>   - *Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence* (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of pertuzumab (PERJETA®) for the following indications:

Use in combination with trastuzumab and chemotherapy as:

- neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer
- adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence

The basis for this recommendation is a favorable benefit-risk profile for pertuzumab when added to trastuzumab and chemotherapy as part of a complete treatment regimen for early breast cancer in patients who have a high risk of disease recurrence. In the randomized, double-blind, placebo-controlled phase 3 APHINITY Study (BO25126), a statistically significant improvement in invasive disease-free survival (IDFS) in treatment with pertuzumab + trastuzumab + chemotherapy as compared to placebo + trastuzumab + chemotherapy was observed (HR=0.82, 95% CI: 0.67, 1.00, p=0.047). The estimated IDFS rate was 94.1% vs. 93.2% at 3 years. This difference is most clinically meaningful and the risk/benefit profile more favorable in those patients who are at high risk of disease recurrence, such as those with node positive disease or those patients with hormone receptor negative disease. (b) (4) Overall survival analysis was not mature at the time of the IDFS analysis.

In the non-randomized, open-label, phase 2 BERENICE Study (sBLA125409/113), the cardiac safety of the combination of pertuzumab and trastuzumab with anthracycline containing regimens was examined and found acceptable. This fulfills PMR#2 under 505(o). In addition, the relationship of pCR with the different molecular tumor subtypes in BERENICE trial (sBLA125409/113) fulfills PMC#4 under section 506B from the September 30, 2013, Accelerated Approval Letter for sBLA 125409/51. The results of BERENICE trial (sBLA125409/113) support the fulfillment PMR#2 under 505(o) and PMC#4 under section 506B from the September 30, 2013, Accelerated Approval Letter for sBLA 125409/51.

The totality of the data submitted, including the APHINITY and BERENICE study results, the known overall survival benefit seen in CLEOPATRA (WO20698/TOC4129g) and the generally tolerable safety profile of pertuzumab supports the conversion of the approval of pertuzumab from accelerated approval under 21 CFR part 601, subpart E to regular approval based on the confirmation of clinical benefit demonstrated in the APHINITY (BO25126) study. Therefore, PMR#1 under 21 CFR 601.41, Subpart E is fulfilled.

In conclusion, all disciplines agreed with approval of pertuzumab, or did not identify any outstanding issues that precluded approval. In summary, pertuzumab for use in combination with trastuzumab and chemotherapy as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence demonstrates a favorable benefit-risk profile with enough evidence to recommend approval.

1.3. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer diagnosis in women in the U.S. with an estimated 252,710 new cases diagnosed in 2017 (National Cancer Institute 2017). It is the second most common cause of cancer related death in women in the U.S., with over 40,000 women expected to die from this disease in 2017 (American Cancer Society 2017).

While many patients are cured of their breast cancer with combined modality therapy including surgery, chemotherapy, radiation therapy, and endocrine therapy where appropriate, there continue to be 20-30% of patients with early breast cancer who develop distant metastatic disease (Kennecke, Yerushalmi et al. 2010). When this occurs, the disease is no longer curable and is likely to lead to death.

Approximately 20% of breast cancers strongly overexpress human epidermal growth factor receptor 2 (HER2) which is a protein that belongs to the HER family. HER2 overexpression in breast cancer is associated with more aggressive disease and an increased recurrence rate (Mitri, Constantine et al. 2012). Despite advances in treatment of patients with HER2-positive early breast cancer with anti-HER2 therapies, there remain a proportion of patients who go on to develop distant recurrences which can be associated with significant morbidity and decline in function. Once HER2-positive breast cancer recurs distantly, it is no longer curable and these patients will eventually die due to metastatic disease.

The addition of pertuzumab to trastuzumab based regimens has demonstrated a statistically significant and clinically meaningful improvement in both progression free and overall survival in the metastatic setting based on results from the CLEOPATRA study. Additionally, the NEOSPHERE study demonstrated that the addition of pertuzumab to standard neoadjuvant therapy was associated with a significantly higher rate of pathological complete response (pCR) which has been associated with improved outcomes such as disease free and overall survival.

The APHINITY study demonstrated a statistically significant improvement in IDFS with the addition of pertuzumab to standard adjuvant chemotherapy and trastuzumab with a 18% reduction in the risk of disease recurrence or death (HR=0.82, 95% CI: 0.67, 1.00, p=0.047). This improvement is most clinically meaningful for those patients at increased risk of disease recurrence. Subgroup analysis indicated that certain high risk subgroups such as those with node positive disease (HR=0.77, 95% CI: 0.62, 0.96) as well as hormone receptor negative disease (HR=0.76, 95% CI: 0.56, 1.04) may also benefit more from therapy.

The addition of pertuzumab to standard chemotherapy increased the incidence of patients with adverse events, including diarrhea, fatigue, anemia, and rash. The incidence of grade 3-4 adverse events was similar in the treatment arms except for diarrhea (10% vs. 4%). More patients

required hospitalization for diarrhea in the pertuzumab treatment arm. The choice of the chemotherapy backbone (anthracycline vs. non-anthracycline) had an impact on the safety profile, including the types and severity of adverse events.

In conclusion, pertuzumab demonstrated a statistically significant improvement in IDFS in a large, randomized, double-blind clinical study. Despite immature OS data, in patients with high risk HER2-positive EBC, this IDFS improvement represents a clinically meaningful benefit. The safety profile is acceptable in the intended population. Appropriate labeling in Warnings and Precautions for left ventricular dysfunction, embryo-fetal toxicity, infusion related reactions, and hypersensitivity, as well as description of increase in diarrhea discussed in section 6, identifies these concerns to prescribers and assists with appropriate management.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2017, it is estimated that breast cancer will be diagnosed in 252,710 women in the U.S. Of these, approximately 15-20% of new diagnoses will have overexpression of HER2, which is associated with increased risk of disease recurrence.	• HER2-positive EBC breast cancer is a serious condition and if it recurs, it can be life-threatening.
Current Treatment Options	• The treatment of early breast cancer is curative in nature with a goal to prevent disease relapse and improve overall survival. Current treatment options for patients with early HER2-positive include surgery, radiation therapy, adjuvant/neoadjuvant chemotherapy with trastuzumab +/- pertuzumab and adjuvant neratinib.	• Despite advances in treatment of patients with HER2-positive EBC there remain a proportion of patients who go on to develop distant recurrence. • There is an unmet need to improve the outcomes of patients with HER2-positive operable breast cancer.
Benefit	• The clinical data from the randomized, double-blind, placebo-controlled Phase 3 Trial (BIG 4-11/BO25126/TOC4939g, APHINITY) in women with operable HER2-positive breast cancer presented in this sBLA demonstrates an improvement in 3 year IDFS for Ptz+H+chemotherapy as compared to PL+H+chemotherapy. The 3 year IDFS rate was 94.1% in the Ptz+H+chemotherapy arm and 93.2% in the PL+H+chemotherapy arm (HR=0.82, 95% CI: 0.67, 1.00,	• The IDFS benefit derived from pertuzumab is statistically significant. • It is most clinically meaningful in patients with high risk for disease recurrence, including, but not limited to those patients with lymph node involvement. • OS is immature.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	p=0.047). Key secondary endpoints of IDFS-SPNBC and DFS, included in the hierarchical testing procedure for control of Type I error, showed numerical improvements with 3 year IDFS-SPNBC 93.5% in the Ptz+H+chemotherapy arm and 92.5% in the PL+H+chemotherapy arm (HR=0.83, 95% CI: 0.68, 1.00) and 3 year DFS of 93.4% in the Ptz+H+chemotherapy arm and 92.3% in the PL+H+chemotherapy arm (HR=0.82, 95% CI: 0.68, 0.99). OS data were not mature at the time of analysis with 96.7% of patients in the Ptz+H+chemotherapy arm and 96.3% of patients in the PL+H+chemotherapy arm alive at the time of analysis (HR=0.89, 95% CI: 0.66, 1.21).	• Supportive secondary endpoint results and subgroup analyses further substantiate the evidence of pertuzumab benefit particularly in higher risk subgroups.
Risk and Risk Management	• The addition of pertuzumab to standard chemotherapy and trastuzumab increased the incidence of adverse events, including diarrhea, fatigue, anemia, and rash. The incidence of grade 3-4 adverse events was similar in the treatment arms except for diarrhea (10% vs. 4%) • In the APHINITY trial, 302 patients age ≥65 years were treated with pertuzumab. Compared with those age <65 years, the older patients had a higher incidence of grade 3-4 TEAEs, SAEs, deaths, deaths due to AEs, all grades of diarrhea, and grade 3-4 diarrhea. There were 30 patients in APHINITY age ≥75 years in the pertuzumab treatment arm. Black patients are another under-represented subgroup in the APHINITY trial, with only 32 Black patients exposed to pertuzumab.	• The safety profile of pertuzumab is acceptable for the intended population. • In view of the enhanced toxicity observed with pertuzumab for patients age ≥65years, and extremely limited data for patients age ≥75 years, caution is indicated. • The safe use of pertuzumab can be managed through accurate labeling and routine oncology care. • No REMS is indicated.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

√	The patient experience data that was submitted as part of the application, include:							Section where discussed, if applicable
	√	Clinical outcome assessment (COA) data, such as:						
			√	Patient reported outcome (PRO)				Sections 8.2.6 and 19.5
			□	Observer reported outcome (ObsRO)				
			□	Clinician reported outcome (ClinRO)				
			□	Performance outcome (PerfO)				
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)						
	□	Patient-focused drug development or other stakeholder meeting summary reports						
	□	Observational survey studies designed to capture patient experience data						
	□	Natural history studies						
	□	Patient preference studies (e.g., submitted studies or scientific publications)						
	□	Other: (Please specify)						
□	Patient experience data that was not submitted in the application, but was considered in this review.							

Laleh Amiri-Kordestani, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Breast cancer is the most common cancer diagnosis in women in the U.S., with an estimated 252,710 new cases diagnosed in 2017 (National Cancer Institute 2017). It is the second most common cause of cancer-related death in women in the U.S., with over 40,000 women expected to die from this disease in 2017 (American Cancer Society 2017).

While many patients are cured of their breast cancer with combined modality therapy including surgery, chemotherapy, radiation therapy, and endocrine therapy where appropriate, there continue to be 20-30% of patients with early breast cancer who develop distant metastatic disease (Kennecke, Yerushalmi et al. 2010). When this occurs, the disease is no longer curable and is likely to lead to death.

Approximately 20% of breast cancers strongly overexpress human epidermal growth factor receptor 2 (HER2) which is a protein that belongs to the HER family. HER2 overexpression in breast cancer is associated with more aggressive disease and an increased recurrence rate (Mitri, Constantine et al. 2012). Despite advances in treatment of patients with HER2-positive EBC, there remain patients who develop distant disease relapse which may be associated with significant morbidity and mortality.

2.2. Analysis of Current Treatment Options

In the adjuvant and neoadjuvant setting, there are multiple agents approved for the treatment of HER2-positive breast cancer. Table 1 below summaries FDA-approved therapies for patients with HER2-positive early breast cancer who are being treated with curative intent.

Table 1. Available Therapies for Patients with HER2-positive Early Breast Cancer in the (Neo)Adjuvant Setting

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]					
Trastuzumab	During and following paclitaxel, docetaxel, or docetaxel/ carboplatin and as a single	2006	Intravenous administration with an initial dose of 4 mg/kg over 90 minutes then at 2 mg/kg as an intravenous infusion over	At 8.3 years of median follow-up, OS was estimated to be 86.9% in the AC→TH arm and 79.4% in the AC→T arm (HR 0.64, 95% CI: 0.55, 0.74, p<0.0001)	Fatigue, infection, hot flashes, anemia, rash, cardiomyopathy, left ventricular dysfunction

	agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens		30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin) One week following the last weekly dose of trastuzumab, administer 6 mg/kg as an IV infusion every 3 weeks. Initial dose of 8 mg/kg as an IV infusion over 90 minutes with subsequent infusions of 6 mg/kg as an IV infusion over 30-90 minutes every 3 weeks		
Neratinib	The extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy	2017	Oral administration of 240 mg (6 tablets) given once daily with food continuously for one year	Estimated iDFS at 24 months 94.2% in the neratinib arm vs. 91.9% in the placebo arm with a HR of 0.66 (95% CI 0.49, 0.90, p=0.008)	Diarrhea, including 40% of patients experiencing Grade 3 diarrhea, nausea, abdominal pain, vomiting, fatigue

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pertuzumab (PERJETA®) was granted regular approval by the FDA on June 8, 2012, for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

On September 30, 2013, pertuzumab was granted accelerated approval by the FDA for use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication was based on demonstration of an improvement in pathological complete response (pCR).

Multiple Post-Marketing Requirements (PMR) and Commitments (PMC) were agreed upon with the Agency at the time of the sBLA125409/51 accelerated approval. PMRs and PMCs addressed in this review include:

PMR 2446-1 (PMR#1)

> "Submit the final efficacy (disease-free survival) and safety results from Trial BO25126 (APHINITY) as defined in your protocol and Statistical Analysis Plan (SAP)."

PMR 2446-2 (PMR#2)

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

PMC 2446-4 (PMC#4)

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

3.2. Summary of Presubmission/Submission Regulatory Activity

May 2001: Initial pre-IND meeting for evaluation of pertuzumab (RO4368451, rhuMAb 2C4) in patients with advanced cancer.

June 2001: Initial IND submission evaluation of pertuzumab (RO4368451, rhuMAb 2C4) in patients with advanced cancer.

May 2011: Type C Meeting to reach agreement on the plans for submission of CLEOPATRA

(WO20698/TOC4129g) data in support of BLA 125409 for the safety and efficacy of pertuzumab in combination with docetaxel and trastuzumab for metastatic HER2 positive breast cancer.

May 26, 2011: Protocol for BIG-04-11/BO25126/TOC4939g APHINITY study submitted for review. There was no special protocol assessment requested for this study. Amendments to this protocol are explained in detail in section 8.1.1.

August 2011: CMC pre-BLA 125409 meeting discussed a quality by design approach for the drug product, stability data, and the statistical plan for qualification of the scale down models.

September 2011: A Type B pre-BLA meeting was held to discuss the efficacy and safety results of CLEOPATRA (WO20698/TOC2129g). During this meeting it was determined that high level safety results and stand-alone datasets would also be submitted for TRYPHAENA (BO22280).

December 2011: BLA 125409 was submitted for the first-line treatment of HER2 positive MBC.

June 2012: FDA approved pertuzumab in combination with trastuzumab and docetaxel for the first-line treatment of HER2-positive MBC.

December 2012: The Agency and Sponsor discussed the Sponsor's current breast cancer portfolio including possible filing of a supplemental application based on pathological complete response (pCR).

December 2012: Supplement 32 for BLA 12509 was submitted to the Agency. This supplement provided overall survival data from the second interim analysis of the CLEOPATRA study (WO20698/TOC2129g) for first-line therapy with docetaxel, trastuzumab and pertuzumab or placebo in the HER2-positive MBC setting.

January 2013: A Type-B pre-sBLA meeting was held to discuss the proposed content and format of an sBLA supporting the proposed indication of: "Pertuzumab in combination with trastuzumab and chemotherapy is indicated for the neoadjuvant treatment of HER2-positive breast cancer patients."

April 2013: Supplement 32 received FDA approval and updated the USPI to include confirmatory OS data in the pertuzumab USPI.

April 2013: Supplement 51 was submitted to BLA 125409 which was a submission of the NEOSPHERE and TRYPHAENA data supporting the neoadjuvant use of pertuzumab based on an increased rate of pCR.

September 12, 2013: Supplement 51 was presented at the ODAC meeting and the panel voted 13 to 0 with one abstention that pertuzumab demonstrated a favorable benefit-risk profile for the neoadjuvant treatment of early breast cancer. FDA reviewers and the ODAC members indicated that they considered the pertuzumab application to be favorable based on the totality of evidence which included:

- Data in the metastatic setting from the CLEOPATRA study demonstrating a statistically significant and clinically robust improvement in overall survival with the addition of pertuzumab to trastuzumab and docetaxel.
- Full accrual of the adjuvant APHINITY trial.
- Evidence that trastuzumab, a similar agent, improved disease-free and overall survival in the adjuvant setting.
- Evidence from the NEOSPHERE study isolating the effect of pertuzumab on improving the pCR rate.
- A large database of patients exposed to pertuzumab in a variety of breast cancer settings demonstrating an acceptable safety profile.

September 30, 2013: PERJETA® was granted accelerated approval for use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. Submission of the final efficacy (disease-free survival) and safety results from the ongoing Trial BO25126 (APHINITY) was stipulated as a post-marketing requirement (PMR) for verification of clinical benefit under subpart E of 21 CFR 601.41 with timelines agreed upon with the Agency. An additional post-marketing requirement under 505 (o)(3) of the Food, Drug and Cosmetic Act (FDCA) was stipulated to further evaluate the cardiac safety of PERJETA® in combination with chemotherapy regimens commonly used in the US. This requirement was to "conduct a clinical trial to further assess the cardiac safety of neoadjuvant anthracycline/taxane-based chemotherapy regimens when administered in combination with neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early stage HER2-positive breast cancer." Additionally, a post-marketing commitment (PMC) was stipulated to "Conduct a study of pretreatment molecular subtyping of tumors from patients in the postmarketing cardiac safety trial (PMR #2) and submit and exploratory analysis of the relationship of pathologic complete response with the different tumor subtypes."

February 28, 2017: Supplement 113 submitted to BLA 125409 with the clinical study report from the BERENICE Trial (WO29217) evaluating PERJETA® in combination with anthracycline-based chemotherapy.

June 13, 2017: Pre-sBLA Type B meeting held to discuss the planned submission of a supplemental biologics license application (sBLA) based on the data from the phase 3 APHINITY study (BIG-04-11/BO25126/TOC4939g). At that time, the Agency expressed concern for the (b) (4) indication proposal and recommended the applicant consider rewording the indication to (b) (4) a high-risk population. The Agency indicated that the applicant could submit with the proposed ITT indication, however should provide justification and rationale for this. It was also indicated that, depending on the discussions regarding the indication during the review process, that external advice from an Oncologic Drug Advisory Committee (ODAC) Meeting may be required. It was additionally discussed that the data from the APHINITY study would be evaluated as fulfillment of the PMR for the neoadjuvant indication of PERJETA®. Agreements for

the applicant's proposed 90-day safety submission were made as well.

July 28, 2017: Supplement 118 submitted to BLA 125409 with the clinical study report from the APHINITY Trial (BIG-04-11/BO25126/TOC4939g) evaluating chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer.

August 14, 2017: Teleconference held to set up a future meeting to discuss possibility of an ODAC Meeting as well as to discuss review timelines including whether this supplement would receive Priority Review.

August 29, 2017: Teleconference held to discuss clarification of the purpose of the upcoming teleconference on September 8, 2017, including the possibility of an ODAC meeting for this supplement should a (b) (4) indication be pursued, as well as to discuss review timelines.

September 8, 2017: Teleconference held to discuss applicant's newly proposed indication wording. Based on discussions with the applicant it was felt that the newly proposed wording for a high-risk population, with final wording to be determined through the course of the review process, would not require external advice from an ODAC meeting.

September 26, 2017: Notification of completion of filing review was given and notification of Priority Review provided. Priority Review was granted as PERJETA® (b) (4)

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was requested to audit sites for sBLA 118, the APHINITY study. The OSI inspected three sites which were chosen based on high enrollment and no previous inspection history. A summary of the site inspections is provided in Table 2.

Table 2. OSI findings for the APHINITY Study (BIG 4-11/BO25126/TOC4939g)

Inspection	Site # and # of Subjects	Inspection Date	Interim Classification
Zhimin Shao 399 Ling-Ling Road, Shanghai 200032 Shanghai China	Site: 250841 Subjects: 94	December 4-8, 2017	NAI
Zbigniew Nowecki Roentgena 5 02-781 Warszawa Poland	Site: 210267 Subjects: 51	December 11-15, 2017	NAI
Jonathan Polikoff Kaiser Permanente San Diego, CA	Site: 230959 Subjects: 25	December 11, 2017-open	VAI*

* The outcome of the inspection of this site is pending. Based on email correspondence received from Lauren Iacono-Connor on 12/19/2017, the preliminary classification appears to be VAI. The site inspector does not think that the inspectional observations placed subjects at undue risk or have significant impact on study outcomes. This reviewer concurs with this assessment.

See Clinical Inspection Summary written by Lauren Iancono-Connors, PhD, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, OSI, for full details.

4.2. Product Quality

Please see the chemistry, manufacturing, and controls (CMC) reviews of the original BLA 125409. The CMC review of BLA 125409 was conducted by the Division of Monoclonal Antibodies (DMA) in the Office of Biotechnology Products/CDER and the Biotech Manufacturing Assessment Branch (BMAB) in the Office of Manufacturing and Product Quality/Office of Compliance/CDER.

The DMA product quality reviewers of BLA 125409 were Dr. Kathryn King (Traditional Elements) and Laurie Graham, MS (Quality by Design). The BMAB reviewers were Drs. Bo Chi (Drug Substance) and Colleen Thomas (Drug Product). Please see the memorandum of review provided by Dr. Kathryn King regarding the immunogenicity assay revalidation submitted as part of supplement 113.

4.3. Clinical Microbiology

Please see the CMC reviews by Drs. Chi and Thomas in the BLA 125409 initial review.

4.4. Devices and Companion Diagnostic Issues

No companion device or diagnostic is included in this application.

5 Nonclinical Pharmacology/Toxicology

Please see the Pharmacology/Toxicology review by Dr. Kimberly Ringgold in the initial BLA 125409 review.

6 Clinical Pharmacology

6.1. **Executive Summary**

In the current submissions, the applicant proposed labeling changes in Sections 6.2 Immunogenicity, 7 Drug Interactions, and 12.3 Pharmacokinetics based on data from trial APHINITY, and a population PK study report 1080205, as well as updated immunogenicity results from trials CLEOPATRA and BERENICE.

It was concluded that the applicant's proposed labeling updates are acceptable. The small percentage of patients in treatment arm with PK data (38 of 2400) precludes the meaningful exposure-response analyses for efficacy or safety. PK analyses suggested that there is no significant drug-drug interaction (DDI) between pertuzumab and trastuzumab or significant impact by pertuzumab on paclitaxel or carboplatin.

6.1.1. **Clinical Pharmacology Findings**

- There is no significant impact of trastuzumab on the PK of pertuzumab.
- There is no significant impact of pertuzumab on the PK of trastuzumab.
- There is no impact of pertuzumab (in combination with trastuzumab) on the PK of paclitaxel or carboplatin.
- No noticed difference in steady-state concentrations of pertuzumab was observed between early BC (EBC) and metastatic BC (MBC) settings.
- No dose adjustments are needed for pertuzumab when administered in combination with trastuzumab and an EBC chemotherapy regimen.
- The updated immunogenicity data suggested that 3.3% (13/389) of patients in the Pertuzumab (PERJETA®)-treated group and 6.7% (25/372) of patients in the placebo group in CLEOPATRA, and 0.3% (1/383) of patients treated with Pertuzumab (PERJETA®) in BERENICE were tested positive for anti-drug antibodies (ADA).

Please refer 16.4 OCP Appendices (Technical documents supporting OCP recommendations) for the details of the clinical pharmacology evaluations.

Primary Reviewer
Xia Huiming, PhD

Team Leader
Pengfei Song, PhD

APPEARS THIS WAY ON ORIGINAL

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The phase 3 APHINITY trial (BIG 4-11/BO25126/TOC4939g), submitted in supplement 118, is the primary basis for evaluation of the safety and efficacy of Pertuzumab for (b) (4) . The phase 2 BERENICE (WO29217) trial, submitted in supplement 113, was to support the cardiac safety, as well as general safety and efficacy of Pertuzumab in combination with trastuzumab and anthracycline/taxane-based chemotherapy regimens in early breast cancer.

Additionally, data from 8 biopharmaceutic studies were submitted to supplement 118 and data from 2 biopharmaceutic studies were submitted to supplement 113 (Table 3).

Table 3 Listing of Clinical Trials Relevant to this sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
BIG 4-11/BO25126/TOC4939g	NCT01358877	A randomized, multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer	Chemotherapy, intravenous, trastuzumab and pertuzumab/placebo were administered every three weeks; chemotherapy was administered every 1, 2 or 3 weeks depending on the regimen used.	IDFS, IDFS-SPNBC, DFS, OS, RFI, and DRFI	One year treatment, follow up for approximately 10 years from the date of randomization of the last patient (8/31/2013)	4805 were randomized	Patients with operable HER2 positive breast cancer	548 centers in 42 countries

		Studies to Support Safety						
WO29217	NCT02132949	A Multicenter, Multinational, Phase II Study to Evaluate Perjeta in Combination with Herceptin and Standard Neoadjuvant Anthracycline-Based Chemotherapy in Patients with HER2-Positive, Locally Advanced, Inflammatory, or Early-Stage Breast Cancer	Chemotherapy, intravenous, trastuzumab and pertuzumab/placebo were administered every three weeks; chemotherapy was administered every 1, 2 or 3 weeks depending on the regimen used.	Cardiac safety: Incidence of NYHA Class III and IV heart failure and the incidence of LVEF decline	One year of treatment, follow up for	401	Patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (with primary tumors >2 cm in diameter or node-positive disease who were scheduled to receive neoadjuvant chemotherapy with a baseline LVEF ≥55%	75 centers in 12 countries

7.2. **Review Strategy**

The clinical and statistical review is based on the data submitted and the clinical study reports for the phase 3 APHINITY trial in the adjuvant setting for operable HER2 positive breast cancer as well as the phase 2 BERENICE study. For the APHINITY study, the efficacy review was conducted by Dr. Lynn Howie and the safety review by Dr. Nancy Scher. The statistical review was conducted by Dr. Lijun Zhang. For the BERENICE study, the review was conducted by Dr. Lynn Howie. Items reviewed included the primary datasets submitted by the applicant, case report forms, selected narratives, study reports for other pertuzumab clinical trials, review of FDA databases regarding the regulatory history for the pertuzumab IND/BLA, and a literature review regarding the role of adjuvant and neoadjuvant therapy for HER2-positive breast cancer.

8 Statistical and Clinical and Evaluation

8.1. **Review of Relevant Individual Trials Used to Support Efficacy**

8.1.1. **APHINITY**

Trial Design

The APHINITY study is a randomized, multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy for patients with operable HER2–positive primary breast cancer. The primary objective of this study was to compare invasive disease free survival (IDFS) (excluding second non-breast cancers) in patients with HER2-positive early breast cancer randomized to chemotherapy plus one year of trastuzumab plus placebo or chemotherapy plus one year of trastuzumab plus pertuzumab.

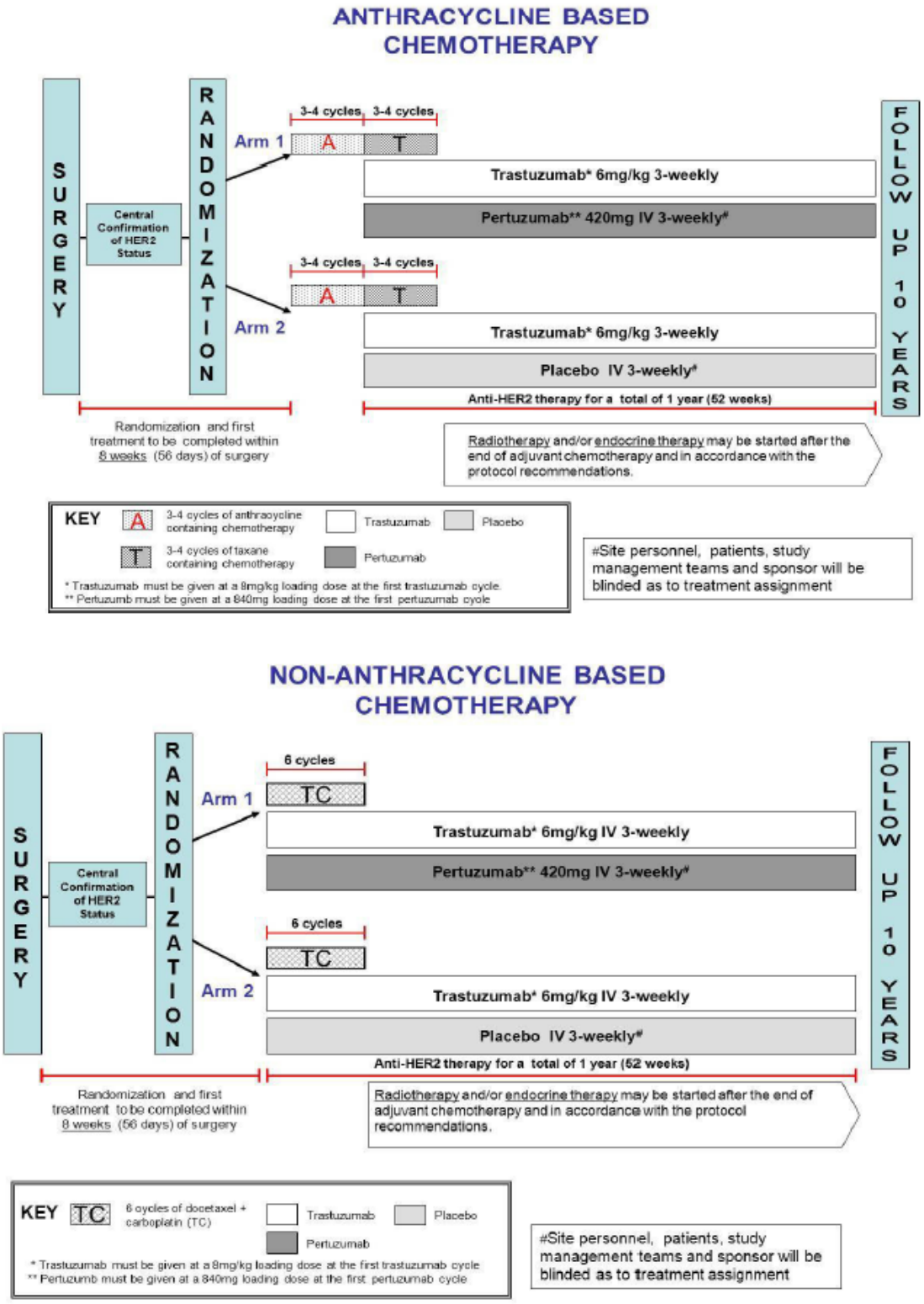
Secondary objectives were to compare IDFS including second primary non-breast cancers, DFS, overall survival (OS), recurrence free interval (RFI), distant recurrence free interval (DRFI), cardiac safety, overall safety, and health related quality of life (HRQoL) in the two treatment arms.

Figure 1 demonstrates the study scheme below. There was one study scheme for anthracycline containing regimens and an alternate for non-anthracycline containing regimens given the need to not concurrently administer anthracyclines with trastuzumab and pertuzumab due to increased risk of cardiotoxicity. Patients were randomized (1:1) using the method of stratified permuted blocks to receive chemotherapy plus trastuzumab plus pertuzumab or chemotherapy plus trastuzumab plus placebo. Randomization was stratified by the following factors:

- Nodal status and tumor size
    - No positive nodes and tumor ≤ 1cm (Not included since Protocol Amendment B)

    - No positive nodes and tumor > 1cm (Not included since Protocol Amendment B)
    - 1-3 positive nodes
    - ≥ 4 positive nodes
- Adjuvant chemotherapy regimen
    - Anthracycline containing regimen
    - Non-anthracycline containing regimen
- Centrally assessed hormone receptor status
    - Both ER and PR negative
    - Either ER positive or PR positive or both positive
- Geographical region:
    - USA
    - Canada/Western Europe/Australia-New Zealand/South Africa
    - East Europe
    - Asia-Pacific
    - Latin America
- Protocol version (Added since Protocol Amendment B)
    - Protocol A
    - Protocol Amendment B

Figure 1 APHINITY Study Schema



Source page 52 Applicant APHINITY CSR

Pertuzumab was administered as an 840 mg intravenous (IV) loading dose followed by 420 mg IV every three weeks. Trastuzumab was administered as an 8 mg/kg IV loading dose followed by 6 mg/kg every three weeks.

The anthracycline and non-anthracycline based chemotherapy regimens were based on published data, clinical guidelines, and routine clinical use.

The study population for this trial included patients with newly diagnosed, operable, primary invasive HER2-positive breast cancer who would be treated with adjuvant systemic chemotherapy following definitive surgery.

Reviewer Comments: *The study design and population appears appropriate. The doses of therapy appear appropriate as well and differences in the chemotherapy backbone regimen were reflective of current global treatment practices for early and locally advanced HER2-positive breast cancer.*

Inclusion Criteria:

1. Age ≥18 years
2. ECOG performance status ≤1
3. Non-metastatic, operable primary invasive breast carcinoma that was:
    a. Histologically confirmed
    b. Adequately excised
    c. Patients must have undergone total mastectomy or breast conserving surgery (BCS).
    d. For patients who underwent BCS, the margins had to be free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor t the line of resection, re-excision could be performed to obtain clear margins. If tumor was still present at the resected margin after re-excisions, the patient had to undergo total mastectomy to be eligible. Patients with margins positive for lobular carcinoma in situ (LCIS) were eligible without additional resection.
    e. For patients who underwent mastectomy, margins had to be free of gross residual tumor. Patients with microscopic margins were eligible.
4. pTNM staging:
    a. Pathological classification of regional lymph nodes: micrometasteses (tumor deposits >0.2 mm) were considered pN1 but isolated tumor cells were considered pN0.
    b. For patients with node-positive disease (pN ≥1), any tumor size except T0.
    c. For patients with node-negative disease (pN0) (applicable to Protocol A ONLY):
        i. Tumor size had to be >1.0 cm

        OR

        ii. For tumor size between >0.5 cm and ≤1.0 cm, at least one of the following features had to be present:

1. Histologic/nuclear grade 3 or
2. Negative for ER and PgR or
3. Age <35 years

iii. Enrollment of patients of node-negative tumors ≤1.0 cm were limited to <10% of the total number of randomized patients.

d. For multifocal disease (the presence of two or more tumor foci within a single quadrant), or multicentric disease (the presence of two or more tumor foci within different quadrants of the same breast), the size of the largest invasive tumor was used to determine the T stage.
e. Known hormone receptor status (ER and PgR)
f. The interval between definitive surgery for breast cancer and the first dose of chemotherapy had to be no more than 8 weeks (56 days). All procedures, including randomization, had to occur by this time. The first cycle of chemotherapy had to be administered within 7 days of randomization or day 56 whichever occurred first.
g. Baseline LVEF of ≥55% measured by ECHO (preferred) or MUGA scan.
h. HER2-positive breast cancer confirmed by a central laboratory and defined as:
    i. IHC 3+ in >10% immunoreactive cells or c-erbB2 gene amplification by in situ hybridization [ISH] (ratio of c-erbB2 gene signals to centromere 17 signals ≥2).
        1. Availability of formalin fixed paraffin embedded (FFPE) tissue block with at least 5 mm of invasive tumor, and wherever possible, a minor component of non-neoplastic breast tissue for central confirmation of HER2 eligibility, hormone receptor status, and biomarker evaluation was mandatory (a minimum of 4 and up to 7 x 1 mm-cores were taken for translational research and the block returned to site.
i. Completion of all necessary baseline laboratory and radiologic investigations prior to randomization.
j. Women of childbearing potential and male participants with partners of childbearing potential had to agree to use a highly effective, non-hormonal form of contraception or two effective forms of non-hormonal contraceptive by the patient and/or the partner. Contraception had to continue for the duration of study treatment and for at least 7 months after the last dose of study treatment.
k. Signed informed consent.

Exclusion Criteria:

Patients meeting any of the following criteria were not eligible for this study:

1. Prior invasive breast cancer (ipsi or contralateral).
2. History of non-breast malignancies within 5 years of study entry except the following: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinoma of the skin. Malignancies occurring more than 5 years prior to study entry were permitted if curatively treated with surgery alone.
3. Any “clinical” T4 tumor as defined by TNM, including inflammatory breast cancer.

4. Any node negative tumor (applicable to patients randomized under Protocol Version B onwards).
5. Any previous systemic therapy (e.g., neoadjuvant or adjuvant) for cancer OR radiation therapy for cancer.
    a. Patients with a history of DCIS and/or LCIS were not allowed to enter the study if they had received systemic therapy for its treatment OR radiation therapy to the ipsilateral breast where invasive cancer subsequently developed.
    b. Patients who had their DCIS/LCIS treated with surgery only were allowed to enter the study.
    c. High risk patients who had received chemoprevention drugs were not allowed to participate in the study.
6. Prior use of anti-HER2 therapy (e.g. lapatinib, neratinib, or other tyrosine kinase inhibitors (TKIs) for any reason or other prior biologic or immunotherapy for cancer
7. Concurrent anticancer therapy in another investigational trial including hormone therapy, bisphosphonate therapy, and immunotherapy.
8. Serious cardiac illnesses or medical conditions including but not limited to:
    a. History of documented heart failure or systolic dysfunction (LVEF <50%).
    b. High risk uncontrolled arrhythmias such as atrial tachycardia with a heart rate of ≥100 bpm at rest, significant ventricular arrhythmia (tachycardia), or higher grade atrioventricular (AV) block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block).
    c. Angina pectoris requiring anti-angina medication.
    d. Clinically significant valvular heart disease.
    e. Evidence of transmural infarction on electrocardiogram (ECG).
    f. Poorly controlled hypertension (e.g. systolic >180 mmHg or diastolic >100 mmHg).
9. Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness (e.g., infections or poorly controlled diabetes).
10. Any of the following abnormal laboratory tests immediately prior to randomization:
    a. Serum total bilirubin >1.5 x upper limit of normal (ULN); in cases of knownGilberts syndrome a total bilirubin of 2 x ULN is permitted.
    b. Alanine amino transferase (ALT) and/or aspartate amino transferase (AST) >1.25 x ULN
    c. Alkaline phosphatase (ALP) >2.5 x ULN
    d. Serum creatinine >1.5 x ULN
    e. Total white blood cell count (WBC) <2,500/mm^3 (<2.5 x 10^9/L)
    f. ANC <1,500/mm^3 (<1.5 x 10^9/L)
    g. Platelets <100,000/mm^3 (<100 x 10^9/L)
11. Pregnant or lactating women or women of childbearing potential without a negative pregnancy test (serum), within 7 days of randomization, irrespective of the method of contraception used.

12. Women of childbearing potential or less than one year after menopause (unless surgically sterile) who were unable or unwilling to use the contraceptive measures required by this protocol during and 7 months after the last dose of study medication.
13. Sensitivity to any of the study medications or any of the ingredients or excipients of these medications, including sensitivity to benzyl alcohol.

Reviewer Comments: *The eligibility criteria are acceptable. Of note, after Protocol Amendment B, no additional node negative patients were enrolled as there was a higher rate than anticipated of node negative patients enrolled. As compared to previous trials of adjuvant trastuzumab, there were also smaller tumors enrolled. For example, N9831 initially only enrolled patients with node positive disease, and when node negative patients were enrolled, tumors were to be >2 cm in diameter or high risk as defined by being hormone receptor negative (Romond 2005). In the B31 study, only patients with node positive disease were enrolled (Romond 2012). In the BCIRG-006 study, patients either had node positive disease or at least one of the following factors: tumor size >2 cm, ER and/or PR negative, histologic grade 2-3, or age <35 years. Inclusion of patients with a tumor size >1.0 cm or 0.5 cm to 1 cm with high risk features likely made this a lower risk population than those represented in adjuvant trastuzumab trials.*

Study Endpoints

The primary endpoint of this study was invasive disease free survival (IDFS). IDFS was defined as the time from randomization until the date of the first occurrence of one of the following events:

- Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion);
- Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall and/or skin of the ipsilateral breast);
- Distant recurrence (i.e., evidence of breast cancer in any anatomic site—other than the two abovementioned sites—that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer);
- Contralateral invasive breast cancer
- Death attributable to any cause including breast cancer, non-breast cancer or unknown cause

All second primary non-breast cancers and in situ carcinomas (including DCIS and LCIS) and non-melanoma skin cancers were excluded as an event in this endpoint.

Patients who have not had an event at the time of data analysis were to be censored at the date last known to be alive and event free.

Secondary endpoints included:

- Invasive disease free survival including second primary non-breast cancer (IDFS-SPNBC), defined in the same way as the primary endpoint IDFS, but including second primary non-breast invasive cancer as an event (except for non-melanoma skin cancers and in situ carcinoma of any site).
- Disease free survival, defined as the time between randomization and the date of the first occurrence of an invasive disease-free survival event including second primary non-breast cancer event or contralateral or ipsilateral DCIS.
- Overall survival, defined as the time from randomization to death attributable to any cause.
- Recurrence-Free Interval (RFI), defined as the time between randomization and the date of local, regional, or distant breast cancer recurrence.
- Distant Recurrence-Free Interval (DRFI), defined as the time between randomization and the date of distant breast cancer recurrence.

Reviewer Comments*: The choice of IDFS excluding second primary non-breast cancer was based on Agency advice. IDFS-SPNBC, consistent with the STEEP criteria definition of DFS was a secondary endpoint. As noted by Hudis and colleagues in the 2007 publication "Proposal for Standardized Definitions of Efficacy End Points in Adjuvant Breast Cancer Trials: The STEEP System," the inclusion of SPNBC as events in the IDFS endpoint given difficulty in distinguishing second primaries in a non-breast site from distant recurrences of the primary breast cancer and includes possible treatment related cancers. It was noted that inclusion of other events may dilute the treatment effect of adjuvant therapy as it may count events unrelated to the primary cancer or its treatment. Currently, the Agency also accepts IDFS defined consistent with the STEEP criteria to be used as the primary endpoint.*

Patient-Reported Outcomes (PRO) were assessed using three instruments: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), its breast cancer specific module (EORTC QLQ-BR23), and EuroQOL 5 Dimension (EQ-5D-3L). See Section 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability and Appendix 19.5 for detailed patient-reported outcomes review.

Reviewer Comments: *The EORTC QLQ-C30 is a questionnaire with modular domains including separately scored physical function, role function, and other symptom and functional scales. The EORTC QLQ-BR23 is a breast cancer disease module that contains an additional 23 questions that primarily relate to the effects of surgical and radiation therapy interventions. The EQ-5D-3L asks about mobility, self-care, usual activities, pain/discomfort and anxiety/depression on three levels and includes a visual analogue scale for assessment of health-related quality of life. This is a generic preference-based measure that can be converted to provide a single health utility index value for use in economic analyses;* [redacted] (b) (4)

Statistical Analysis Plan

Sample size Consideration

Study APHINITY was designed to have 80% power to detect a hazard ratio (HR) of 0.75 at a two-sided significance level of 5%. Under these assumptions, approximately 379 IDFS events were required for the primary analysis of IDFS. The study was initially designed to enroll 3806 patients but was expanded to 4800 patients and only randomized patients with node-positive disease following the implementation of Protocol Amendment B. This amendment was due to the unexpected high proportion of patients with node-negative disease enrolled which resulted in a population inconsistent with the assumptions upon which the protocol design was based. The purpose of Amendment B was to bring the study population closer to the original assumptions.

The annual decrease in the Kaplan-Meier estimate of the IDFS function in the placebo control arm was anticipated to be 1.9% during the first year after randomization, 4.5% during Year 2, 4.4% during Year 3, and 1.8% during Year 4 and beyond. Under these assumptions, the 3-year Kaplan-Meier estimate of IDFS for the placebo control arm was expected to be 89.2%. These assumptions were based on 5-year follow-up data from BCIRG-006. Under the alternative hypothesis and with the assumption that IDFS for both arms is exponentially distributed, the magnitude of treatment effect in terms of increase in IDFS at 3 years would be 2.6%, resulting in an expected Kaplan-Meier IDFS rate of 91.8% at 3 years for the pertuzumab arm.

The final analysis of OS was planned to be conducted when 640 deaths have occurred. This would provide approximately 80% power to detect a hazard ratio of 0.8, at an alpha level of 0.05 (2-sided).

Reviewer Comments: *As discussed above, BCIRG-006 included a different patient population than was included in the APHINITY study and the estimates of IDFS in trastuzumab alone based on this population may be lower than would be observed in a study that includes greater numbers of patients with smaller tumor sizes who may be at lower risk for a recurrence event.*

Analysis Populations

The primary analysis population for all efficacy endpoints was to be the intent-to-treat (ITT) population. All randomized patients were to be included in the ITT population. Patients were to be grouped according to the treatment assigned at randomization.

Patients who received any amount of study medication (chemotherapy, pertuzumab/placebo, trastuzumab) were to be included in the safety population. Patients were to be analyzed as treated: patients who received at least one full or partial dose of pertuzumab were to be included in the pertuzumab arm; all other treated patients were to be included in the placebo control arm.

Reviewer Comments: *The primary analysis population and the safety population were appropriate.*

Efficacy Analysis Methods

The primary IDFS analysis included any IDFS events occurring on or before the clinical cutoff date, regardless of the initiation of non−protocol-specified anticancer therapy (NPT) or missing visits. Patients who have not had an IDFS event at the clinical cutoff date were censored at the date last known to be event free. IDFS data for patients with no post-baseline assessments and no death captured in the clinical database were censored at the date of randomization plus 1 day.

A descriptive summary of the number of patients with IDFS events in each category was to be provided according to their first IDFS event, as determined by date of assessment. If the patient experienced >1 IDFS event on the same date, the following hierarchy was applied to assign the patient to the appropriate category:

- Distant recurrence
- Locoregional recurrence
- Contralateral breast cancer
- Death without prior IDFS event

An additional summary was produced, where patients were categorized according to the above hierarchy, based on any IDFS event reported within 61 days (i.e., 2 months) of their first IDFS event.

Secondary endpoints included IDFS-SPNBC, DFS, OS, RFI, and DRFI. The overall two-sided significance level of the secondary endpoints was controlled at 5% by use of a hierarchical testing procedure. If the primary endpoint reached statistical significance, the following secondary endpoints were to be tested in the following order: IDFS-SPNBC, DFS, and OS. RFI and DRFI were to be tested but not included in the multiplicity adjustment.

Secondary endpoints were analyzed in a similar manner as the primary endpoint, i.e., the two treatment arms were compared using the stratified log-rank test and the hazard ratio was estimated using the stratified Cox proportional hazards model. The primary analyses for all secondary endpoints except OS was performed at the time of the primary analysis of the primary endpoint IDFS. Analyses were based on the ITT population.

PRO analyses were based on the ITT population, and included patients who were ongoing in the study at the expected date of the scheduled visit and had not experienced disease recurrence. Summary statistics of absolute scores of the EORTC QLQ-C30 and QLQ-BR23 scales and their changes from baseline were calculated at each assessment time point for the two treatment arms.

Reviewer Comments: *There was no alpha allocated to the analyses of PRO endpoints; therefore, no statistical inference could be drawn from PRO analyses. All PRO analyses are considered descriptive.*

Interim Analysis

There was no interim analysis planned for the primary endpoint IDFS. Three interim analyses were planned for OS. The first OS interim analysis was planned to be conducted at the same time of the primary IDFS analysis, along with other analyses of safety and efficacy. Two further interim analyses of OS were to be performed approximately 2.5 and 5 years after the primary analysis of IDFS. The final event-driven OS analysis was planned to take place when 640 deaths have occurred. The overall type I error rate for OS analyses was controlled at two-sided 0.05 using the O'Brien-Fleming boundary.

Two formal, safety-only interim analyses were planned after the first 200 and 800 patients were enrolled and treated for 6 months. At each of these time points, the results of the safety analyses were presented to the IDMC while the Sponsor remained blinded. If an absolute difference of more than 3% in the incidence of heart failure NYHA Classes III to IV or definite or probable cardiac death was observed between treatment arms, the IDMC would consider recommending stopping or modifying the trial. After reviewing safety data at each occasion, the IDMC had no objections to the continuation of the study.

Reviewer Comments: *The use of O'Brien-Fleming efficacy boundary for multiplicity adjustment in OS sequential testing is appropriate.*

Protocol and SAP Amendments

The original protocol for the APHINITY study is referred to as Protocol A. There were three protocol amendments including Protocol Amendment B (November 20, 2012), Protocol Amendment C (December 3, 2013), and Protocol Amendment D (February 2, 2015).

Protocol Amendment B, dated November 20, 2012, revised the inclusion/exclusion criteria to no longer include those patients with node negative disease given higher than expected recruitment of node-negative patients. At the time of the original protocol, statistical assumptions had been made based on the proportion of node-positive/node-negative patients seen in prior trastuzumab adjuvant studies (particularly BCIRG-006). As of September 2012, the population in APHINITY was not consistent with these assumptions. As a result, the sample size was increased from N=3806 to N=4800 and node-negative patients were no longer allowed to enroll. The recruitment period was adjusted from 27 to 25 months and a clause was added to ensure that the primary analysis did not occur until at least 30 months after the last patient enrolled. Additional modifications were to increase the time from randomization to first treatment from 7 to 8 weeks, reduce the number of enrolling sites from 700 to 600, modify the number of cycles of FEC/FAC to 3 or 4 to more closely reflect local practice, include reporting of non-breast second primary malignancies, adjust the minimum observation period after pertuzumab to be consistent with the current pertuzumab label, modify TCH administration to update it to current practice, modify contraception guidelines, and to clarify: information collected at the time of partial withdrawal from the study, guidelines for surgical management of the axilla, assessments for patients on anthracycline based chemotherapy, guidelines for continuing targeted treatment when chemotherapy was discontinued due to toxicity, use of

concomitant medications including steroids for hypersensitivity to clarify the evaluation of cardiac endpoints; and to modify the SAP to add additional sensitivity analyses to ensure the robustness of the assessment of the primary endpoint.

Protocol Amendment C updated the background to include recent data from other clinical studies of pertuzumab, to add the language regarding the modification of the adjuvant chemotherapy regimen in the event of significant toxicity, to clarify the reporting period for concomitant medications, to clarify excluded therapies, to clarify the study schedule and assessments after patients discontinue study therapy, and to clarify that the analysis of the primary variable would be delayed until 30 months after the last patient was randomized in the event that 379 IDFS events were reached sooner than 30 months after the last patient was enrolled.

Protocol Amendment D updated information regarding the washout period for trastuzumab and pertuzumab for pregnancy, clarification that endocrine therapy is administered per local practice, added an additional plasma sample to be collected at the time of disease recurrence, clarified the definitions for second primary malignancy and disease recurrence (excluding non-melanoma skin cancers and carcinoma in situ of any site), and clarification regarding AE and SAE reporting during follow-up.

The first version of statistical analysis plan was released on 13 June 2011, and amended twice thereafter. The major changes in each amendment are summarized in Table 4.

Table 4 SAP Amendment Summary

SAP version (Final Date)	**Major Changes**
Version 2 (31 October 2012)	• Updates to the sample size assumptions resulting from the capping of node negative patients implemented in protocol amendment B. • Clarification that the timing of OS analyses was not impacted by protocol amendment B. • Addition of protocol version as a randomization stratification factor.
Version 3 (24 September 2015)	• New exploratory endpoint added, the evaluation of the Breast Cancer-Free Interval. • Further clarity provided on the definitions of a primary cardiac endpoint and a secondary cardiac endpoint.

Reviewer Comments: *The primary analysis of IDFS was performed when 381 IDFS events have occurred, which was approximately 39 months after the last patient randomized. The analysis time has ensured the minimum follow-up of 30 months as required in protocol Amendment B.*

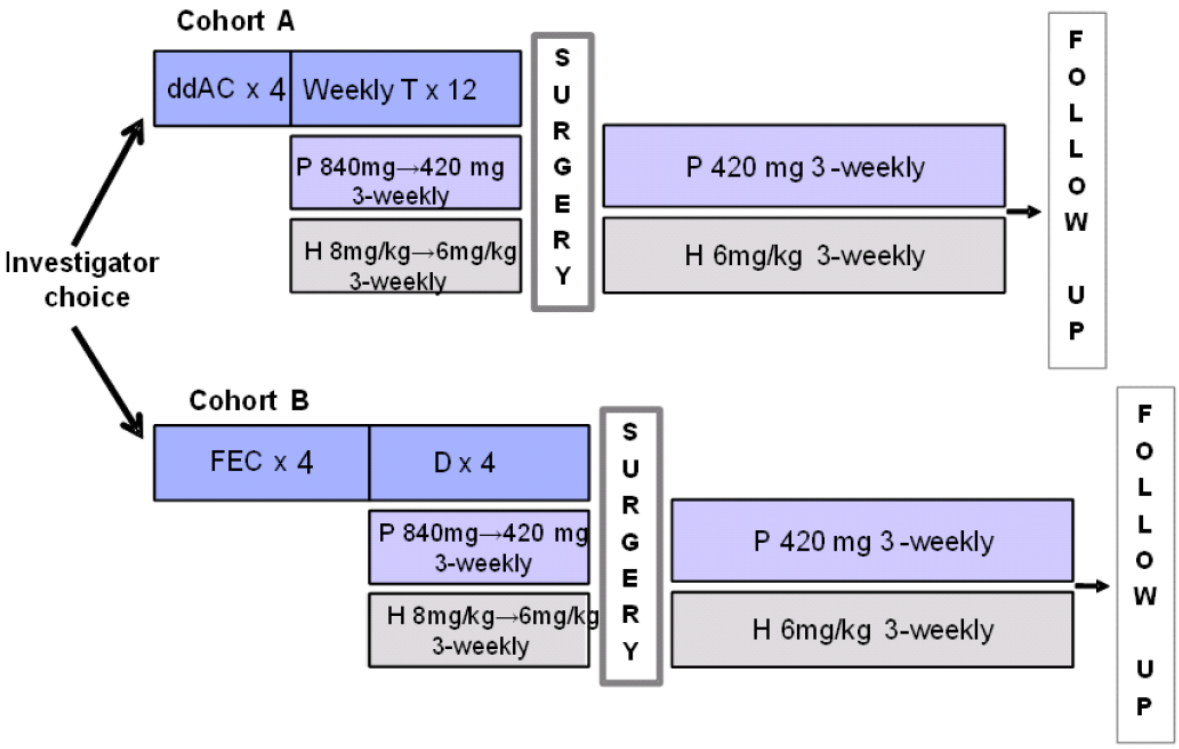
8.1.2. **BERENICE**

Trial Design

The BERENICE study was a non-randomized, open-label, multicenter, multinational, phase 2 study to evaluate pertuzumab in combination with trastuzumab and standard neoadjuvant anthracycline based chemotherapy in patients with HER2-positive locally advanced, inflammatory, or early stage breast cancer in two parallel groups of patients. Patients suitable for neoadjuvant therapy with trastuzumab plus anthracycline and taxane based chemotherapy were allocated to receive one of two treatment regimens. The choice of anthracycline and taxane based regimen was made by investigators on a site-specific basis (i.e. that only one cohort was open at a time at a specific site).

After surgery, patients in each treatment cohort were to receive adjuvant pertuzumab and trastuzumab every three weeks for 13 cycles so that a total of 17 cycles of pertuzumab and trastuzumab were administered through the course of the study. Radiation therapy and adjuvant endocrine therapy were also administered as clinically indicated. The study schema is characterized in Figure 2 below.

Figure 2. BERENICE Study Schema



D = docetaxel; ddAC = dose-dense Adriamycin® (doxorubicin) and cyclophosphamide; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; H = Herceptin® (trastuzumab); P = Perjeta® (pertuzumab); T = Taxol® (paclitaxel).

Source: BERENICE CSR page 29

The primary objective of WO29217 was to evaluate the cardiac safety of the addition of pertuzumab to the anthracycline and taxane based chemotherapy regimens of Cohort A and Cohort B during neoadjuvant treatment. The primary endpoint relates to safety rather than efficacy.

Reviewer Comments: *The primary objective of the BERENICE study was to describe the safety of the addition of pertuzumab to anthracycline containing regimens, particularly doxorubicin containing regimens which were not studied in the NEOSPHERE or TRYPHAENA studies.*

Inclusion Criteria

Patients had to meet the following criteria for study entry:

- Male and female patients with locally advanced, inflammatory, or early-stage, unilateral and histologically confirmed invasive breast cancer. Patients with inflammatory breast cancer who were able to have a core needle biopsy.

- Primary tumor >2 cm in diameter, or >5 mm in diameter and node positive (clinically, on imaging, or on cytology/histopathology).
- HER2-positive breast cancer confirmed by a central laboratory (3+ by IHC or HER2 amplification by in situ hybridization with a ratio of HER2 gene signals to centromere 17 signals of ≥2.0).
- Availability of formalin-fixed, paraffin-embedded (FFPE) tumor tissue block for central confirmation of HER2 status, hormone receptor status, and molecular subtyping.
- Able and willing to provide written informed consent and comply with study protocol.
- Age ≥18 years.
- Baseline LVEF ≥55% as measured by ECHO or MUGA.
- ECOG performance status of 0 or 1.
- At least 4 weeks since major unrelated surgery with full recovery.
- Negative serum pregnancy test for premenopausal women and women <12 months after the onset of menopause unless they had undergone surgical sterilization.
- Women of childbearing potential and male participants with partners of childbearing potential who agreed to use a "highly effective" non-hormonal form of contraception or two "effective" forms of non-hormonal contraception by the patient and/or partner. Contraception must have continued for the duration of study treatment and for at least 7 months after the last dose of study treatment.

Exclusion Criteria

- Metastatic disease (Stage IV) or bilateral breast cancer.
- Patients who had an incisional biopsy of the primary tumor or the primary tumor excised.
- History of non-breast malignancies within 5 years of study entry except for carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal or squamous cell carcinoma of the skin. Patients with malignancies more than 5 years prior to study entry were permitted if curatively treated with surgery alone.
- Any previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, and antitumor vaccines) for cancer, or radiation therapy for cancer.
    - Patients with a history of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) were not allowed to enter the study if they had received any systemic therapy for its treatment or radiation therapy to the ipsilateral breast (they were allowed to enter the study if treated with surgery alone).
    - High-risk patients who had received chemopreventive drugs in the past were not allowed to enter the study.
- Inadequate bone marrow function (e.g. absolute neutrophil count <1.5 x 10^9/L, platelet count <100 x 10^9/L, and hemoglobin <9 g/dL).
- Impaired liver function (e.g. total bilirubin >1.25 x upper limit of normal (ULN) with the exception of Gilbert's syndrome, AST and ALT >1.25 x ULN, albumin <25 g/L).
- Inadequate renal function with serum creatinine >1.5 x ULN.

- Poorly controlled hypertension (e.g. SBP >180 mmHg and/or diastolic blood pressure >100 mmHg), angina requiring anti-anginal medication, history of CHF of any NYHA classification, serous or uncontrolled cardiac arrhythmia requiring treatment (exceptions: controlled atrial fibrillation with heart rate ≤100 bpm at rest, and paroxysmal supraventricular tachycardia), history of myocardial infarction within 6 months of enrollment, or LVEF <55%.
- Dyspnea at rest or other diseases that require continuous oxygen therapy.
- Severe, uncontrolled, systemic disease.
- Patients with poorly controlled diabetes or with evidence of clinically significant diabetic vascular complications.
- Pregnant or lactating women.
- Patients who received any investigational treatment within four weeks of study initiation.
- Patients with known HIV, hepatitis B or C infection.
- Current chronic daily treatment with corticosteroids with doses >10 mg of methylprednisolone or equivalent excluding inhaled steroids.
- Known hypersensitivity to any of the study drugs or excipients.
- Patients assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.

Reviewer Comments: *The inclusion and exclusion criteria appear appropriate.*

Study Endpoints

The primary objective of BERENICE (WO29217) was to evaluate the cardiac safety of neoadjuvant treatment with each of the two treatment regimens. Cardiac safety was evaluated by assessing the following endpoints:

- The incidence of NYHA class III and IV heart failure and the associated 95% CIs for each treatment during the neoadjuvant period (primary objective) and adjuvant and follow-up periods.
- The incidence of LVEF declines of ≥10% points from baseline and to a value of <50% with the associated 95% CIs during the neoadjuvant period (primary objective) and adjuvant and follow-up periods.

Secondary safety objectives were to evaluate the safety profiles of the two treatment regimens during the neoadjuvant, adjuvant and follow-up periods based on the following:

- The incidence and severity of AEs and SAEs.
- Laboratory test abnormalities.
- Serum levels and the incidence of ATAs to pertuzumab and their relationship to safety events and efficacy.

Efficacy was to be assessed at the time of the primary analysis (the completion of neoadjuvant treatment) and at other key time points. Efficacy outcome measures for this study are assessed in the intent to treat population (ITT) and are as follows:

- Total pathologic complete response (tpCR) defined as eradication of invasive disease in the breast and axilla (ypT0/is ypN0) according to local pathologist assessment. Patients who do not undergo surgery or do not have a valid tpCR assessment will be considered non-responders.
- Clinical response, as defined by complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) prior to surgery. The clinical response rate is defined as the proportion of patients in the ITT population who achieve a CR or PR prior to surgery. A responder is a patient with at least one overall response of either CR or PR and all other patients are identified as non-responders. Response will be assessed by the local investigator per local practice on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1.
- Event-free survival (EFS) as defined by the time from enrollment to the first occurrence of progressive disease or relapse as determined by the investigator or death from any cause. Ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in suite carcinomas and non-melanoma skin cancers) will not be counted as progressive disease or relapse.
- Invasive disease free survival (IDFS) as defined by the time from the first date of no disease (i.e. the date of primary surgery) to the first documentation of progressive invasive disease, relapse, or death from any cause. Ipsilateral and contralateral in situ disease and second primary non-breast cancers (including in suite carcinomas and non-melanoma skin cancers) will not be counted as progressive disease or relapse. This analysis only includes patients who have undergone surgery and patients who withdraw from the neoadjuvant phase will be excluded from the analysis.

Exploratory Efficacy Outcome Measures include:

- Breast pathological complete response (bpCR) defined as eradication of invasive disease in the breast (ypT0/is).
- Residual cancer burden (RCB) class.
- To assess pCR rates according to subtypes of breast cancer defined by molecular profiles as defined by the PAM50 classifier.
- German breast group (GBG) pCR, defined as no residual invasive or in situ disease in the breast or invasive disease in the axilla (ypT0 ypN0).
- Breast conserving surgery as defined as quadrantectomy or lumpectomy.
- Re-excision surgery, defined as surgery on a separate occasion (i.e. requiring a separate anesthetic) following BCS to remove residual tumor.
- Gene expression, as determined by messenger RNA expression levels.

Reviewer Comments: *The primary and secondary endpoints are appropriate for this study where the primary objective is to evaluate the safety of pertuzumab in combination with anthracycline containing regimens as well as the safety of combined trastuzumab and*

pertuzumab as adjuvant therapy to complete one year of anti-HER2 therapy. The efficacy endpoints are exploratory. The evaluation of pCR by PAM50 molecular subtype was planned to fulfill a PMC to evaluate the relationship of pathological complete response to different molecular subtypes.

Statistical Analysis Plan

No formal sample size calculation was determined as the results are being summarized descriptively for each treatment cohort with no statistical hypothesis testing.

The study sought to enroll 200 patients into each treatment cohort. This sample size was expected to provide sufficient data for evaluation of cardiac safety of each treatment regimen with an acceptable precision based on Clopper-Pearson 95% CIs around the expected rates.

Both efficacy and safety were to be analyzed after patients have completed neoadjuvant therapy (or have withdrawn from the study or are lost to follow-up) as this was the primary analysis timepoint. The secondary timepoint was after all patients had completed adjuvant therapy (or have withdrawn from the study or are lost to follow-up), and at the end of study (5 years after the last patient was enrolled, or when all patients had died or the trial was terminated by the sponsor, whichever was earliest.

Reviewer Comments: *The statistical analysis plan is appropriate for a descriptive study primarily evaluating safety.*

Protocol and SAP Amendments

Two protocol amendments were prepared by the applicant prior to the first patient visit (version 2 dated February 26, 2014, and version 3 dated June 17, 2014). These amendments clarified the definition of the relapse/recurrence, recommendations regarding pregnancy and breastfeeding, and the safety instructions for LVEF assessment after completion of anthracycline and prior to initiation of targeted therapy. One protocol update (version 4 dated May 26, 2016) occurred after the first patient visit, however this occurred after the cutoff date for the primary analysis and did not impact the information presented in the clinical study report. This update made minor modifications to the exclusion criteria, in the wording of the study completion/early termination visit, clarification regarding the radiological assessments, and addressed discrepancies in the pathology manual. The first version of statistical analysis plan was released on August 15, 2014, and there was no amendment thereafter.

Reviewer Comments: *The protocol amendments are unlikely to have impacted the study outcomes as they were made prior to initiation of enrollment and after completion of enrollment.*

8.1.3. Study Results

Data Quality and Integrity

The overall data quality and integrity are acceptable to the reviewers. The submitted datasets are generally consistent and variables are clearly labeled and/or explained. Based on the submitted data and reports, the reviewers believe that analyses and results are reliable for regulatory decision making.

The electronic submission including Protocols, Statistical Analysis Plan (SAP), Clinical Study Reports (CSRs) and SAS transport datasets for the sBLA submission are located in the following network paths:

BERENICE: \\cdsesub1\evsprod\bla125409\0326

APHINITY: \\cdsesub1\evsprod\bla125409\0360

These sources were utilized to perform the clinical and statistical review of this application.

Compliance with Good Clinical Practices

The applicant stated that both the APHINITY study and the BERENICE study were conducted in accordance with the protocol, the principles of the Declaration of Helsinki, and the ICH6 guideline for Good Clinical Practice (GCP) including compliance with applicable laws and regulations.

Financial Disclosure

APHINITY

The applicant collected and evaluated the financial disclosure information for Study BIG 4-11/BO25126/TOC4939g for all principal and sub-investigators for the disclosure of financial interests in or receipt of significant payments from Genentech. Of the 4728 principle and sub-investigators for this study, 4657 (98.5%) responded. Twelve of the 4657 investigators who responded reported disclosable financial interests. These disclosures are summarized in Table 5 below. No disclosable interest was reported by 4645 investigators with a signed financial disclosure not obtained for 71 investigators.

Table 5. Financial Disclosures for APHINITY (Study BIG 4-11/BO25126/TOC4939g)

Country	Clinical Site Number	Number of Patients Enrolled at Site	Investigator Name	Investigator Type	Disclosure
				(b) (6)	Share holder >$50,000
					Honoraria for consulting, lectures and

					(b) (6) >$25,000
(b) (6)					(b) (6) part funded by Roche >$25,000
					Grant from Roche to (b) (6) £$50,000
					Roche Stock >$50,000
					Form dated August 11, 2011: Participates as a speaker and consultant >$50,000 Form dated November 26, 2012: Participates as a speaker >$25,000
					Participates as a speaker >$25,000
					Honorarium-Speaker Bureau GNE >$25,000
					Honoraria and consultation $35,000 to

					$50,000
[redacted]					Form dated February 27, 2013: Institution received $286,562 grant from GNE Form dated July 7, 2016: Participate in Compensated [redacted] >$25,000
					ImmunoGen Stock >$50,000
					Speaking and consulting fees for GNE <$25,000

Source: Section 1.3.4.1 Overview and Summary of Findings

Reviewer Comments: *While multiple investigators received payments from the Study Sponsor, these sites enrolled a small proportion of the total patient population (n=128, 2.7%) making the introduction of bias less likely.*

BERENICE

The applicant collected and evaluated the financial disclosure information for Study WO29217 for all principal and sub-investigators for the disclosure of financial interests in or receipt of significant payments from Genentech. Of the 705 principal and sub-investigators for this study, 702 (99.6%) responded. Signed financial disclosures were not obtained from 3 sub-investigators. Of the *investigators* who responded, disclosable financial interests were reported by 3 investigators. These disclosures are summarized in Table 6 below. No disclosable interest was reported by 699 investigators/sub-investigators.

Table 6. Financial Disclosures for BERENICE WO29217

Country	Clinical Site Number	Number of Patients Enrolled at Site	Investigator Name	Investigator Type	Disclosure
(b) (6)					Participates as a speaker and consultant >$25,000
					Payments received from GNE >$25,000
					Participates in Speakers Bureau >$25,000

Source: Section 1.3.4.1 Overview and Summary of Findings

Reviewer Comments: While there are three investigators who received payments from the sponsor, these sites collectively enrolled a small number of patients (4.2%), making the introduction of bias less likely.

Patient Disposition

APHINITY

There were 6263 patients screened and 4805 patients randomized to treatment in the APHINITY study. Patients were enrolled from November 8, 2011, to August 31, 2013. Of the patients randomized, one was excluded from the ITT population as this patient had falsified data regarding her identity for insurance purposes. This patient had been randomized to the trastuzumab and placebo arm.

Of the patients randomized, 2400 patients were randomized to the pertuzumab + trastuzumab + chemotherapy arm and 2404 were randomized the placebo + trastuzumab + chemotherapy arm. Additional information is included in Table 7 below:

Table 7. Patient Disposition for APHINITY Study

	Chemotherapy, trastuzumab and pertuzumab N=2400 n (%)	**Chemotherapy, trastuzumab and placebo N=2404 n (%)**
Received no study treatment	22 (0.9)	13 (0.5)
Received chemotherapy and pertuzumab	2340 (97.5)	24 (1.0)
Received chemotherapy and placebo	38 (1.6)	2367 (98.5)
Safety population	2364	2405
Discontinued pertuzumab/placebo	372 (15.5)	304 (12.6)
Completed pertuzumab/placebo	2028 (84.5)	2100 (87.4)
Discontinued pertuzumab/placebo for safety reasons	186 (7.8)	155 (6.4)
Discontinued pertuzumab/placebo for non-safety reasons	186 (7.8)	149 (6.2)
Alive and remain on study	2178 (90.8)	2186 (90.9)
Alive, no longer on study	142 (5.9)	129 (5.4)
Dead	80 (3.3)	89 (3.7)

Source: Modified from APHINITY CSR page 101, Information Request dated August 16, 2017

Reasons for study discontinuation are included in Table 8 below.

Table 8. Reasons for Study Discontinuation for the APHINITY Study

	Chemotherapy, trastuzumab and pertuzumab N=2400 n (%)	**Chemotherapy, trastuzumab and placebo N=2404 n (%)**
Discontinued pertuzumab/placebo	372 (15.5)	304 (12.2)
Discontinued pertuzumab/placebo for safety reasons	186 (7.8)	155 (6.4)
Adverse event	176 (7.3)	149 (6.2)
Death	9 (0.4)	6 (0.2)
Pregnancy	1 (<0.1)	0
Discontinued pertuzumab/placebo for non-safety reasons	186 (7.8)	149 (6.2)
Lost to follow up	0	1 (<1)
Non-compliance	44 (1.8)	29 (1.2)
Physician Decision	30 (1.3)	15 (0.6)
Protocol Violation	1 (<0.1)	3 (<0.1)
Disease recurrence	20 (0.8)	29 (1.2)
Contralateral breast cancer	2 (0.1)	0
Withdrawal by subject	55 (2.3)	47 (2.0)
Other	34 (1.4)	25 (1.0)

Source: APHINITY CSR page 102

Reviewer Comments: There was a numerically higher proportion of patients who discontinued pertuzumab as compared to placebo. This suggests that there may be increased toxicity of combined anti-HER2 therapy with pertuzumab. There were also numerically greater deaths on combined anti-HER2 therapy, though the numbers are small. Review of on treatment deaths is found in section 8.2.4.

BERENICE

There were 523 patients screened and 401 patients enrolled for treatment in the BERENICE study. Patients were enrolled from July 14, 2014, to August 25, 2015.

Of the patients enrolled, 199 patients were enrolled in Cohort A (dose dense AC followed by weekly paclitaxel) and 202 were enrolled in Cohort B (FEC followed by docetaxel). Additional information is included in Table 9 below:

Table 9. Patient Disposition for the BERENICE Study

	Cohort A N=199 n (%)	**Cohort B N=202 n (%)**
Withdrawal prior to study drug	1 (0.5)	3 (1.5)
Received treatment from alternate cohort	0	1 (0.5)
Started neoadjuvant treatment	199 (100)	198 (98.0)
Early surgery with incomplete treatment	4 (2.0)	3 (1.5)
Discontinuation due to AE	6 (3.0)	3 (1.5)
Discontinued due to disease progression/lack of efficacy	1 (0.5)	2 (1.0)
Discontinued due to physician decision	2 (1.0)	0
Discontinued due to withdrawal by patient	1 (0.5)	0
Discontinued due to other	3 (1.5)	1 (0.5)
Completed neoadjuvant treatment	182 (91.5)	189 (93.6)
Started adjuvant treatment	181 (91.0)	190 (94.1)
Discontinued adjuvant treatment	18 (9.0)	14 (6.9)
Discontinued adjuvant treatment due to adverse event	8 (4.0)	9 (4.5)
Discontinued adjuvant treatment due to Protocol Deviation/Noncompliance	2 (1.0)	1 (0.5)
Discontinued adjuvant treatment due to disease relapse/progression	0	2 (1.0)
Discontinued adjuvant therapy due to withdrawal by patient	3 (1.5)	1 (0.5)
Discontinued adjuvant therapy due to physician decision	2 (1.0)	0
Discontinued adjuvant therapy due to pregnancy	1 (0.5)	0
Discontinued adjuvant therapy due to other	2 (1.0)	1 (0.5)
Completed adjuvant treatment	163 (81.9)	176 (87.1)
Started treatment free follow up	162 (81.4)	187 (92.6)

Source: BERENICE CSR page 60 and BERENICE Four Month Safety Update (June 2017)

Reviewer Comments: *At the time of the safety update, data cutoff January 7, 2017, of the 401 patients who enrolled into the BERENICE study, 339 patients (84.5%) had completed study*

treatment, defined as completing four cycles of neoadjuvant treatment and 17 cycles of adjuvant treatment. Fifty-eight patients discontinued study treatment, 36 patients in Cohort A and 22 patients in Cohort B. There were 354 patients who were part of treatment free follow up at this time. Thirty-two patients discontinued adjuvant treatment with combined trastuzumab and pertuzumab with 18 patients (9.9%) discontinuing treatment in Cohort A and 14 patients (7.4%) discontinuing treatment in Cohort B. Compared to historical data, these rates of discontinuation are similar to the rates of discontinuation of trastuzumab alone after completion of anthracycline based chemotherapy (Romond 2005).

Protocol Violations/Deviations

APHINITY

Approximately 28% of patients in each treatment arm had at least one major protocol deviation. There was a similar incidence of protocol deviations in each arm regardless of type. The most common protocol deviations in 4% or more of patients were related to time interval between definitive surgery and randomization, ability to initiate therapy within one week of randomization, completion of necessary baseline laboratory and radiographic investigations, and abnormal laboratory values prior to randomization.

One major protocol deviation led to a patient being excluded from both the safety and efficacy populations as this patient was found to have provided false information regarding her insurance status. This patient had been randomized to the placebo arm. There were no safety or efficacy data included regarding this patient as these data were considered unreliable.

Two patients at the time of randomization had metastatic disease. One patient did not start study treatment and the other patient completed study treatment. Neither patient was considered to have an IDFS event in the primary analysis. The patient was censored at the time of randomization for efficacy for each efficacy endpoint other than overall survival.

Protocol deviations for the APHINITY study are characterized in Table 10 below.

Table 10. Protocol Deviations for the APHINITY Study

	Chemotherapy, trastuzumab and pertuzumab N=2400	Chemotherapy, trastuzumab and placebo N=2404
Patients with at least one major protocol deviation	674 (28.1)	688 (28.6)
Major inclusion criteria deviations	310	308
Major exclusion criteria deviations	192	211
Major on-study deviations	402	432
Patients with at least one major inclusion criterion deviation	285 (11.9)	280 (11.6)
Patients with at least one major exclusion criterion deviation	189 (7.9)	200 (8.3)

Source: APHINITY CSR, pages 106-107

Reviewer Comments: *There were similar proportions of patients with protocol deviations in each arm of the study. The most common violations for inclusion/exclusion criteria were failure to complete all baseline assessments prior to randomization, appropriate timing of initiation of therapy after surgery, abnormal laboratory tests immediately prior to randomization, and lack of negative serum pregnancy testing within 7 days of randomization. The proportion of patients with these violations was similar in each of the treatment arms. Given this, it is unlikely that these deviations would introduce bias in the study results. A sensitivity analysis of IDFS was performed by excluding patients with major protocol deviations and the results are presented in the efficacy results section of study APHINITY.*

BERENICE

Major protocol deviations for the BERENICE study were identified in 17 patients (8.5%) in Cohort A and 55 patients (27.2%) in Cohort B. Major protocol violations in this study included failure to follow protocol defined cardiac procedures or HER2 dosing algorithm following LVEF drops. Table 11 includes the major protocol deviations for the BERENICE study.

Table 11. Protocol Deviations for the BERENICE Study

	Cohort A (ddAC followed by paclitaxel) N=199 n (%)	**Cohort B (FEC followed by docetaxel) N=202 n (%)**
Patients with at least one major protocol deviation	17 (8.5)	55 (27.2)
Failure to follow the study safety procedures	10 (5.0)	28 (13.9)
Failure to follow the cardiac safety procedures	1 (0.5)	12 (5.9)
Not repeating LVEF as per cardiac algorithm	1 (0.5)	2 (2.0)
Medication Associated	4 (2.0)	6 (3.0)
Inclusion/Exclusion Criteria	2 (1.0)	9 (4.5)

Source: Reviewer modification of Table 4, BERENICE CSR page 65

Reviewer Comments: *There were numerically more protocol deviations in Cohort B than in Cohort A. As the largest number of these deviations occurred with safety assessments, including cardiac safety assessments, there may have been an underreporting of events in Cohort B.*

Demographic Characteristics

The baseline demographics for patients in the ITT population on APHINITY are shown in Table 12.

Table 12. APHINITY Demographics

Demographic Parameters	Chemotherapy, trastuzumab and pertuzumab N=2400 n (%)	Chemotherapy, trastuzumab and placebo N=2404 n (%)
Sex		
Male	3 (0.1)	8 (0.3)
Female	2397 (99.9)	2396 (99.7)
Age		
Mean years (SD)	51.7 (10.9)	51.4 (10.7)
Median (years)	51	51
Min, max (years)	22, 86	18, 85
Age Group		
< 65 years	2085 (86.9)	2111 (87.8)
≥ 65 years	315 (13.1)	293 (12.2)
≥75 years	30 (1.3)	26 (1.1)
Race		
White	1705 (71.0)	1694 (70.5)
Black or African American	32 (1.3)	41 (1.7)
Asian	590 (24.6)	598 (24.9)
American Indian or Alaska Native	57 (2.4)	56 (2.3)
Native Hawaiian or Other Pacific Islander	3 (0.1)	7 (0.3)
Other[1]	13 (0.5)	8 (0.3)
Ethnicity		
Hispanic or Latino	45 (1.9)	42 (1.7)
Not Hispanic or Latino	432 (18.0)	386 (16.1)
Not Reported/Unknown	1923 (80.1)	1976 (82.2)
Region		
United States	296 (12.3)	294 (12.2)
Rest of the World	2104 (87.7)	2110 (87.8)
Canada	64 (2.7)	46 (1.9)
Central and South America	55 (2.3)	54 (2.2)
Europe	1345 (56.0)	1340 (55.7)
Asia	394 (16.4)	380 (15.8)
Australia/New Zealand	53 (2.2)	75 (3.1)

[1] Data on ethnicity were collected primarily at US sites.

Reviewer Comments: *Most patients treated in the APHINITY study were younger than 65 and there were few male breast cancer patients represented in this study cohort. There were few patients over 75 included in this study. Most of the study population was recruited from outside of the United States. There are small proportions of Black or African-American patients included in this study as well as small numbers of Native American/Pacific Islander patients included. Caucasian and Asian patient are the highest represented racial groups.*

Other Baseline Characteristics

The other baseline characteristics for patients in the ITT population on APHINITY are shown in Table 13.

Table 13. Baseline Disease Characteristics for the APHINITY Study

	Chemotherapy, trastuzumab and pertuzumab N=2400 n (%)	**Chemotherapy, trastuzumab and placebo N=2404 n (%)**
Nodal status		
Negative	903 (37.6)	910 (37.9)
1-3 Positive	937 (39.0)	921 (38.3)
≥4 positive	560 (23.3)	573 (23.8)
Pathological Tumor Size and Nodal Status		
<1cm and node negative	58 (2.4)	60 (2.5)
≥1- <2cm and node negative	417 (17.4)	391 (16.3)
≥2cm and node negative	421 (17.5)	450 (18.7)
<1cm and node positive	86 (3.6)	68 (2.8)
≥1- <2cm and node positive	416 (17.3)	425 (17.7)
≥2cm and node positive	999 (41.6)	1007 (41.9)
Hormone receptor status		
ER and/or PR positive	1536 (64.0)	1546 (64.3)
ER and PR negative	864 (36.0)	858 (35.7)
HER2 status (central)		
0	6 (0.3)	2 (<0.1)
1+	16 (0.7)	9 (0.4)
2+	193 (8.0)	200 (8.3)
3+	2184 (91.0)	2190 (91.2)
Primary Surgery		
Breast Conservation	1118 (46.7)	1076 (44.8)
Mastectomy	1280 (53.3)	1327 (55.2)
Anthracycline based chemotherapy regimen	1865 (77.7)	1877 (78.1)

Source: APHINITY CSR, Table 12, page 109 and reviewer analysis using asl.xpt and abiom.xpt datasets

Reviewer Comments: *At the time of Protocol Amendment B, the proportion of node positive patients was about 50% of the study population. Adoption of this Amendment enriched the patient population with node negative patients as demonstrated above. Additionally, it is notable that approximately two-thirds of patients in each arm were HR-positive. Data from previous trastuzumab trials including B-31, N9831 and BCIRG-006 had populations that were closer to 50-60% HR-positive (Romond 2005; Slamon 2011).*

The primary efficacy analysis performed by the applicant was based on stratification data collected in eCRFs. Following the intent-to-treat principle, the agency's standard is to use IxRS-based stratification data in the primary analysis, and eCRF-based stratification data could be used in a sensitivity analysis. The concordance and discordance between IxRS- and eCRF-based stratification data are summarized in Table 14.

Table 14 Concordance and Discordance of Stratification Data between eCRF and IxRS

	Chemotherapy, trastuzumab and pertuzumab N=2400 n (%)	**Chemotherapy, trastuzumab and placebo N=2404 n (%)**
Adjuvant chemo regimen, n (%)		
Discordance	8 (0.3)	12 (0.5)
Concordance	2392 (99.7)	2392 (99.5)
Hormone receptor status, n (%)		
Discordance	46 (1.9)	46 (1.9)
Concordance	2354 (98.1)	2358 (98.1)
Nodal status, n (%)		
Discordance	134 (5.6)	114 (4.7)
Concordance	2266 (94.4)	2290 (95.3)

Note: Region was used as a stratification factor in randomization but not used in the primary analysis.
Source: reviewer analysis of data asl.xpt

Reviewer Comments: *The differences between the randomization stratification and the CRF based stratification data were not notably different between arms. Given these differences, analyses based on both sources of the stratification factor data were performed and results are shown in the section of efficacy results for APHINITY.*

Baseline demographics for patients in the BERENICE study are shown in Table 15.

Table 15. BERENICE Demographics

Demographic Parameters	Cohort A (ddAC followed by paclitaxel) N=199 n (%)	Cohort B (FEC followed by docetaxel) N=201 n (%)
Sex		
Male	0	200 (99.5)
Female	199 (100)	1 (0.5)
Age		
Mean years (SD)	49.8 (11.7)	49.5 (11.5)
Median (years)	49	49
Min, max (years)	21, 77	24, 78
Age Group		
< 65 years	176 (88.4)	176 (87.1)
≥ 65 years	23 (11.6)	25 (12.4)
Race		
White	169 (84.9)	163 (81.1)
Black or African American	11 (5.5)	0
Asian	6 (3.0)	4 (2.0)
American Indian or Alaska Native	6 (3.0)	0
Other	7 (3.5)	35 (17.4)
Ethnicity		
Hispanic or Latino	24 (12.1)	46 (22.9)
Not Hispanic or Latino	147 (73.9)	115 (57.2)
Not Reported/Unknown	28 (14.1)	41 (20.4)
Region		
United States	91 (45.7)	0
Canada	15 (7.5)	6 (3.0)
Central and South America	5 (2.5)	1 (0.5)
Europe	88 (44.2)	95 (47.3)

Source: Reviewer analysis using asl.xpt dataset.

Reviewer Comments: *While 199 patients were enrolled in Cohort A and 202 patients were enrolled in Cohort B, there was one patient in Cohort A who was never treated and one patient in Cohort B who was treated with the Cohort A regimen. The demographic tables were generated using the data from those patients who initiated therapy. This is appropriate in this setting where the primary objective of the study is to evaluate the safety of the combination of trastuzumab and pertuzumab with anthracycline based chemotherapy regimens.*

The baseline disease characteristics for patients in the BERENICE trial are shown in Table 16.

Table 16. BERENICE Baseline Disease Characteristics

	Cohort A (ddAC followed by paclitaxel) N=199 n (%)	Cohort B (FEC followed by docetaxel) N=201 n (%)
Nodal status		
Nx	8 (4.0)	9 (4.5)
N0	80 (40.2)	74 (36.8)
N1	92 (46.2)	98 (48.8)
N2	16 (8.0)	15 (7.5)
N3	3 (1.5)	5 (2.5)
Tumor size		
Tx	0	1 (0.5)
T0	1 (0.5)	0
T1	18 (9.0)	12 (6.0)
T2	138 (69.3)	130 (64.7)
T3	33 (16.6)	45 (22.4)
T4	9 (4.5)	13 (6.5)
Hormone receptor status		
ER and/or PR positive	128 (64.3)	123 (61.2)
ER and PR negative	65 (32.7)	75 (37.3)
HER2 status (central)		
0	0	0
1+	2 (1.0)	4 (2.0)
2+	19 (9.5)	21 (10.4)
3+	177 (88.9)	176 (87.6)

Source: Reviewer analysis using asl.xpt dataset

Reviewer Comments: *The BERENICE study included patients who had T2 or greater tumors with any nodal status and node positive patients with any tumor size at baseline. There were numerically greater patients in both cohorts who had HR positive disease*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

In the APHINITY study, treatment compliance and accountability were assessed by maintaining drug dispensing and return records. As study drug was administered IV under medical supervision, assessing dosing compliance was not thought to be a significant issue.

In the BERENICE study, accountability and compliance were assessed using drug dispensing and return records. These records contained information about the documentation of drug shipments received from the sponsor, the disposition of unused study drug, and the dates and identification of the patients that the drug was dispensed to.

Reviewer Comments: *As demonstrated in Table 8, the rate of study discontinuation due to non-compliance was low in both the APHINITY and the BERENICE studies. In the APHINITY study, the primary efficacy analysis was performed in the ITT population without censoring of non-compliant patients.*

Concomitant Medications

APHINITY

Nearly all patients in the APHINITY study received at least one concomitant medication with 94.5% of patients receiving concomitant therapy in the pertuzumab + trastuzumab + Chemotherapy arm and 93.6% of patients receiving concomitant therapy in the Placebo + trastuzumab + Chemotherapy arm. The primary concomitant medications are summarized in Table 17.

Table 17 Concomitant Medication Use in APHINITY

Drug Type	Chemotherapy, trastuzumab and pertuzumab N=2364 n (%)	Chemotherapy, trastuzumab and placebo N=2405 n (%)
Corticosteroids	2184 (92.4)	2163 (90.0)
5-HT3 Antagonists	2126 (89.9)	2118 (88.1)
G-CSF	1255 (53.1)	1188 (49.4)
Antidiarrheal medication	958 (40.5)	460 (19.1)

Source: Reviewer table using acm.xpt

Reviewer Comments: *There was slightly greater concomitant medication use in various medication classes in the APHINITY trial. The use of corticosteroids and 5-HT3 antagonists was consistent with the use of anthracycline and taxane based chemotherapy backbones. It is notable that twice as many patients were on antidiarrheal medications in the pertuzumab arm as compared to the placebo arm and this corresponds with the known increase in diarrhea associated with this therapy.*

BERENICE

Nearly all patients in the BERENICE study received concomitant medications during their neoadjuvant treatment (99.7%, n=396). Patients who were in Cohort A received more concomitant medications than those in Cohort B. The most common medications received in

the neoadjuvant or preneoadjuvant therapy period (>20% of patients in either arm) are captured in Table 18 below:

Table 18. Concomitant Medication Use in BERENICE

Drug Type	Cohort A (ddAC followed by paclitaxel) N=199 n (%)	Cohort B (FEC followed by docetaxel) N=198 n (%)
Steroids	179 (89.9)	166 (82.1)
5-HT3 antagonists	179 (89.9)	161 (81.3)
Antiemetics	159 (79.9)	138 (69.7)
Colony stimulating factors	154 (77.4)	120 (60.6)
Analgesics	114 (57.3)	118 (59.6)
Proton Pump Inhibitors	77 (38.7)	91 (46.0)
NSAIDs	70 (35.2)	61 (31.8)
Antibiotics	109 (54.7)	110 (55.6)
Benzodiazepines	76 (38.2)	50 (25.3)
Laxatives and stool softeners	48 (24.1)	43 (21.7)
Antidiarrheals	67 (33.7)	48 (24.2)
Supplements	113 (56.8)	58 (29.3)
Antihistamines	153 (76.9)	61 (30.8)

Source: BERENICE CSR pages 527-639

Reviewer Comments: *As expected in patients on anthracycline and taxane based chemotherapy regimens, there was prominent use of steroids, 5-HT3 antagonists, and antiemetics. There was increased use of antidiarrheals in both arms, though numerically greater in the paclitaxel arm (Cohort A) than in the docetaxel arm (Cohort B). This is somewhat surprising as docetaxel is also associated with diarrhea as an adverse effect. This imbalance may have affected the reporting of diarrhea as an adverse effect in treatment arms.*

Efficacy Results – Primary Endpoint

APHINITY

The primary analysis of IDFS was performed when 381 IDFS events were reported. At the clinical cutoff date of 19 December 2016, IDFS events had occurred in 171 patients (7.1%) in the pertuzumab arm and 210 patients (8.7%) in the placebo arm. Median follow up for IDFS was 45.4 months in both treatment arms. Table 19 presents the results of primary analysis for IDFS in the ITT population. There was a statistically significant improvement in IDFS for patients randomized to the pertuzumab arm compared to patients randomized to the placebo arm with a hazard ratio of 0.82 (95% CI: 0.67, 1.00). A summary of site of first IDFS event applying a hierarchy and time window of 61 days is also shown in Table 19. Estimates of IDFS rates were

94.06% vs. 93.24% at 3 years in the pertuzumab vs. placebo arms, respectively. The Kaplan-Meier curves of IDFS are shown in Figure 3.

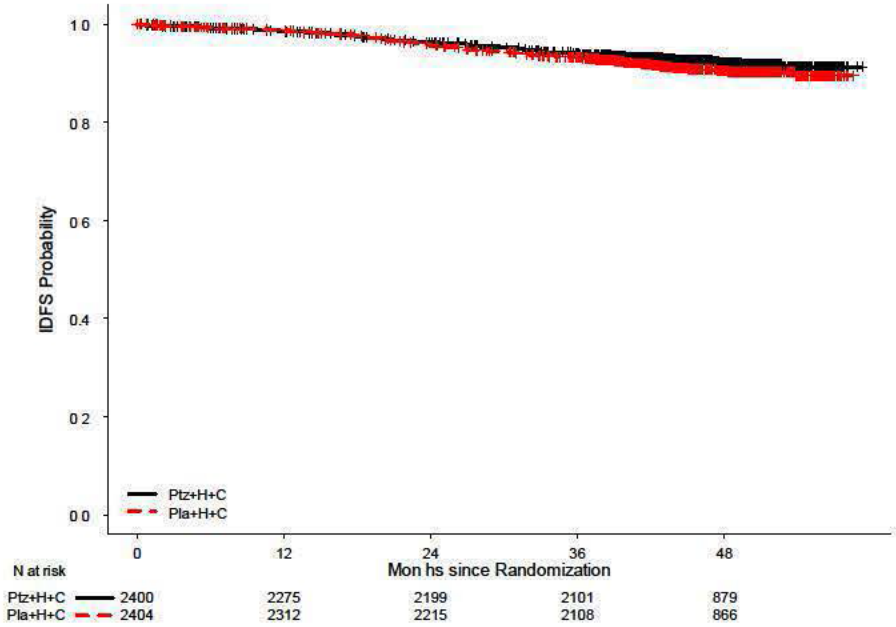
Table 19 FDA's Analysis of Invasive Disease Free Survival, in the ITT Population of APHINITY

	Chemotherapy, trastuzumab and pertuzumab N=2400 n (%)	**Chemotherapy, trastuzumab and placebo N=2404 n (%)**
# of IDFS events	171 (7.1%)	210 (8.7%)
Distant recurrence	112	139
Locoregional recurrence	26	34
Contralateral breast cancer	5	11
Death without prior IDFS events	28	26
3-yr IDFS rate (95% CI)	94.06% (93.09, 95.03)	93.24% (92.21, 94.26)
Stratified HR (95% CI)[a]	0.82 (0.67, 1.00)	
Stratified log-rank p-value[a]	0.047	

[a]Stratified by randomization stratification factors collected from IxRS: nodal status, hormone receptor status, chemotherapy regimen, and protocol version.
Source: CSR Tables 23 and 24; data ate.xpt

Reviewer Comments: *Following the intent-to-treat principle, the review team used stratification factor data collected from IxRS in the primary IDFS analysis, as shown in* Table 19*. The applicant used eCRF-based stratification factor data in their primary analysis and reported a hazard ratio of 0.81 (95% CI 0.66, 1.00) with a p-value of 0.045. Results from these two analyses are consistent. The last patient was randomized on August 31, 2013, and the data cutoff data was December 19, 2016; therefore, the minimum follow-up time was about 39 months. Prior to year 3, censoring for IDFS is minimal (approximately 5-7%) in both arms; while approximately 50% of patients in both arms were censored from year 3 to year 4. Given the degree of censoring, estimates of IDFS rates at time points beyond 3 years are not considered reliable.*

Figure 3 Kaplan-Meier Curves for IDFS, in the ITT Population of APHINITY



Source: CSR Figure 4 and dataset ate.xpt

Censoring information of IDFS

Overall, 2229 patients in the pertuzumab arm and 2194 patients in the placebo arm were censored in the primary IDFS analysis. The reason for censoring has been categorized as follows, based on the patient's status in the study.

- Censored at date of randomization.
- Patient no longer in the study, last known to be IDFS event free.
- Patient agreed to follow-up for overall survival only without prior IDFS event (i.e., refers to patients who withdrew consent for study procedures other than survival follow-up).
- Patient remains in the study, IDFS event free at last follow-up.

A summary of the number of patients in each of these distinct categories is provided in Table 20.

Table 20 Summary of Reasons for censoring for IDFS in APHINITY

	Chemotherapy, trastuzumab and pertuzumab N=2400	**Chemotherapy, trastuzumab and placebo N=2404**
Number of censored patients	2229	2194
Reason for censoring: n (%)		
Censored at date of randomization	17 (0.8%)	10 (0.5%)
Patient no longer in study, last known to be IDFS event free	121 (5.4%)	109 (5.0%)
Patient agreed to follow-up for overall survival only without prior IDFS event	10 (0.4%)	5 (0.2%)
Patient remains in study, IDFS event free at last follow-up	2081 (93.4%)	2070 (94.3%)

Source: information request response dated 8/16/2017, Table 1

Reviewer Comments: *Majority of the patients in both arms were still under follow-up in study and censored due to data cutoff for the primary analysis.*

Sensitivity Analyses of IDFS

A series of sensitivity analyses for IDFS were conducted by both the agency and the applicant to evaluate the potential for assessment bias and to assess the robustness of IDFS results. Some of the sensitivity analyses performed by the applicant are listed in Table 21.

Table 21 Sensitivity Analyses of IDFS per Applicant in APHINITY

Sensitivity Analysis	**HR (95% CI)**
1. Censor at NACT if start date prior to first IDFS event	0.81 (0.65, 0.99)
2. Count patients as having an event at date of NACT if date prior to first IDFS event	0.94 (0.79, 1.11)
3. Censor patients who discontinued study follow-up at last assessment known to recurrence-free (ignores late reported deaths as events)	0.77 (0.62, 0.96)
4. Patients who discontinued study follow-up without a recurrence are considered to have a recurrence at the date of the next planned assessment, had they continued in the study	0.93 (0.80, 1.07)
5. Count patients who withdrew from targeted treatment due to toxicity as having an IDFS event 1 day after date last known to be recurrence-free	0.95 (0.82, 1.11)
6. Unstratified analysis	0.82 (0.67, 1.00)

NACT: new anti-cancer therapy
Source: APHINITY CSR Table 25

Reviewer Comments: *In all the sensitivity analyses, the HR point estimates were below 1, supportive of the primary analysis.*

The review team conducted additional sensitivity analyses for IDFS to evaluate the robustness of the observed results.

FDA Sensitivity Analysis 1: IDFS analysis in the safety population, which included patients who received any amount of study treatment and treatment arm according to the treatment actually received. A total of 4769 patients were included in this analysis (2364 patients in the pertuzumab arm and 2405 in the placebo arm). The HR of IDFS was 0.74 (95% CI: 0.60, 0.91) from a stratified Cox proportional hazards model, and estimates of IDFS rates were 94.45% vs. 92.92% at 3 years in the pertuzumab vs. placebo arms, respectively.

FDA Sensitivity Analysis 2: IDFS analysis in the ITT population excluding patients with major protocol deviations. A total of 1362 patients had major protocol deviations and were excluded from the ITT population in this sensitivity analysis. In this analysis, the HR of IDFS was 0.88 (95% CI: 0.70, 1.12) from a stratified Cox proportional hazards model.

FDA Sensitivity Analysis 3: IDFS analysis with patients with IDFS events occurring right after more than one missing assessment. A total of 14 patients (6 in the pertuzumab arm and 8 in the placebo arm) had events after 2 or more missing assessments. In the sensitivity analysis, those patients were censored at the last assessment before the missing assessments, and the HR of IDFS was 0.82 (95% CI: 0.66, 1.00) from a stratified Cox proportional hazards model.

Overall, the sensitivity analysis results were consistent with that of the primary IDFS analysis. The results of sensitivity analyses support the primary efficacy findings.

Efficacy Results – Secondary and other relevant endpoints

Key secondary endpoints were tested using a hierarchical testing procedure to control the overall alpha level at 0.05, 2-sided, in the order of: IDFS-SPNBC, DFS, and OS.

Invasive Disease-Free Survival Including Second Primary Non-Breast Cancer (IDFS-SPNBC)

At the clinical cutoff date, 189 patients (7.9%) in the pertuzumab arm and 230 patients (9.6%) in the placebo arm had an IDFS-SPNBC event, with a hazard ratio of 0.83 (95% CI: 0.68, 1.00) as summarized in Table 22. At 3 years, estimates of the IDFS-SPNBC event-free rates were 93.50% vs. 92.51% in the pertuzumab and placebo arms, respectively.

Table 22 FDA's IDFS-SPNBC Analysis, in the ITT Population of APHINITY

	Chemotherapy, trastuzumab and pertuzumab N=2400	Chemotherapy, trastuzumab and placebo N=2404
Number of IDFS-SPNBC events	189 (7.9%)	230 (9.6%)
3-yr IDFS rate (95% CI)	93.50% (92.49, 94.51)	92.51% (91.43, 93.58)
Stratified HR (95% CI)[a]	0.83 (0.68, 1.00)	
Stratified logrank p-value[a]	0.051	

[a]Stratified by randomization stratification factors collected from IxRS: nodal status, hormone receptor status, chemotherapy regimen, and protocol version.
Source: CSR Table 26 and dataset ate.xpt

Reviewer Comments: *Following the intent-to-treat principle, the analysis should be based on stratification factor data from IxRS as shown in Table 22, instead of using eCRF stratification data as the applicant did. This applies to the analyses of all the endpoints.*

The log-rank p-value of IDFS-SPNBC is 0.051 which is higher than the pre-specified significance level of 0.05. Therefore, no more alpha could be transferred to the next two secondary endpoints: DFS and OS. As a result, no p-value is reported for DFS and OS.

Disease-Free Survival

At the clinical cutoff date, a DFS event had occurred in 192 patients (8.0%) in the pertuzumab arm compared with 236 patients (9.8%) in the placebo arm, with a hazard ratio of 0.82 (95% CI: 0.68, 0.99) as shown in Table 23. At 3 years, estimates of the DFS event-free rates were 93.42% vs. 92.29% in the pertuzumab and placebo arms, respectively.

Table 23 FDA's DFS Analysis, in the ITT Population of APHINITY

	Chemotherapy, trastuzumab and pertuzumab N=2400	Chemotherapy, trastuzumab and placebo N=2404
# of DFS events	192 (8.0%)	236 (9.8%)
3-yr DFS rate (95% CI)	93.42% (92.40, 94.43)	92.29% (91.21, 93.38)
Stratified HR (95% CI)[a]	0.82 (0.68, 0.99)	

[a]Stratified by randomization stratification factors collected from IxRS: nodal status, hormone receptor status, chemotherapy regimen, and protocol version.
Source: CSR Table 28 and dataset ate.xpt

Overall Survival

The first interim analysis of OS was performed at the time of the IDFS primary analysis. At that time, 80 patients in the pertuzumab arm and 89 patients in the placebo arm

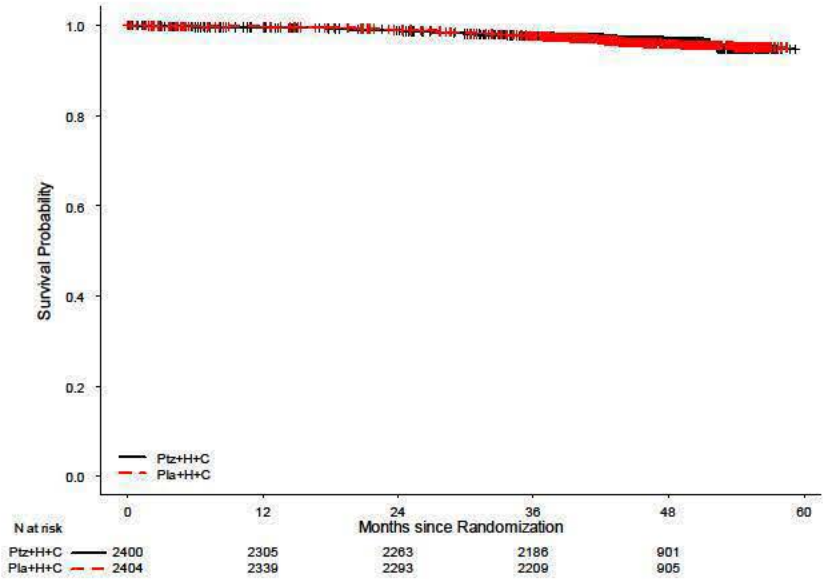
died. The hazard ratio of pertuzumab versus placebo was 0.89 with a 95% confidence interval of 0.66 to 1.21 (Table 24). Kaplan-Meier curves of overall survival are presented in Figure 4.

Table 24 FDA's Analysis of Overall Survival (the First Interim Analysis), in the ITT Population of APHINITY

	Chemotherapy, trastuzumab and pertuzumab N=2400	Chemotherapy, trastuzumab and placebo N=2404
# of deaths/# of patients(%)	80 (3.3%)	89 (3.7%)
Stratified HR (95% CI)[a]	0.89 (0.66, 1.21)	

[a]Stratified by randomization stratification factors collected from IxRS: nodal status, hormone receptor status, chemotherapy regimen, and protocol version.
Source: CSR Table 29 and dataset ate.xpt

Figure 4 Kaplan-Meier Curves of Overall Survival, in the ITT Population of APHINITY



Source: CSR Figure 7 and dataset ate.xpt

Reviewer Comments: At this interim analysis, survival data was not mature with 26% of the total required events for the final OS analysis. The final analysis of survival is planned to be performed when 640 deaths occur.

BERENICE PCR ANALYSIS

In BERENICE, the main efficacy endpoint was pCR in breast and nodes (ypT0/is ypN0) evaluated after surgery, following a scheduled eight cycles of neoadjuvant treatment. The pCR rate was 61.8% (95% CI: 54.7%, 68.6%) in Cohort A and 60.7% (95% CI: 53.6%, 67.5%) in Cohort B (Table 25). Patients (14 in Cohort A and 7 in Cohort B) did not undergo surgery or did not have a valid pathology assessment available were considered non-responders in the analysis.

Table 25 Summary of pCR Response (ypT0/is ypN0), Study BERENICE

	Cohort A (ddAC, T+ PH) N=199	**Cohort B (FEC, D+PH) N=201**
pCR, n (%)	123 (61.8%)	122 (60.7%)
95% CI	(54.7%, 68.6%)	(53.6%, 67.5%)

Source: BERENICE CSR Table 44

Reviewer Comments: *While the primary objective of the BERENICE study was to evaluate the safety of the addition of pertuzumab to anthracycline and trastuzumab based regimens, the rates of pCR were evaluated. The rate of pCR in Cohort A was estimated to be 61.8% (95% CI 54.7. 68.6) and the rate of pCR in Cohort B was estimated to be 60.7% (95% CI 53.6, 67.5). These estimates are consistent with the estimates of pCR obtained in the TRYPHAENA study which was 54.7% (42.7, 66.2) for FEC + docetaxel + trastuzumab + pertuzumab and 63.6% (51.9. 74.3) for docetaxel + carboplatin + trastuzumab + pertuzumab (BLA 125409 supplement 51 review).*

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

APHINITY

Patient reported outcomes were assessed for the APHINITY study using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30, the BR-23 which is its breast cancer module, and the EuroQoL (EQ-5D) questionnaires. These data were reviewed and were not considered part of the efficacy analysis but were considered as important data for the review of safety and tolerability. This review is located in Section 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability and Appendix 19.5.

Additionally, please see the COA consult review from Drs. Yasmin Choudhry and Selena Daniels.

Additional Analyses Conducted on the Individual Trial

APHINITY

Exploratory subgroup analyses of IDFS by demographics and baseline disease characteristics are presented in Table 26.

Table 26 Subgroup Analyses of IDFS per Baseline Characteristics, Study APHINITY

	Number of events/Total N (%)		IDFS at 3-year (%)		HR (95% CI)[a]
	Chemotherapy, trastuzumab and pertuzumab	Chemotherapy, trastuzumab and placebo	Chemotherapy, trastuzumab and pertuzumab	Chemotherapy, trastuzumab and placebo	
Age					
<65	147/2085 (7.0)	176/2111 (8.3)	94.2 (93.1, 95.2)	93.6 (92.4, 94.6)	0.85 (0.68, 1.05)
≥65	24/315 (7.6)	34/293 (11.6)	92.9 (89.1, 95.3)	90.6 (86.6, 93.5)	0.70 (0.41, 1.17)
Race					
White	118/1705 (6.9)	141/1694 (8.3)	94.4 (93.2, 95.4)	93.4 (92.0, 94.5)	0.84 (0.66, 1.07)
Asian	45/590 (7.6)	54/598 (9.0)	93.2 (90.8, 95.0)	93.1 (90.8, 94.9)	0.85 (0.57, 1.26)
Black	1/32 (3.1)	2/41 (4.9)	96.3 (76.5, 99.5)	97.5 (83.5, 99.6)	0.77 (0.04, 8.03)
Other	6/66 (9.1)	12/69 (17.4)	94.1 (93.0, 95.0)	93.2 (92.1, 94.2)	0.52 (0.18, 1.33)
Region					
USA	13/296 (4.4)	20/294 (6.8)	95.8 (92.6, 97.7)	94.1 (90.5, 96.3)	0.66 (0.32, 1.31)
Canada/W Europe/Aus-NZ/SA	93/1294 (7.2)	101/1289 (7.8)	94.4 (92.9, 95.5)	94.1 (92.6, 95.3)	0.93 (0.70, 1.23)
East Europe	17/200 (8.5)	28/200 (14.0)	93.0 (88.3, 95.9)	88.3 (82.9, 92.0)	0.61 (0.33, 1.11)
Asia-Pacific	42/550 (7.6)	50/557 (9.0)	93.3 (90.8, 95.1)	93.2 (90.7, 95.0)	0.85 (0.56, 1.28)
Latin America	6/60 (10.0)	11/64 (17.2)	89.6 (78.4, 95.2)	88.7 (77.8, 94.5)	0.59 (0.22, 1.61)
Hormone receptor status					
Positive	100/1536 (6.5)	119/1546 (7.7)	94.8 (93.5, 95.8)	94.4 (93.1, 95.4)	0.86 (0.66, 1.13)
Negative	71/864 (8.2)	91/858 (10.6)	92.8 (90.8, 94.3)	91.2 (89.0, 92.9)	0.76 (0.56, 1.04)
Nodal status					
Negative	32/897 (3.6)	29/902 (3.2)	97.5 (96.3, 98.4)	98.4 (97.3, 99.0)	1.13 (0.68, 1.86)
Positive	139/1503 (9.2)	181/1502 (12.1)	92.0 (90.5, 93.3)	90.2 (88.5, 91.6)	0.77 (0.62, 0.96)

Protocol version					
Protocol A	120/1828 (6.6)	143/1827 (7.8)	94.7 (93.6, 95.7)	94.1 (92.9, 95.1)	0.84 (0.66, 1.08)
Protocol Amendment B	51/572 (8.9)	67/577 (11.6)	91.9 (89.3, 93.9)	90.6 (87.9, 92.8)	0.77 (0.53, 1.11)
Menopausal status at screening					
Pre-menopausal	93/1152 (8.1)	96/1173 (8.2)	93.7 (92.1, 95.0)	93.7 (92.1, 95.0)	0.99 (0.75, 1.32)
Post-menopausal	78/1242 (6.3)	113/1220 (9.3)	94.5 (93.1, 95.7)	92.7 (91.1, 94.1)	0.68 (0.51, 0.91)
Surgery type for primary cancer					
Breast-conserving	52/1118 (4.6)	66/1076 (6.1)	96.6 (95.4, 97.6)	95.3 (93.8, 96.4)	0.75 (0.52, 1.08)
Mastectomy	119/1280 (9.3)	144/1327 (10.8)	91.8 (90.1, 93.2)	91.6 (90.0, 93.0)	0.88 (0.69, 1.11)
Adjuvant Chemotherapy Regimen					
Anthracycline	139/1865 (7.4)	171/1877 (9.1)	93.8 (92.6, 94.8)	93.0 (91.8, 94.1)	0.82 (0.66, 1.03)
Non-Anthracycline	32/535 (6.0)	39/527 (7.4)	94.9 (92.6, 96.6)	94.0 (91.5, 95.8)	0.82 (0.51, 1.31)

[a] HR is based on unstratified Cox proportional hazards model

Reviewer comments: *There was consistent evidence of benefit across all subgroups; however, in the node negative group the hazard ratio was 1.13 and the confidence interval included 1. It was noted that the number of events in this group was small and recurrence risk is lower compared to the node positive subgroup (in the placebo arm, 3-year IDFS rate of the node negative subgroup was 98.4% vs. 90.2% in the node positive subgroup).*

Pertuzumab has shown benefit in both hormone receptor positive and negative subgroups; while the hormone receptor negative subgroup had numerically higher hazard ratio compared to the hormone receptor positive subgroup. Per the 3-year IDFS rate in the placebo arm, the hormone receptor negative subgroup of patients had higher recurrence risk than the hormone receptor positive subgroup.

BERENICE

Exploratory subgroup analyses of pCR by demographics and baseline disease characteristics are presented in Table 27.

Table 27 Subgroup Analyses of pCR per Baseline Characteristics, Study BERENICE

	Cohort A (ddAC, T+PH)		Cohort B (FEC, D+PH)	
	#of pCR/# of patients	**pCR, % (95% CI)**	**#of pCR/# of patients**	**pCR, % (95% CI)**
Age				
<65	110/176	62.5 (54.9, 69.7)	106/176	60.2 (52.6, 67.5)
≥65	13/23	56.5 (34.5, 76.8)	16/25	64.0 (42.5, 82.0)
Region				
Europe	57/88	64.8 (53.9, 74.7)	117/194	60.3 (53.1, 67.3)
North America	62/106	58.5 (48.5, 68.0)	5/6	83.3 (35.9, 99.6)
South America	4/5	80.0 (28.4, 99.5)	0/1	0
Race				
White	104/169	61.5 (53.8, 68.9)	99/163	60.7 (52.8, 68.3)
Black	7/11	63.6 (30.8, 89.1)	0	0
Asian	2/6	33.3 (4.3, 77.7)	3/4	75.0 (19.4, 99.4)
Other	10/13	76.9 (46.2, 95.0)	20/34	58.8 (40.7, 75.4)
Central Hormone Receptor Status				
Positive	66/128	51.6 (42.6, 60.5)	71/124	57.3 (48.1, 66.1)
Negative	53/65	81.5 (70.0, 90.1)	51/75	68.0 (56.2, 78.3)
Tumor Staging				
T2	84/138	60.9 (52.2, 69.1)	84/130	64.6 (55.8, 72.8)
T3	20/33	60.6 (42.1, 77.1)	24/45	53.3 (37.9, 68.3)
T4	5/9	55.6 (21.2, 86.3)	7/13	53.9 (25.1, 80.8)
Nodal Staging				
NX	2/8	25.0 (3.2, 65.1)	4/9	44.4 (13.7, 78.8)
N0	52/80	65.0 (53.5, 75.3)	48/74	64.9 (52.9, 75.6)
N1	60/92	65.2 (54.6, 74.9)	58/98	59.2 (48.8, 69.0)
N2+N3	9/19	47.4 (24.5, 71.1)	12/20	60.0 (36.1, 80.9)

Source: BERENICE CSR Table 48

Reviewer Comments: *The BERENICE study demonstrated rates of pathological complete response that were consistent with previous studies. The pCR (ypT0/is ypN0) rates were 61.8% (95% CI: 54.7, 68.6) and 60.7% (95% CI: 53.6, 67.5) for patients treated with ddAC followed by pertuzumab plus trastuzumab and paclitaxel, or FEC followed by pertuzumab plus trastuzumab and docetaxel. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 51.6% (95% CI: 42.6, 60.5%) and 57.3% (95% CI: 48.1, 66.1%) than with hormone receptor-negative tumors: 81.5% (95% CI: 70.0, 90.1%) and 68.0% (95% CI: 56.2, 78.3%).*

A post-marketing commitment to evaluate the pretreatment molecular subtyping of tumors from patients treated in the BERENICE study and to perform an exploratory analysis of the relationship of pCR with the different molecular subtypes was fulfilled with analysis of patients in this study demonstrating the following results captured in Table 28.

Table 28: Rates of PCR by PAM50 Molecular Subtype

	Cohort A (ddAC, paclitaxel, H&P) N=199	***Cohort B (FEC, docetaxel, H&P) N=201***
Overall	*123 (61.8)*	*122 (60.7)*
Luminal A	*15/33 (45.5)*	*14/31 (45.2)*
Luminal B	*10/24 (41.7)*	*7/15 (46.7)*
Basal-like	*5/11 (45.5)*	*1/5 (20.0)*
HER2 Enriched	*60/80 (75.0)*	*70/95 (73.7)*
Data unable to obtain/missing	*33/51 (64.7)*	*30/55 (54.5)*

Source: Table 55 BERENICE CSR, page 155

Reviewer Comments: *The highest rate of pCR was in the HER2 enriched population. However, the PAM50 molecular profile has not yet been prospectively validated to direct care, and a sizeable proportion of patients in each molecular subtype did achieve a pCR after neoadjuvant treatment. These data are interesting and hypothesis generating, but have limited translation into clinical practice. Also, the relationship between molecular subtype, pCR, and clinical outcomes is unclear.*

Integrated Review of Effectiveness

Pertuzumab in combination with chemotherapy was initially approved in September 2013 for the neoadjuvant treatment of HER2 positive early or locally advanced breast cancer with tumors >2 cm in diameter and/or those with evidence of lymph node involvement. This accelerated approval was based on data from the TRYPHAENA and NEOSPHERE trials that demonstrated an increase in the rate of pathological complete response (pCR) with the addition of pertuzumab to chemotherapy and trastuzumab when compared to trastuzumab alone. These data, in combination with data from the phase 3 CLEOPATRA study demonstrating improvement in progression free and overall survival with the addition of pertuzumab to docetaxel and trastuzumab for the initial treatment of metastatic HER2 positive breast cancer, supported the indication for the approval.

At the time of the accelerated approval of this agent based on the increased rate of pCR, the randomized, placebo controlled, phase 3 APHINITY study was ongoing to establish the clinical benefit of pertuzumab in the adjuvant setting. This study enrolled a broad range of tumor stages and included tumors at least 1 cm as well as those 0.5-1 cm that were HR negative, histological grade 3, or where the patient was younger than 35 years old. This included a group of patients with a variety of recurrence risks based on their initial tumor stage and characteristics.

When it was noted that a greater number of patients without evidence of lymph node involvement had enrolled than was expected, the applicant amended the protocol to enrich the patient population with patients who had node positive disease. This resulted in a patient population that was primarily node positive and was more consistent with the study populations in the previous adjuvant trastuzumab trials.

The overall analysis of the ITT population demonstrated a modest but statistically significant improvement in IDFS which was the study's primary endpoint. This improvement is most clinically meaningful to patients with high risk of recurrence. Certain subgroups at higher risk appeared to benefit more from pertuzumab such as patients with hormone receptor negative disease and lymph node positive disease.

The addition of pertuzumab to standard chemotherapy and trastuzumab adds a clinically meaningful benefit in improving IDFS, particularly for those at higher risk of disease recurrence. This is supported by evidence from the NEOSPHERE, TRYPHAENA, and CLEOPATRA studies.

8.1.4. **Assessment of Efficacy Across Trials**

The APHINITY study demonstrates a statistically significant improvement in IDFS for patients with operable HER2 positive breast cancer. The clinical significance of this improvement is most clinically meaningful for those patients who are at high risk of disease recurrence, such as those with hormone receptor negative disease as well as those with lymph node involvement.

The data from the APHINITY study, along with data from the CLEOPATRA study, which demonstrated a statistically significant and clinically meaningful improvement in both progression free and overall survival in patients treated in the first-line setting for HER2 positive metastatic breast cancer, demonstrate the clinical benefit of the addition of pertuzumab to standard chemotherapy in multiple settings for patients with HER2 positive breast cancer.

The totality of evidence in the metastatic as well as early breast cancer settings demonstrates that the addition of pertuzumab to trastuzumab based regimens improves clinical outcomes.

Primary Endpoints

The primary endpoints of the NEOSPHERE and TRYPHAENA studies was the rate of pCR in early/locally advanced breast cancer, defined as the absence of invasive cancer in the breast and lymph nodes at the time of definitive surgery. The primary endpoint of the CLEOPATRA study, in patients with metastatic HER2 positive breast cancer, was progression-free survival with a supportive endpoint of overall survival. Invasive disease free survival (IDFS) is an accepted endpoint for adjuvant breast cancer therapy trials, though as noted previously, the generally agreed upon definition includes second primary non-breast cancers while the APHINITY study IDFS primary endpoint did not.

The APHINITY study is somewhat difficult to use as a confirmation of the validity of the use of pCR as a surrogate endpoint based on the fact that the APHINITY study included a number of patients with smaller tumor sizes than those included in the neoadjuvant studies. Additionally, while larger node negative tumors did not appear to derive benefit from the addition of pertuzumab to standard chemotherapy, it is unknown whether neoadjuvant treatment in this setting might have been associated with improved outcomes.

Secondary and Other Endpoints

The APHINITY study had multiple secondary endpoints, including IDFS counting second non-primary breast cancer (IDFS-SPNBC), DFS, and overall survival. These endpoints were part of the statistical hierarchy; however, the IDFS-SPNBC was not statistically significant (p=0.051) and the overall survival data were immature. (b) (4)

(b) (4)

The Agency does agree that physical and role function assessments are important to patients and did feel in the review of the PRO data that physical and role function were well assessed with the instruments used. The Agency's full review of the PRO data submitted as part of the APHINITY application are contained in section 19.5.

Subpopulations

Based on subgroup analysis, in the adjuvant and neoadjuvant setting, the greatest benefit of the addition of pertuzumab to standard chemotherapy and trastuzumab based regimens appears to come to those patients with the highest risk of disease recurrence. This is demonstrated in subgroups such as those patients with hormone receptor negative disease as well as those patients with lymph node involvement. The increased numbers of node negative patients and hormone receptor positive patients who made up the APHINITY study population likely affected the performance of the control arm, as these patients have excellent outcomes with trastuzumab based chemotherapy at the 3-year time point.

Of note, there are few patients older than 75 years in the entire pertuzumab clinical development program. This limits our understanding of the degree of benefit for this population as well as of the risks associated in this population. Additionally, very few African-

American or Black patients were enrolled in this study, thus limiting our understanding in this patient population. However, there is no biological reason to think there would be significant differences in safety or efficacy in these patients.

While male patients were not excluded, they also made up a very small proportion of the study population. Again, there is no biological reason to think there would be significant differences in safety or efficacy in these patients.

Of note, while it is often thought that younger patients have a higher risk of disease recurrence, the estimated 3-year IDFS rate for patients <65 years of age was higher than that in those ≥65 years of age and the estimated 3-year IDFS rate for premenopausal patients was higher than that for post-menopausal patients. Worth noting is that the premenopausal subgroup demonstrated a 0.99 HR; however, there was uncertainty in this point estimate, suggesting there may be clinical benefit. For this patient population, it is unclear what may be the best time point to determine evidence of IDFS benefit, as younger patients remain "at risk" for a longer period of time to develop distant disease recurrence. Improved understanding of differences in tumor biology based on patient age may help to better understand the impact of therapy in these patients.

As noted previously, patients with lymph node involvement and those with hormone receptor negative disease appeared to derive greater clinical benefit. It is notable that in neoadjuvant studies, the rate of pCR in patients with hormone receptor negative disease was greater than that in patients with HR positive disease.

Those that appeared to derive the least benefit were those with node negative disease who, in the placebo arm, had a 3-year IDFS rate of 98.4%.

Additional Efficacy Considerations

The use of pertuzumab in the post-marketing setting may include a broader age range of patients than that seen in the clinical trial setting, particularly patients over 65 and those over 75 years of age. For these patients, there may be increased toxicity as compared to younger patients. However, given that this agent has been on the market in the neoadjuvant setting with post-marketing off-label use in the adjuvant setting as well, providers may be familiar with the risks and benefits in this patient population though it is less well characterized in trial data.

Though only 12% of the study population was from the U.S., it is expected that the efficacy results will be similar in the U.S. post-market setting.

8.1.5. Integrated Assessment of Effectiveness

The addition of pertuzumab to the efficacy of treatment of HER2 breast cancer in both the early, locally advanced, and metastatic settings, has demonstrated substantial evidence of efficacy across indications and across clinical endpoints. While the overall results of the

addition of pertuzumab to adjuvant chemotherapy and trastuzumab in the operable HER2 positive breast cancer setting is statistically significant, it is noted that this benefit is most clinically relevant to patients at higher risk of disease recurrence. These patients include those with node positive disease and those with hormone receptor negative disease.

The results of the APHINITY trial, demonstrate evidence of efficacy of pertuzumab with the greatest clinical benefit in those patients at high risk of recurrent disease.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety data were reviewed from Trial BO25126 (APHINITY), submitted on July 28, 2017, in supplement 118, and trial WO29217 (BERENICE), submitted on February 28, 2017, in supplement 113. (See table of Clinical Studies in section 7.1 of this review.) BERENICE was designed as a phase 2, cardiac safety trial of two neoadjuvant anthracycline/taxane-based chemotherapy regimens administered in combination with neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early stage HER2-positive breast cancer, and followed by continued adjuvant pertuzumab + trastuzumab. The primary clinical data cutoff date was March 3, 2016. The 4-month safety update for BERENICE was submitted June 21, 2017, with a clinical cutoff date of January 7, 2017.

The APHINITY study is an ongoing, phase 3, randomized, multicenter, double-blind, placebo-controlled comparison of chemotherapy (chemo) plus trastuzumab plus pertuzumab (PTZ) versus chemotherapy plus trastuzumab (H) plus placebo (PL) as adjuvant therapy for patients with operable HER2-positive primary breast cancer. The primary clinical data cutoff date for APHINITY was December 19, 2016. The 3-month safety update was submitted October 23, 2017, with a clinical cutoff date of May 15, 2017.

8.2.2. Review of the Safety Database

Overall Exposure

APHINITY

The safety population included patients who received any amount of study medication (chemotherapy, pertuzumab/placebo, or trastuzumab), classified by the actual treatment received. There were 4769 patients in the safety population (2364 patients in the PTZ+H+Chemo (PTZ) arm and 2405 in the PL+H+Chemo (PL) arm). Thirty-eight patients randomized to the PTZ arm received treatment without pertuzumab and, therefore, were included in the PL arm for safety analysis. (These patients did not receive trastuzumab or taxane therapy on study, but 3 subjects received trastuzumab/taxane therapy off-study.) There

were 24 patients randomized to the PL arm who received at least one dose of pertuzumab and these subjects were included in the pertuzumab arm for safety analysis.

In the APHINITY trial, patients were to be treated with one of the protocol-approved adjuvant chemotherapy regimens (anthracycline or non-anthracycline based regimens) and randomized to receive trastuzumab plus placebo or trastuzumab plus pertuzumab (see section 8.1.1 of this review for further details). The randomized targeted treatment was to start concurrently with the taxane component of chemotherapy. A loading dose of pertuzumab 840 mg IV was administered at the first cycle of targeted therapy and then 420 mg every 3 weeks. Randomized targeted treatment was to be administered for a total of 52 weeks plus a window of 3 days for a maximum of 18 cycles within 1 year.

The duration of treatment includes 28 days (of observation) after the last dose of study therapy. The median duration of study treatment (64 weeks) and targeted treatment (55 weeks) was the same for the PTZ and PL treatment arms.

The following table summarizes duration of patient exposure to study treatment for the safety population, by treatment arm.

Table 29: APHINITY Treatment Duration for Safety Population by Regimen

		Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	**Placebo + Trastuzumab + Chemotherapy (N=2405)**
Study Treatment Period Duration[a] (weeks)	N	2364	2405
	Median	64	64
	Range	4-80	4-74
Anthracycline Treatment Duration[b] (weeks)	N	1834	1894
	Median	11	13
	Range	4-26	4-18
Taxane + Targeted Treatment Duration[b] (weeks)	N	2364	2338
	Median	55	55
	Range	4-59	4-70
Targeted Treatment Duration[b] (weeks)	N	2364	2335
	Median	55	55
	Range	4-59	4-70

[a] Source dataset: atx.xpt.
[b] Source dataset: aex.xpt.
Additional source, CSR p.172, Table 45

Exposure to anthracycline-based chemotherapy was similar in both treatment arms, with 86.5% in the PTZ arm and 84.5% in the PL arm completing both anthracycline-based chemotherapy

and targeted therapy. Exposure to treatment components was similar, independent of which anthracycline-based regimen was chosen. Exposure to taxanes was similar for patients who received paclitaxel and docetaxel regimens.

For patients who received non-anthracycline based chemotherapy (TC = docetaxel + carboplatin), a lower proportion completed both chemotherapy and targeted therapy in the PTZ arm compared to the PL arm. The next table summarizes exposure information for patients treated with non-anthracycline chemotherapy.

Table 30: APHINITY Exposure for non-Anthracycline Chemotherapy Treated Patients

	Ptz + H + Chemo (N=528)	Pla + H + Chemo (N=510)
Completed docetaxel and carboplatin (TC)	448 (84.1%)	469 (91.6%)
Completed TC+ targeted therapy	416 (78.8%)	448 (87.8%)
Completed targeted therapy but not TC	37 (7.0%)	13 (2.5%)
Median treatment duration[a] (range)	55 (4–59)	55 (4–59)

TC= docetaxel+carboplatin.

[a] Duration of docetaxel and carboplatin and + targeted treatment (weeks).

Source: CSR p.176, Table 48

Diarrhea was the most common AE that led to discontinuation of any study therapy (PTZ 2.5% vs. PL 0.6%).

At the time of the clinical cutoff for the primary analysis, 86.2% and 84.9% of all patients, respectively, had received at least 17 (of 18 planned) cycles of treatment with PTZ or placebo in the respective treatment arms. The median number of cycles of PTZ/PL was 18 in both arms (range 1-22 in the PTZ arm vs. 1-18 in the PL arm). The median cumulative dose of PTZ for patients in the PTZ arm was 7980 mg (range 420-9660 mg).

No PTZ/PL dose delays occurred in 48.9% of patients in the PTZ arm vs. 49.6% of patients in the PL arm. Trastuzumab was administered without dose delays in 48.3% of patients in the PTZ arm vs. 49.0% of patients in the PL arm. The number of dose adjustments/delays for adverse events for PTZ and for trastuzumab was the same, with 2364 for each of PTZ and trastuzumab in the PTZ arm and 2335 for each in the PL arm. The median cumulative dose of trastuzumab for patients in the PTZ arm was 6765 mg (range 336-16546 mg) and the median cumulative dose was 6930 mg in the PL arm (range 410-16758 mg).

Overall Exposure

BERENICE

There were 401 patients enrolled in the phase 2 Berenice trial (199 in Cohort A and 202 in Cohort B). The safety population consisted of 397 patients, of whom 199 were in Cohort A (ddAC + T+PH) and 198 were in Cohort B (FEC, D+PH). One patient with HER2- disease was enrolled in Cohort B and was excluded from analysis Several patients withdrew before treatment. One Cohort B patient received Cohort A treatment and was included in the Cohort A safety population.

The majority of patients completed all four scheduled cycles of their anthracycline, 194/199 (97.5%) in Cohort A and 197/198 (99.5%) in Cohort B. Similarly, the majority of patients completed all four scheduled cycles of taxane based therapy, 176/199 (90.3%) in Cohort A and 176/198 (89.8%) in Cohort B. Patients in Cohort A received a median cumulative dose of 1595 mg of paclitaxel and patients in Cohort B received a median cumulative dose of 530 mg of docetaxel. Sixty-four of 199 (32.9%) of patients in Cohort A and 51/198 (26.0%) of patients in Cohort B had a dose modification or delay due to an adverse event.

At the time of clinical cut off for the 120-day safety update (January 7, 2017), 339 patients (84.5%) had completed overall study treatment. The majority of patients, 150 (83.3%) in Cohort A and 152 (80.0%) in Cohort B completed all 13 cycles of adjuvant pertuzumab and trastuzumab. Most infusions were given without dose delays or interruptions and dose adjustments for pertuzumab were not allowed. The median treatment duration in weeks for the adjuvant period was 39.0 for each cohort. The median cumulative dose of pertuzumab for the adjuvant period was 5880 for each cohort. The median cumulative dose of trastuzumab for the adjuvant period was 5266 for those in Cohort A and 5042 for those in Cohort B. There were a numerically greater number of patients in Cohort A (165, 91.2%) who completed the adjuvant period with no dose modifications or delays due to an adverse event than those in Cohort B (164, 86.3%).

Relevant characteristics of the safety population:

Demographic and other baseline information for patients in the APHINITY trial are summarized in section 8.1.2 of this review in Table 12 and Table 13 and characteristics appear balanced between the treatment arms. (There were 4804 patients in the ITT population and 4769 in the safety population.) Almost all patients were female (0.2% males); 71% were Caucasian, 25% Asian race, and 1.5% black. The median age was 51 years, with a range of 18 to 86 years. There were 30 patients (1.3%) in the PTZ arm and 26 patients (1.1%) in the placebo arm who were age 75 or older. There were 315 patients (13.1%) in the PTZ arm and 293 patients (12.2%) in the placebo arm who were age 65 or older. In the overall population, 48.5% were pre-menopausal (48.1% in the PTZ arm and 49.0% in the placebo arm).

Demographic and other baseline information for patients in the BERENICE trial are summarized in Table 15 and Table 16. Of the 397 patients in the safety population (401 total enrolled), patients in both cohorts were similar. All patients were female except one. Most patients were Caucasian (83%), with 10 patients (2.5%) Asian race and 11 (2.8%) black. The median age was

49 years, with a range of 21-78 years. There were 41 patients (10.3%) older than age 65. Most patients were pre-menopausal (n=240, 60.2%).

Adequacy of the safety database:

In the APHINITY trial, 4769 patients in the safety population received adjuvant therapy, with 2364 patients treated in the pertuzumab arm and 2405 in the placebo arm. The BERENICE trial provided additional cardiac and general safety data for 397 patients in the safety population who were treated in the neoadjuvant setting with anthracycline-based chemotherapy plus pertuzumab and trastuzumab, with continuation of targeted therapy into the adjuvant setting. The overall safety database was considered adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The BLA submission contained all required components of the eCTD. The overall quality and integrity of the application were adequate for substantive review to be completed.

Categorization of Adverse Events

APHINITY

In the APHINITY study, the applicant defined Adverse Events (AEs) consistent with ICH guidelines as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Pre-existing conditions which worsen during a study are to be reported as AEs. After informed consent but before therapy, only serious adverse events (SAEs) caused by a protocol-mandated intervention (e.g. biopsy) were to be reported. The definition of SAE was any AE that met the following criteria:

- Fatal (i.e., the adverse event causes or leads to death)
- Life threatening
- Requires or prolongs inpatient hospitalization
- Results in significant or persistent disability or incapacity
- Congenital anomaly or birth defect in a neonate or infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment that would jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalizations solely due to recurrence of primary malignancy were not to be reported as SAEs.

AEs were graded for severity according to the NCI-CTCAE version 4.0 on a five-point scale (1-5). Treatment-emergent adverse events (TEAEs) were defined as events reported up to 28 days after the last dose of study medication. AEs occurring during the study and up to 28 days after the last dose of study drug were reported in detail on the electronic Case Report Form (eCRF) and followed until resolution or end of study. Heart failure was also graded according to the New York Heart Association (NYHA) classification. Recurrence of the underlying malignancy was not to be reported as an AE. Treatment-emergent abnormal laboratory tests were to be recorded as a single diagnosis on the AE eForm in the eCRF if there were associated clinical symptoms, changes in study medication or concomitant therapy. Verbatim descriptions of AEs were mapped to MedDRA version 19.1 thesaurus terms. AEs were summarized by primary system organ class (SOC). Safety coding appeared generally appropriate.

"Events to Monitor" were prospectively defined based on the known pertuzumab AE profile, using standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) if available, or baskets of Roche Standard MedDRA Adverse events group terms (AEGTs). These Events to Monitor included the following AEs of special interest: Diarrhea, Rash, Hypersensitivity and Anaphylaxis, Infusion-related reactions, Mucositis, Leukopenia, Febrile neutropenia, and Interstitial lung disease.

Left Ventricular Systolic Dysfunction (LVSD), both symptomatic and asymptomatic, were study-specific cardiac AEs. Symptomatic LVSD (heart failure) was to be reported as an SAE, "congestive heart failure." Asymptomatic declines in LVSD were not to be reported as AEs, unless certain criteria were met, since LV Ejection Fraction (LVEF) data were collected separately in the eCRF. The following table from CSR section 3.8.3.4 summarizes the reporting conventions for LVSD and Heart Failure.

Table 31: APHINITY Reporting Conventions for Left Ventricular Systolic Dysfunction/Heart Failure (Applicant Table)

Observation	Protocol guidance for how to report	Term to be Reported	Grading
Asymptomatic decline in LVEF < 10% points from baseline or to an LVEF ≥ 50%	No additional reporting required, LVEF results to be reported on eCRF	N/A	N/A
Asymptomatic decline in LVEF ≥ 10% points from baseline to an LVEF < 50%	AE (eCRF AE e-form)	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of Perjeta/placebo and Herceptin	AE (eCRF AE e-form) and to be reported on SAE form as an AE of special interest	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Heart failure (symptomatic left ventricular systolic dysfunction)	AE (eCRF AE e-form) and SAE (SAE form)	Heart failure	NCI CTCAE for "heart failure" and NYHA Class

Any symptomatic left ventricular systolic dysfunction event had to be reported as "heart failure"
[a] Report the status "asymptomatic" and the LVEF value in the comments field as appropriate

Source: CSR p.82, Table 6

In addition, Primary and Secondary Cardiac Endpoints were defined in the protocol and analyzed. See definitions and results below, in Section 8.2.4, "Significant Adverse Events," of this review.

The selected AEs listed below were to be followed and recorded for up to 10 years after completion of study therapy:

- Study treatment-related SAEs
- Cardiac AEs (irrespective of causality)
- Pregnancies
- Non-breast -related second primary malignancies and myelodysplastic syndrome, irrespective of causality.

BERENICE

In the BERENICE study, the applicant defined an adverse event (AE) according to ICH guidelines for GCP as any untoward medical occurrence in a clinical investigation patient who was administered a pharmaceutical product without regard to causal attribution. An AE could be any of the following:

- An unfavorable or unintended sign, including abnormal laboratory findings, symptoms, or disease temporally associated with the use of a medicinal product regardless of whether considered related to the medicinal product.
- New disease or exacerbation of existing disease except as described in the protocol.

- Recurrence of an intermittent medical condition (e.g. headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test such as ECG or x-ray associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- AEs that are related to protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g. screening invasive procedures such as biopsies).

Reviewer Comment: *This definition of AE, particularly with regard to the laboratory and clinical test being associated with symptoms, or a change in study treatment, may have led to underreporting of these findings in patients who were on the BERENICE study.*

A serious adverse event (SAE) was defined as any adverse event that met the following criteria:

- Fatal (i.e., the adverse event causes or leads to death)
- Life threatening
- Requires or prolongs inpatient hospitalization
- Results in significant or persistent disability or incapacity
- Congenital anomaly or birth defect in a neonate or infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment that would jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed above.

All AEs and SAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. AEs were summarized by dictionary derived term, body system or organ class, primary system or organ class (SOC). Treatment emergent adverse events were defined as events reported up to 28 days after the last dose of study medication.

Routine Clinical Tests

APHINITY

In the APHINITY study, baseline evaluation included physical examination and determination of ECOG status, which were to be repeated at least every 3 months. Baseline studies also included breast imaging (mammogram or breast MRI) and chest X-ray/CT/MRI/PET within 6 months of randomization. Women of child bearing potential were required to have a negative pregnancy test within 7 days of randomization and every 9 week during targeted therapy. Routine laboratory tests included CBC with platelets and neutrophil count, serum chemistries (blood urea nitrogen, creatinine, serum electrolytes [phosphorus, calcium, sodium, potassium, and chloride]), and liver function tests (bilirubin total, direct and indirect, alkaline phosphatase, AST, ALT, and LDH). These studies were collected at baseline within 7 days prior to randomization and were to be repeated within 3 days of the beginning of each cycle of adjuvant therapy and

at 28 days after therapy completion, except liver function tests were not required cycle 7 and 8 (weeks 19 and 22) of targeted therapy.

An electrocardiogram (ECG) was required at baseline and after completion of therapy or at week 52. “Additional ECGs to be performed as clinically indicated.”

Left ventricular ejection fraction (LVEF) was to be assessed by echocardiogram (preferred) or MUGA scan at baseline within 14 days prior to randomization. The same method was to be utilized throughout the study for each patient. LVEF was to be assessed every 12 weeks just prior to the next scheduled cycle. For patients receiving anthracyclines, an additional assessment was required after completion of anthracycline therapy but before starting anti-HER2-targeted therapy, to assure that the LVEF was at least 50%.

BERENICE

In the BERENICE study, routine laboratory tests including a complete blood count (CBC) with platelet and differential and serum chemistries and electrolytes (glucose, blood urea nitrogen, creatinine, bicarbonate, uric acid, total protein, albumin, total, direct and indirect bilirubin, alkaline phosphatase, AST, ALT, LDH, and serum electrolytes [phosphorus, calcium, sodium, potassium, and chloride]) were collected at every cycle of neoadjuvant therapy (either every 14 days or every 21 days depending on treatment regimen). During the adjuvant period, CBC and limited chemistries including AST, ALT, LDH, total, direct, and indirect bilirubin and creatinine were collected as per local practice for trastuzumab dosing.

A 12-lead electrocardiogram was collected at screening and after completion of the anthracycline portion of the neoadjuvant regimen.

Echocardiogram or multiple-gated acquisition (MUGA) scan to assess left ventricular ejection fraction were performed at study screening, prior to the initiation of taxane, trastuzumab, and pertuzumab during the neoadjuvant period, at the midpoint of taxane, trastuzumab and pertuzumab during the neoadjuvant period, and prior to cycles 9, 12, 15, and 18 during the adjuvant period (21 day cycles) and at study completion visit. After completion of adjuvant therapy, LVEF assessment was to be performed every 6 months for two years and then annually for two additional years or until initiation of other systemic therapy.

Serum anti-therapeutic antibodies were obtained at screening/baseline and weeks 5, 14, 18, at any time between cycle 8 day 21 and surgery, and at the study completion or early termination visit.

8.2.4. Safety Results

Deaths

APHINITY

As of the time of the clinical data cut-off for the primary analysis, December 19, 2016, there were 73 deaths in the PTZ treatment arm (3.1%) and 95 deaths (4.0%) in the PL treatment arm for the safety population. Disease recurrence was the most common cause of death, 48 patients in the PTZ arm (2.0%) and 63 patients (2.6%) in the PL arm. Deaths due to AEs any time during the study period occurred in 18 patients (0.8%) in the PTZ arm and 20 patients (0.8%) in the PL arm. Among these fatal AEs were Second Primary Non-Breast Cancers (SPNBC), 9 reported in the PTZ arm and 8 events in the PL arm. Of 39 SAEs resulting in death in 38 patients, the sponsor attributed one death in each treatment arm to study therapy.

- Patient (b) (6), PTZ arm: This 58-year-old female patient died on study day 685 of a malignant tongue neoplasm.
- Patient (b) (6), PL arm: This 58-year-old woman died suddenly of cardiac failure on study day 1373. She had received 4 cycles of epirubicin-cyclophosphamide, followed by left chest wall radiation. She experienced grade 3 heart failure 2 months after PL +trastuzumab therapy but had recovered.

Reviewer Comments: *Both fatalities occurred remotely from study therapy, in the follow-up period, and true attribution is uncertain.*

During or within 30 days of PTZ/PL therapy, there were 6 deaths in the PTZ arm (0.3%) and 8 deaths in the PL arm (0.3%). The causes of death are listed in the following table.

Table 32: APHINITY Cause of Death within 30 Days of PTZ/PL Study Therapy by Treatment Arm

Cause of Death	PTZ + Trastuzumab + Chemo n=2364	PL + Trastuzumab + Chemo n=2405
Cerebral/Subarachnoid hemorrhage	1	
Febrile neutropenia	1	
Hyperkalemia	1	
Pneumonia aspiration	1	
Road traffic accident	1	
Sepsis/septic shock	1	2
Cardiac arrest		1
Intestinal ischemia		1
Lung infection		1
Pulmonary embolism		1
Pulmonary fibrosis		1
Suicide		1
TOTAL	6 (0.3%)	8 (0.3%)

Reviewer Comments: *Based on review of the narratives, of the 4 patients who died with febrile neutropenia or sepsis, the deaths all seem to be chemotherapy related. Two of these patients had not yet started the PTZ/PL phase of therapy.*

As of the primary clinical data cut-off, December 19, 2016, all patients had completed study treatment (or discontinued/never started), and 2178 patients (90.8%) in the PTZ arm and 2186 patients (90.9%) in the PL arm were alive and remained in the study. As of the time of the clinical data cut-off for the 3-month safety update, May 15, 2017, 2153 patients (89.7%) in the PTZ treatment arm and 2171 patients (90.3%) in the PL treatment arm were alive and remained in the study.

An additional 18 patients died (10 in the PTZ arm vs. 8 patients in the PL arm) between the December 2016 and May 2017 clinical cut-off dates. Overall, a total of 186 patients died during the study, 83 patients (3.5%) in the PTZ arm and 103 patients (4.3%) in the PL arm. Disease recurrence was the most common cause of death in each arm, 54 PTZ patients (2.3%) vs. 69 PL patients (4.3%). Deaths due to AEs at any time during the study occurred in 19 patients in the PTZ arm and 22 patients in the PL arm. The following table summarizes the causes of death in the safety population any time during the trial, including post-therapy follow-up, as of the May 15, 2017, (safety update) cut-off date.

Table 33: APHINITY Summary of Deaths by Treatment Regimen, Safety Population

	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Total No. of Deaths	83 (3.5%)	103 (4.3%)
Primary Cause of Death		
RECURRENCE OF DISEASE	54 (2.3%)	69 (2.9%)
ADVERSE EVENT	19 (0.8%)	22 (0.9%)
OTHER	10 (0.4%)	12 (0.5%)

Source: 3-month Safety Update, p.16, Table 4

The 3 new fatal AEs that occurred between the times of the primary and updated data cut-off dates were all SPNBC events, which had been previously reported as part of the secondary efficacy endpoint, and subsequently resulted in death. Two patients in the PL arm died of breast angiosarcoma on day 1225 (attributed to radiation) and malignant peritoneal neoplasm on study day 1529, respectively. A 72-year-old patient in the PTZ arm, with a smoking history, died of lung cancer on day 1107. The following table lists the deaths due to AEs anytime during the trial, including post-therapy follow-up, as of the date of the 3-month clinical safety update.

Table 34: APHINITY Deaths due to AEs by Treatment Regimen

Cause of Death SOC/Preferred Term	PTZ + Trastuzumab + Chemo n=2364	PL + Trastuzumab + Chemo n=2405
Blood and Lymphatic Disorders		
Febrile neutropenia	1	0
Cardiac Disorders		
Acute myocardial infarction	0	1
Cardiac arrest	0	1
Cardiac failure	0	1
Cardiogenic shock	1	0
Mitral valve disease	1	0
Gastrointestinal (GI) Disorders		
GI perforation	0	1
Intestinal ischemia	0	1
Neutropenic colitis	0	1
Infections and Infestations		
Lung infection	0	1
Sepsis	1	1
Septic shock	0	1
Injury, Poisoning, Procedural		
Subarachnoid hemorrhage	1	0
Road traffic accident	1	0
Metabolism and Nutrition Disorders		
Hyperkalemia	1	0
Neoplasms, Benign and Malignant		
Acute myeloid leukemia	2	1
Adenocarcinoma	1	0
Adenocarcinoma of pancreas	0	2
Breast angiosarcoma	0	1
Gastric cancer	1	0
Gastric neoplasm	0	1
GI carcinoma	1	0
Glioblastoma	1	0
Lung neoplasm malignant	2	2
Malignant peritoneal neoplasm	0	1
Metastatic malignant melanoma	1	0
Myeloid leukemia	0	1
Small cell lung cancer	0	1
Tongue neoplasm malignant	1	0
Nervous System Disorders		
Cerebral hemorrhage	1	0
Psychiatric Disorders		
Suicide Attempt	0	1
Respiratory, Thoracic, Mediastinal		
Interstitial lung disease	1	0
Pneumonia aspiration	1	0
Pulmonary embolism	0	1
Pulmonary fibrosis	0	1
TOTAL	19 (0.8%)	22 (0.9%)

Source: 3-Month Safety Update, p.18, Table 5

Reviewer Comments: *The number of deaths early in the trial and overall, including the follow-up period, do not suggest a safety signal for pertuzumab.*

BERENICE

At the time of the clinical cut-off for the adjuvant period of the BERENICE study (January 7, 2017), four patients had died (2 in cohort A and 2 in cohort B). All deaths occurred during the treatment-free follow up period after adjuvant anti-HER2 therapy had been completed. Of these patients, three were classified as dying due to disease progression and 1 patient died due to a second primary non-breast malignancy, metastatic renal cell carcinoma. An additional patient died after the clinical cutoff period due to disease progression. Narratives of these patient deaths are reviewed below.

Reviewer Comments: *Review of each death narrative is provided below. Based on this reviewer's assessment, the causes of death are consistent with those provided in the study report and in the information request dated October 4, 2017. There are no treatment related deaths reported. While one of the patients who died did have evidence of reduced ejection fraction while on study, this patient developed a second malignancy for which she was receiving treatment at the time of her death and it is not clear that her earlier cardiac event played any role in her death. Review of these deaths in the BERENICE study supports that the cardiac toxicity profile of pertuzumab in combination with anthracycline based chemotherapy.*

(b) (6) This was a 49-year-old female who was initially diagnosed with a T3N2 ER positive, PR negative, and HER2-positive right breast cancer with a tumor diameter of 8.4 cm, histological grade 3. The patient's medical history was significant for a previous smoking history, drug hypersensitivity to penicillin and cephalosporins, and seasonal allergies. She received treatment per cohort A with dose dense AC followed by paclitaxel, trastuzumab and pertuzumab. During her therapy (Cycle 8, Day 1, (b) (6)), she developed an SAE of cellulitis and was admitted to the hospital. Blood cultures were negative and she received an unspecified surgery. On Study day 131 (b) (6) the patient was assessed to have disease progression and treatment with trastuzumab, pertuzumab and paclitaxel was discontinued on study day 132, (b) (6). She underwent mastectomy and right axillary lymph node dissection on study day 134, (b) (6) . On study day 327, (b) (6), the patient died due to disease progression and no autopsy was performed.

Reviewer comments: *Given the evidence of clinical progression while on neoadjuvant chemotherapy it is likely the patient died due to disease progression. Given that the patient's death occurred approximately 200 days after her last treatment with paclitaxel, trastuzumab, and pertuzumab, it is not likely related to this therapy.*

(b) (6) This was a 64-year-old postmenopausal female who was initially diagnosed with a T2N0 ER positive, PR negative, HER2-positive right breast cancer in (b) (6) with the largest tumor diameter being 3.9 cm, histological grade 2. The patient's past medical history was

significant for hypothyroidism. She received treatment per Cohort A starting on [redacted]. On study day 134, [redacted], Cycle 8, Day 8, the patient underwent MUGA which revealed an LVEF of 43% which was down 16% from the patient's baseline LVEF of 59% and the patient was diagnosed with an asymptomatic Grade 2 ejection fraction decrease. She was treated with a beta-blocker, ACE inhibitor, aspirin, and an angiotensin receptor blocker and treatment with pertuzumab and trastuzumab was held per protocol. The event was considered resolved on study day 229 [redacted] when MUGA performed demonstrated an LVEF of 51%. She received radiation therapy and her treatment with trastuzumab and pertuzumab was completed on [redacted], study day 421. On study day 440 [redacted], the patient was diagnosed with renal cancer and treatment with sunitinib was initiated on study day 454 [redacted]. On study day 541 [redacted], the patient died due to renal cancer. No autopsy was performed.

Reviewer Comments: *While the patient did experience adverse events on study therapy, given the timing of the patient's death, approximately 100 days after completion of study therapy, and the new diagnosis of renal cell carcinoma in the interim with additional anticancer therapy, it does not appear that this death was likely due to study therapy.*

[redacted] This was a 60-year-old postmenopausal female with a T3N1 ER negative, PR negative, and HER2-positive left breast cancer with the largest tumor diameter being 10.0 cm, histological grade 2. The patient's past medical history was significant for hypertension and seasonal allergies. The patient received treatment in Cohort B with the first cycle of 5-fluorouracil, epirubicin, and cyclophosphamide on study day 1, [redacted], completed therapy and underwent breast conserving surgery on study day 202, [redacted]. She received adjuvant radiation therapy and treatment with pertuzumab and trastuzumab was complete on study day 470 [redacted]. On study day 570 [redacted], a CT scan showed disease recurrence in the central nervous system. The patient died due to progressive disease on [redacted] (study day 685) and no autopsy was performed.

Reviewer Comments: *The patient's narrative is consistent with the cause of death being reported as study disease given her documented CNS recurrence.*

[redacted] This was a 41-year-old female diagnosed with a T4N1 ER negative, PR negative, and HER2 positive R breast cancer in [redacted]. The tumor diameter was 15.0 cm and it was histological grade 2. She received treatment in Cohort B with the first cycle of 5-fluorouracil, epirubicin, and cyclophosphamide on study day 1, [redacted], and completed therapy on study day 477 [redacted]. She received a right mastectomy and axillary lymph node dissection and adjuvant radiation therapy. On study day 546 [redacted], CT scan demonstrated disease recurrence in the CNS and the patient died on [redacted], study day 603.

Reviewer Comments: *The patient's narrative is consistent with the cause of death being reported as study disease given her documented CNS recurrence.*

(b) (6) This was a 65-year-old postmenopausal female diagnosed with a unifocal T2N0, ER negative, PR negative, HER2 positive left breast cancer in (b) (6), with the largest tumor diameter being 4.8 cm, histological grade 3. The patient's past medical history was significant for osteopenia. The patient received treatment in Cohort B with the first cycle of 5-fluorouracil, epirubicin, and cyclophosphamide on study day 1, (b) (6). The patient received a single dose of pertuzumab, trastuzumab, and docetaxel on study days 86 and 87 (b) (6) prior to discontinuation due to lack of efficacy as breast ultrasound performed on study day 99 (b) (6) demonstrated disease progression with additional lesions in the ipsilateral breast. The patient received adjuvant radiation therapy to the left chest wall in (b) (6). The patient died on (b) (6), study day 436, due to progressive disease and no autopsy was performed.

Reviewer Comments: *The patient had documented disease progression while on study and discontinued study therapy. Approximately one year later, the patient was documented as dying due to progressive disease. Given the timing of the death, it is not likely related to study therapy but rather due to underlying disease.*

Serious Adverse Events

APHINITY

Information from the CSR, the 3-Month Safety Update report, the applicant's narrative summaries, and responses to FDA Information Requests were used to analyze serious adverse events in the APHINITY study.

As of the clinical cut-off date for the primary analysis, the incidence of non-fatal serious adverse events (SAEs) was higher in the PTZ arm (692 = 29.3%) compared with the placebo arm (585 = 24.3 %) for the period that includes 28 days after the last dose of any study treatment. Non-fatal SAEs, including the post-treatment follow-up period, as well, occurred in 721 (30.5%) patients in the PTZ arm and 618 (25.7%) patients in the PL arm. Progression of malignancy and hospitalization for progressive disease were not reported as SAEs.

The highest incidences of non-fatal SAEs during the treatment period were due to febrile neutropenia and diarrhea. There were 208 patients (8.8%) in the PTZ arm and 196 patients (8.1%) in the PL arm who experienced SAE febrile neutropenia. There were 58 patients (2.5%) in the PTZ arm and 18 patients (0.7%) in the PL arm who experienced SAE diarrhea.

In response to an Information Request, the applicant provided information regarding the incidence of hospitalization for diarrhea by treatment group and by treatment phase. The following table is from the applicant's November 9, 2017, response.

Table 35: APHINITY Summary of Hospitalizations for Diarrhea by Treatment Regimen

	Pertuzumab + Trastuzumab + Chemotherapy (N=2364 (%))	Placebo + Trastuzumab + Chemotherapy (N=2405 (%))
Patients with an SAE of Diarrhea	58 (2.5)	18 (0.7)
Patients Hospitalized due to diarrhea	56 (2.4)	18 (0.7)
Treatment Period of Hospitalization		
Anthracycline Alone	2 (<0.1)	2 (0.1)
Targeted Therapy plus chemotherapy	54 (2.3)	15 (0.6)
Targeted Therapy alone	0	1 (<0.1)

Derived from SAE patient narratives.

Almost all the diarrhea SAEs were associated with hospitalization, 56/58 patients in the PTZ arm and 18/18 patients in the PL arm. Almost all these SAEs occurred during the treatment phase when targeted therapy was administered in combination with chemotherapy. Only 1 patient in the PL treatment arm and no patients in the PTZ arm required hospitalization for diarrhea during the targeted therapy alone treatment phase.

Reviewer Comments: *Additional data to be discussed later in the review (AE incidence, Events to Monitor, Patient Related Outcomes) are consistent with PTZ increasing the risk of diarrhea as part of the adjuvant treatment regimen.*

In the 3-month Safety Update Report (data cut-off May 15, 2017), the applicant generated an output for SAEs in the post-treatment period. A total of 26 patients, 15 (0.6%) in the PTZ arm vs. 11 patients (0.5%) in the PL arm experienced at least one post-treatment SAE considered possibly study treatment related. The largest number of these serious and related AEs was in the category of Cardiac Disorders 9 patients (10 events) in the PTZ arm and 7 patients (7 events) in the PL arm. This information is displayed in the following table, from the applicant's Table 9 (p.29 3-Month Safety Update).

Table 36: APHINITY Serious and Related AEs Post Treatment Period, Safety Population

MedDRA Preferred Term	PTZ + Trastuzumab + Chemo n=2364	PL + Trastuzumab + Chemo n=2405
Total # of patients with ≥1 AE	9 (0.4)	7 (0.3)
Cardiac Failure	7 (0.3)	3 (0.1)
Atrial Fibrillation	1 (<0.1)	0
Atrioventricular Block	0	1 (<0.1)
Atrioventricular Block Complete	0	1 (<0.1)
Atrioventricular Block 2nd Degree	0	1 (<0.1)
Cardiomyopathy	0	1 (<0.1)
Ventricular Hypokinesia	1 (<0.1)	0
Total # of events	10	7

Source: 3-Month Safety Update p.29, Table 9

An additional 2 patients in the PTZ arm and 1 patient in the PL arm had episodes of SAE ejection fraction decreased

Reviewer Comments: *The number of these cardiac SAEs is numerically small and similar for the treatment groups. See data and discussion of Primary and Secondary Cardiac Events later in this review.*

BERENICE

Information within the CSR, the 120-day safety update report, the applicant's narrative summaries, and CRFs were used to analyze serious adverse events in the BERENICE study. SAEs of any grade up to 28 days following the last dose of study therapy occurred in 97 patients (24.4%) during the neoadjuvant therapy period with 45 (22.6%) in cohort A and 52 (26.3%) in cohort B during this period. In the adjuvant therapy period and follow up, 23 (5.8%) of patients reported an SAE. For the overall study period, 54 patients (27.1%) in Cohort A and 61 (30.8%) of patients in Cohort B reported an SAE.

Table 37. Serious Adverse Events in the BERENICE Study

	Cohort A (ddAC followed by paclitaxel) N=199 n (%)	Cohort B (FEC followed by docetaxel) N=198 n (%)
Febrile Neutropenia	12 (6.0)	27 (13.6)
Infection	17 (8.5)	17 (8.6)
Neutropenic Sepsis	0	7 (3.5)
Device related infection	5 (2.5)	3 (1.5)
Acute Kidney Injury	2 (1.0)	0
Diarrhea	1 (0.5)	11 (5.6)
Pneumonitis	1 (0.5)	0

The primary focus of the BERENICE study was cardiac safety. SAEs reported that were related to cardiac events for the overall study period are reported below.

Table 38. Cardiac SAEs in the BERENICE Study

	Cohort A (ddAC followed by paclitaxel) N=199 n (%)	Cohort B (FEC followed by docetaxel) N=198 n (%)
Cardiac Disorders	8 (4.0)	4 (2.0)
Cardiac Failure	4 (2.0)	3 (1.5)
Acute Myocardial Infarction/Myocardial Ischemia	2 (1.0)	0
Atrial Flutter	1 (0.5)	0
Arterial Thrombosis	0	1 (0.5)
Cardiogenic Shock	1 (0.5)	0
Ejection Fraction Decreased	4 (2.0)	4 (2.0)

Source: BERENICE 120 Day Safety Update, reviewer modification of tables on pages 511-514.

Dropouts and/or Discontinuations Due to Adverse Effects

APHINITY

Discontinuation of any study medication due to at least one AE occurred in 309 (13.1%) of patients in the PTZ treatment arm and in 277 (11.5%) patients in the PL treatment arm.

The most common AEs leading to discontinuation of any study medication were peripheral sensory neuropathy/neuropathy peripheral (1.5% of PTZ patients vs. 1.6% of PL patients), diarrhea (1.6% of patients in the PTZ treatment arm vs. 0.3% of patients in the PL arm), ejection

fraction decreased (1.8% of PTZ patients vs. 2.5% of PL patients), and cardiac failure (1.2% of patients in the PTZ arm vs. 0.6% of patients in the PL arm.)

Discontinuation of PTZ/PL due to at least one AE occurred in 166 (7.0%) of patients in the PTZ treatment arm and 139 (5.8%) of patients in the PL treatment arm. The most common AEs that led to discontinuation of PTZ/PL were in the following System Organ Classes (≥1% of patients by SOC):

- Investigations – 45 vs. 66 patients (1.9% vs. 2.7%), of whom 43 (1.8%) in the PTZ arm and 60 (2.5%) in the PL arm experienced the AE "ejection fraction decreased."
- Cardiac Disorders - 35 vs. 25 patients (1.5% vs. 1.0%), of whom 28 (1.8%) in the PTZ arm vs. 15 patients (0.6%) in the PL arm experienced AE cardiac failure.
- Gastrointestinal Disorders – 26 vs. 5 patients (1.1% vs. 0.2%), of whom 20 (0.8%) in the PTZ arm vs. 2 patients (0.1%) experienced AE diarrhea.

The applicant's analysis by chemotherapy type showed that the number of patients withdrawn from PTZ/P for at least one AE was similar for the anthracycline-based chemotherapy arms and the non-anthracycline based chemotherapy treatment arms.

Reviewer Comments: *For further discussion of cardiac events, see the next sub-section below, "Significant Adverse Events" and for further discussion of diarrhea, see section 8.2.5, entitled "Submission Specific Primary Safety Concerns."*

BERENICE

In the BERENICE safety population, 19 patients (9.5%) in Cohort A and 14 (7.1%) of patients in Cohort B discontinued pertuzumab or trastuzumab due to an adverse event. The most common reasons are included in the table below.

Table 39. Adverse Events Leading to Treatment Discontinuation of Trastuzumab or Pertuzumab in BERENICE

	Cohort A (ddAC followed by paclitaxel) N=199 n (%)	Cohort B (FEC followed by docetaxel) N=198 n (%)
Ejection Fraction Decreased	8 (4.0)	8 (4.0)
Cardiac Disorders	6 (3.0)	2 (1.0)
Cardiac Failure	3 (1.5)	2 (1.0)
Atrial Flutter	1 (0.5)	0
Atrioventricular Block	1 (0.5)	0
Cardiogenic Shock	1 (0.5)	0
Infections and Infestations	2 (1.0)	0
Skin and Subcutaneous disorders	0	2 (1.0)
Respiratory disorders	1 (0.5)	1 (0.5)
Diarrhea	1 (0.5)	0
Acute Kidney Injury	1 (0.5)	0

Source: 120 Day Safety Update, BERENICE CSR, pages 516-517 with reviewer modifications.

Reviewer Comments: *There were similar rates of treatment discontinuation for targeted therapy in each treatment arm. There were a numerically greater number of patients with cardiac failure in Cohort A, though similar numbers with ejection fraction decreased based on ECHO/MUGA findings in each arm. This supports the cardiac safety of this regimen with doxorubicin containing regimens, though there is no direct comparison of the incidence of risk in non-anthracycline containing regimens.*

Significant Adverse Events

APHINITY

For the APHINITY trial, Cardiac Events were considered significant to monitor, because of the known cardiotoxicity associated with HER2-targeted agents. The cardiac safety results of the trial will be discussed in this section. Grade 3-4 AEs are discussed in the Treatment Emergent Adverse Events (TEAE) subsection of section 8.2.4 above. Diarrhea is discussed in section 8.2.5 below, entitled “Submission Specific Primary Safety Concerns.”

The protocol defined Primary and Secondary Cardiac Events.

Primary Cardiac Events/Endpoint
Primary Cardiac Events were defined as either:

- Heart Failure (NYHA class III or IV) *and* a drop in LVEF of at least 10 points from baseline *and* to below 50%
  or
- Cardiac death

Secondary Cardiac Events/Endpoint

The Secondary Cardiac endpoint was defined as:

- Asymptomatic or mildly symptomatic (NYHA Class II) drop in LVEF of at least 10 points from baseline *and* to below 50%, confirmed by a second LVEF assessment within approximately 3 weeks OR confirmed by the Cardiac Advisory Board (see below).

Confirmation of asymptomatic LVEF decrease at 3 weeks was required even during follow-up because assessment of the secondary cardiac endpoint was to be based on data from randomization until the start of any new therapy for disease recurrence. In addition, an event was only considered a secondary cardiac event if the patient did not also experience a primary cardiac event at any time during the study, in which case, the primary event was recorded. (However, these secondary events were still captured as "ejection fraction decreased" in reporting of AEs.)

A Cardiac Advisory Board (CAB) was established to adjudicate cardiac deaths and events that might meet the definition for the secondary cardiac endpoint, but lacked confirmatory LVEF assessment at approximately 3 weeks (7-35 days was acceptable). For cardiac deaths, AEs reported under System Organ Class "Cardiac Disorders" with the outcome "death" were evaluated internally to see if they met the protocol definition of cardiac death. For patients potentially meeting criteria, Case Report Form (CRF) data and SAE reports were sent to the CAB for review and adjudication. The protocol defined cardiac deaths as:

- Definite cardiac death: Due to heart failure, myocardial infarction or documented primary arrhythmia
- Probable cardiac death: Sudden death within 24 hours of a definite or probably cardiac event such as syncope, cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology.

The following table summarizes the incidence of Primary and Secondary Cardiae events as of the primary data cut-off date.

Table 40: APHINITY Primary and Secondary Cardiac Events, Safety Population

	PTZ + Trastuzumab + Chemo N=2364	PL + Trastuzumab + Chemo N=2405
Primary Cardiac Event	17 (0.7%)	8 (0.3%)
Heart Failure	15 (0.6%)	6 (0.2%)
Cardiac Death	2 (0.1%)	2 (0.1%)
Secondary Cardiac Event	64 (2.7%)	67 (2.8%)
Identified by LVEF Assessment	50 (2.1%)	47 (2.0%)
Adjudicated by CAB	14 (0.6%)	20 (0.8%)

Source: Dataset ACE.xpt

The number of Primary Cardiac Events was numerically small, 17 (0.7%) in the PTZ arm and 8 (0.3%) in the PL arm, predominantly due to heart failure events, rather than cardiac deaths. The incidence of heart failure with a (significant) LVEF decline was higher in the PTZ group than the PL group (0.6% vs. 0.2%). Of the patients who experienced symptomatic heart failure, 13 of 15 in the PTZ arm had been treated with anthracycline-based chemotherapy and 5 of 6 patients in the PL arm had been treated with an anthracycline regimen.

There were 2 patients with cardiac deaths in each treatment arm. These patients had all received anthracycline-based chemotherapy, and 3 of the 4 patients had received radiotherapy to the left chest wall. One of these cardiac deaths, due to acute cardiac failure, in the PL arm, occurred on study day 1373, and was investigator-assessed to be related to HER2-targeted therapy, although the investigator also stated that the patient had "known chemotherapy-induced dilated cardiomyopathy."

One of the 25 primary cardiac events occurred during the anthracycline treatment phase, before starting HER2-targeted therapy. This patient, randomized to the PTZ arm but analyzed for safety under the PL arm, developed acute myocardial infarction (AMI) associated with LVEF decline and was withdrawn from treatment during the anthracycline treatment period. Most of the primary cardiac events (16 of 17 in the PTZ arm, and 7 of 8 in the PL arm) occurred during the initial 2 years following randomization. One event in the PTZ arm and one event in the PL arm, occurred 3.5 and 4.5 years, respectively post-randomization.

Recovery of LVEF function was defined as 2 consecutive LVEF assessments ≥50%. As of the time of the primary analysis data cut-off date, for the patients who experienced non-fatal primary cardiac events, recovery of LVEF was achieved in (7/15) 46.7% of PTZ-treated patients and (4/6) 66.7% of PL-treated patients. An additional 2 patients in the PTZ arm were described as "resolved with sequelae." The patient cited above who was analyzed in the PL population because of withdrawal during the anthracycline phase due to AMI was also described as "resolved with sequelae."

Eight patients with a primary cardiac event also experienced an asymptomatic/mildly symptomatic decline in LEVEF, which would have qualified as a secondary cardiac event, except that patients could only be counted in one of these categories, primary *or* secondary. In 5 of 8 patients, the decline in LVEF preceded the primary cardiac event (4 in the PTZ arm vs. 1 in the PL arm).

Secondary Cardiac Events were experienced by 131 patients, 64 (2.7%) in the PTZ arm and 67 (2.8%) in the PL arm. Most of these patients (97) were identified automatically, based on LVEF criteria with confirmatory LVEF assessment within approximately 3 weeks. The remaining 34 patients, 14 (0.6%) in the PTZ arm and 20 (0.8%) in the PL arm were identified by the CAB, referred because of the absence of a second confirmatory LVEF assessment. Four patients in the PTZ arm experienced 2 separate secondary cardiac events, for a total of 68 secondary events in 64 patients.

LVEF recovery (defined as 2 consecutive LVEF assessments ≥50%), was achieved in 54 events in 51 patients (79.7%) of patients in the PTZ arm vs. 54 patients (80.6%) in the PL arm.

Reviewer Comments*: In Section 8.9.2 of the CSR, the applicant reported recovery from secondary cardiac event in 54 patients in the PTZ arm (79.4%), but acknowledged that this should be 54 events in 51 patients in response to FDA Information Request to explain the minor discrepancy in analyses).*

Additional Reviewer Comments: *The number of Primary Cardiac Events was low in each treatment arm (PTZ 0.7% and PL 0.3 %), predominantly heart failure events rather than cardiac deaths of which there were 2 in each group. Almost all Primary Cardiac Events occurred during the initial 2 years after randomization. For Patients with non-fatal Primary Cardiac Events, recovery of LVEF occurred in 7/15 (46.7%) and 4/6 (66.7%) of patients treated with PTZ or PL, respectively. Secondary Cardiac Events occurred in 2.7% of PTZ-treated patients vs. 2.8% of PL-treated patients, with LVEF recovery occurring in 79.7% and 80.6%, respectively. The cardiac risk for the addition of PTZ to standard adjuvant therapy appears acceptable.*

Most secondary cardiac events (87.8%) were reported in patients who were treated with anthracyclines, although 96.9% of patients who received anthracycline-based therapy did not experience a secondary cardiac event.

Between the primary clinical data cut-off date in December 2016, and the 3-Month Safety Update Report cut-off date May 15, 2017, no new primary cardiac events were identified, and no additional patients experienced LVEF drops to < 40%. Between the two clinical data cut-off dates, two additional secondary cardiac events were reported in the PTZ treatment arm. Both patients received anthracycline-based adjuvant chemotherapy and experienced LVEF decline, each meeting the criteria for a secondary cardiac event on study day 1521 and study day 1153, respectively.

BERENICE

The primary objective of the BERENICE study was to evaluate cardiac safety of the addition of pertuzumab to chemotherapy and anthracycline containing regimens during the neoadjuvant treatment period. This was defined as one of the following:

- A decline in left ventricular ejection fraction (LVEF) of ≥10% and a drop to <50%.
- Symptomatic left ventricular systolic dysfunction (LVSD) as defined by New York Heart Association Class III or IV symptoms.

Results of the cardiac safety endpoints for the BERENICE study are summarized in table XX below.

Table 41. BERENICE Study Cardiac Safety Endpoints

	Cohort A (ddAC followed by paclitaxel) N=199 n (%)	**Cohort B (FEC followed by docetaxel) N=198 n (%)**
LVEF drop ≥10% and EF <50%		
Neoadjuvant 2 (taxane, H&P)	13 (6.5) [95% CI 3.5-10.9]	3 (1.5) [95% CI 0.6-5.1]
Adjuvant (H&P)	14 (7.9) [95% CI 4.3-12.6]	20 (10.5) [95% CI 6.5-15.8]
Neoadjuvant 1 (anthracycline)	0	1 (0.5)
NYHA Class III/IV CHF		
Neoadjuvant 2 (taxane, H&P)	3 (1.5) [95% CI 0.31-4.34]	0 [95% CI 0-1.85]
Adjuvant (H&P)	0	1 (0.5)
Neoadjuvant 1 (anthracycline)	0	0

Source: 120 Day Safety Update, BERENICE CSR, page 36-37.

Reviewer Comments: These data support the cardiac safety of doxorubicin containing regimens. Additional data reviewed as above from the APHINITY study further supports this as approximately 75% of patients in this study also received anthracycline based regimens.

Treatment Emergent Adverse Events and Adverse Reactions

APHINITY

When Pertuzumab was administered in combination with trastuzumab and chemotherapy, the most common adverse events (>30%) were diarrhea, nausea, alopecia, fatigue, peripheral neuropathy, and vomiting. The most common grade 3-4 adverse events (≥2%) were neutropenia, febrile neutropenia, diarrhea, leukopenia, anemia, fatigue, nausea, and stomatitis.

The following table shows common TEAEs (grades 1-4) by MedDRA preferred term in the safety population with an incidence of at least 20% of patients in either treatment arm, as of the time of the primary data cut-off date. These AEs occurred up to 28 days after the last dose of any study medication.

Table 42: APHINITY Common Adverse Events All Grades (≥20% of Patients in Either Treatment Arm and ≥ 5% difference), Safety Population

MedDRA Preferred Term	PTZ + trastuzumab + Chemo n=2364	PL + trastuzumab + Chemo n=2405
Diarrhea	1683 (71%)	1086 (45%)
Fatigue	1154 (49%)	1065 (44%)
Anemia	655 (28%)	557 (23%)
Rash	609 (26%)	488 (20%)

Source: CSR Table 52

The following table summarizes the grade 3-4 AEs by Preferred Term for the APHINITY trial with occurrence in either arm at an incidence of ≥2% of patients as of the primary analysis data cut-off date.

Table 43: APHINITY Grade 3-4 Adverse Events (≥2% of Patients in Either Treatment Arm), Safety Population

MedDRA Preferred Term	PTZ + trastuzumab + Chemo n=2364	PL + trastuzumab + Chemo n=2405
Neutropenia*	611 (25.8%)	606 (25.2%)
Febrile Neutropenia	286 (12.1%)	266 (11.1%)
Diarrhea	233 (9.9%)	90 (3.7%)
Leukopenia**	212 (9.0%)	181 (7.5%)
Anemia	163 (6.9%)	114 (4.7%)
Fatigue	92 (3.9%)	61 (2.5%)
Nausea	57 (2.4%)	60 (2.5%)
Stomatitis	53 (2.2%)	25 (1.0%)
Ejection Fraction Decreased	45 (1.9%)	54 (2.2%)

* Neutropenia = neutropenia + neutrophil count decreased + granulocytopenia
**Leukopenia = leukopenia + white blood cell count decreased
Source: Reviewer's analysis from Database AAE.xpt

Reviewer Comments: *The percentage of patients with grade 3-4 AEs appears balanced between the treatment arms for the more common grade 3-4 TEAEs, except the incidence of diarrhea is notably higher for the PTZ group (9.9%) compared with the PL treatment group (3.7%). The incidence of ejection fraction decreased exceeded 2% for the PL treatment arm only.*

Adverse Events by Treatment Phase

In response to an FDA Information Request, the applicant provided Adverse Events tables for the APHINITY trial, with separate tables for the chemotherapy phase of treatment (for anthracycline- and non-anthracyline-based therapy) and for the targeted phase of therapy (PTZ/PL + trastuzumab, only) after completion of chemotherapy.

The following table summarizes all grade AEs ≥10% for patients in either treatment arm during the chemotherapy phase of treatment (anthracycline and non-anthracycline cohorts, combined).

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Table 44: APHINITY, All Grade AEs in ≥10% of Patients in Either Treatment Arm During Chemotherapy Phase of Therapy, Safety Population

MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Alopecia	1562 (66.1%)	1597 (66.4%)
Nausea	1598 (67.6%)	1548 (64.4%)
Diarrhea	1605 (67.9%)	1001 (41.6%)
Fatigue	1070 (45.3%)	997 (41.5%)
Vomiting	732 (31.0%)	690 (28.7%)
Constipation	632 (26.7%)	712 (29.6%)
Stomatitis	651 (27.5%)	554 (23.0%)
Anaemia	621 (26.3%)	523 (21.7%)
Myalgia	505 (21.4%)	603 (25.1%)
Neutropenia	560 (23.7%)	543 (22.6%)
Dysgeusia	581 (24.6%)	493 (20.5%)
Mucosal Inflammation	536 (22.7%)	435 (18.1%)
Decreased appetite	527 (22.3%)	442 (18.4%)
Asthenia	458 (19.4%)	470 (19.5%)
Arthralgia	393 (16.6%)	494 (20.5%)
Headache	424 (17.9%)	424 (17.6%)
Rash	447 (18.9%)	377 (15.7%)
Pyrexia	409 (17.3%)	403 (16.8%)
Peripheral sensory neuropathy	348 (14.7%)	363 (15.1%)
Epistaxis	379 (16.0%)	294 (12.2%)
Oedema peripheral	286 (12.1%)	350 (14.6%)
Neutrophil count decreased	309 (13.1%)	323 (13.4%)
Neuropathy peripheral	297 (12.6%)	308 (12.8%)
Dyspepsia	292 (12.4%)	308 (12.8%)
Insomnia	303 (12.8%)	294 (12.2%)
Lacrimation increased	271 (11.5%)	286 (11.9%)
Febrile neutropenia	286 (12.1%)	264 (11.0%)
Cough	243 (10.3%)	224 (9.3%)
Hot flush	214 (9.1%)	248 (10.3%)

Chemotherapy period includes 3-4 cycles of anthracycline based chemotherapy followed by 3-4 cycles of taxane with concurrent targeted therapy (anthracycline cohort) or 6 cycles of carboplatin and docetaxel with concurrent targeted therapy (non-anthracycline cohort).
Derived from ah_sa877_TRT1A_SE.

Source: Applicant 9 November 2017 Response to FDA Information Request

Two grade 3-4 events with an incidence of at least 10% were reported during the chemotherapy period: Neutropenia (16% PTZ group, 11% PL group)

Reviewer Comments: *The most notable difference between the treatment arms, during the period of chemotherapy (and concomitant trastuzumab + PTZ/PL) is the incidence of patients experiencing all grade diarrhea (67.9% in the PTZ group and 41.6% in the PL group).*

The next table summarizes all grade AEs reported in ≥10% of patients in either treatment arm during the chemotherapy phase of treatment for only the anthracycline cohort.

Table 45: APHINITY, All Grade AEs in ≥10% of Patients in Either Treatment Arm During Chemotherapy Phase of Therapy, Anthracycline Cohort, Safety Population

MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=1834)	Placebo + Trastuzumab + Chemotherapy (N=1894)
Alopecia	1259 (68.6%)	1281 (67.6%)
Nausea	1243 (67.8%)	1226 (64.7%)
Diarrhea	1160 (63.2%)	700 (37.0%)
Fatigue	776 (42.3%)	719 (38.0%)
Vomiting	527 (28.7%)	544 (28.7%)
Constipation	507 (27.6%)	540 (28.5%)
Stomatitis	542 (29.6%)	449 (23.7%)
Myalgia	419 (22.8%)	488 (25.8%)
Neutropenia	439 (23.9%)	431 (22.8%)
Asthenia	398 (21.7%)	404 (21.3%)
Dysgeusia	420 (22.9%)	348 (18.4%)
Mucosal inflammation	416 (22.7%)	337 (17.8%)
Anaemia	399 (21.8%)	345 (18.2%)
Arthralgia	329 (17.9%)	411 (21.7%)
Decreased appetite	386 (21.0%)	330 (17.4%)
Pyrexia	341 (18.6%)	340 (18.0%)
Headache	333 (18.2%)	337 (17.8%)
Rash	337 (18.4%)	297 (15.7%)
Peripheral sensory neuropathy	283 (15.4%)	273 (14.4%)
Neutrophil count decreased	262 (14.3%)	277 (14.6%)
Epistaxis	289 (15.6%)	233 (12.3%)
Oedema peripheral	212 (11.6%)	240 (12.7%)
Dyspepsia	220 (12.0%)	228 (12.0%)
Febrile neutropenia	234 (12.8%)	203 (10.7%)
Insomnia	216 (11.8%)	208 (11.0%)
Neuropathy peripheral	210 (11.5%)	214 (11.3%)
Lacrimation increased	193 (10.5%)	202 (10.7%)
Cough	193 (10.5%)	183 (9.7%)

Chemotherapy period includes 3-4 cycles of anthracycline based chemotherapy followed by 3-4 cycles of taxane with concurrent targeted therapy.
Derived from ah_sa877_TRT2A_ANTH_SE

Source: Applicant 9 November 2017 Response to FDA Information Request

There were three grade 3-4 events reported with an incidence ≥10% during chemotherapy for the anthracycline cohort: Neutropenia (16.3% PTZ arm vs. 15.9 % placebo arm), febrile neutropenia (12.8% PTZ arm vs. 10.7% PL arm), and neutrophil count decreased (10.3% PTZ arm vs. 10.2 % PL arm).

Reviewer Comments: *The most notable difference between the treatment arms, during the period of anthracycline-based chemotherapy followed by 3-4 cycles of taxane with concomitant trastuzumab + PTZ/PL is the 26.2% difference in incidence of patients experiencing all grade diarrhea (67.9% in the PTZ group and 41.6% in the PL group). The difference in incidence of stomatitis for the 2 groups was 5.9% and 4.9% for mucosal inflammation.*

The next table summarizes all grade AEs reported in ≥10% of patients in any treatment arm during the chemotherapy phase of treatment for only the non-anthracycline cohort.

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Table 46: APHINITY, All Grade AEs in ≥10% of Patients in Either Treatment Arm During Chemotherapy Phase of Therapy, Non-Anthracycline Cohort, Safety Population

MedDRA Preferred Term	Pertuzumab + TCH (N=528)	Placebo + TCH (N=510)
Diarrhea	444 (84.1%)	301 (59.0%)
Nausea	355 (67.2%)	322 (63.1%)
Fatigue	294 (55.7%)	278 (54.5%)
Dysgeusia	161 (30.5%)	144 (28.2%)
Anaemia	222 (42.0%)	177 (34.7%)
Vomiting	205 (38.8%)	146 (28.6%)
Constipation	124 (23.5%)	172 (33.7%)
Decreased appetite	141 (26.7%)	111 (21.8%)
Neutropenia	121 (22.9%)	112 (22.0%)
Mucosal inflammation	120 (22.7%)	98 (19.2%)
Stomatitis	109 (20.6%)	105 (20.6%)
Myalgia	86 (16.3%)	115 (22.5%)
Rash	110 (20.8%)	80 (15.7%)
Oedema peripheral	73 (13.8%)	109 (21.4%)
Neuropathy peripheral	87 (16.5%)	94 (18.4%)
Headache	91 (17.2%)	87 (17.1%)
Insomnia	87 (16.5%)	86 (16.9%)
Lacrimation increased	78 (14.8%)	84 (16.5%)
Peripheral sensory neuropathy	65 (12.3%)	90 (17.6%)
Dyspepsia	72 (13.6%)	80 (15.7%)
Epistaxis	90 (17.0%)	61 (12.0%)
Hypomagnesaemia	101 (19.1%)	49 (9.6%)
Abdominal pain	75 (14.2%)	71 (13.9%)
Arthralgia	63 (11.9%)	83 (16.3%)
Pyrexia	67 (12.7%)	63 (12.4%)
Asthenia	59 (11.2%)	66 (12.9%)
Thrombocytopenia	71 (13.4%)	53 (10.4%)
Bone pain	49 (9.3%)	73 (14.3%)
Dyspnoea	59 (11.2%)	61 (12.0%)
Hypokalaemia	80 (15.2%)	39 (7.6%)
Febrile neutropenia	51 (9.7%)	61 (12.0%)
Dizziness	60 (11.4%)	47 (9.2%)
Hot flush	46 (8.7%)	59 (11.6%)
Dehydration	70 (13.3%)	32 (6.3%)

Derived from t_ae_TRT2A_TACH_SE.
Chemotherapy period comprises 6 cycles of carboplatin and docetaxel with concurrent targeted therapy

Source: Applicant 9 November 2017 Response to FDA Information Request

There were three grade 3-4 events reported with an incidence ≥10% during chemotherapy for the non-anthracycline cohort (docetaxel + carboplatin): Neutropenia (15.0% PTZ arm vs. 13.9 %

PL arm), febrile neutropenia (9.5% PTZ arm vs. 12.0% PL arm), and anemia (16.7% PTZ arm vs. 10.7% PL arm).

Reviewer Comments: *For patients treated with non-anthracycline-based chemotherapy (docetaxel and carboplatin), during the period of chemotherapy with concomitant trastuzumab and PTZ/PL, there was a 25.1% greater incidence of patients experiencing all grade diarrhea (84.1% in the PTZ group and 59.0% in the PL group). However, for the non-anthracycline cohort, a 5-10% greater incidence in the PTZ arm for several (all grade) AEs suggests a greater interaction of PTZ with this chemotherapy regimen. For the PTZ arm vs. the PL arm, the difference in incidence was 10.2% higher for vomiting, 9.5% higher for hypomagnesemia, 7.6% higher for hypokalemia, 7.3% higher for anemia, 7% higher for dehydration, and 5.1% higher for rash. The incidence of grade 3-4 anemia was also higher by 6% for the PTZ treatment group.*

The next table summarizes all grade AEs reported in ≥10% of patients in any treatment arm during the targeted treatment alone period.

Table 47: APHINITY, All Grade AEs Reported in ≥10% of Patients in Any Treatment Arm During the Targeted Treatment Alone Period

MedDRA Preferred Term	Pertuzumab + Trastuzumab + Chemotherapy (N=2364)	Placebo + Trastuzumab + Chemotherapy (N=2405)
Arthralgia	362 (15.3%)	397 (16.5%)
Diarrhea	428 (18.1%)	221 (9.2%)
Hot flush	287 (12.1%)	280 (11.6%)
Radiation skin injury	292 (12.4%)	263 (10.9%)
Pruritis	236 (10.0%)	140 (5.8%)

Derived from t_ae_TRT1A_TAPO_SE.
Targeted treatment alone comprises 12 to 15 cycles of targeted therapy after completion of concurrent chemotherapy

Source: Applicant 9 November 2017 Response to FDA Information Request

No grade 3-4 AEs ≥10% were seen during therapy with targeted therapy alone.

Reviewer Comments: *For the targeted treatment alone period, the incidence of all grade diarrhea is less than when administered with chemotherapy, but there is still a difference between the treatment arms (PTZ 18.1% vs. PL 9.2%).*

BERENICE

All grade AEs reported in the neoadjuvant treatment period for BERENICE are reported below in Table 48.

Table 48: TEAEs in the BERENICE Study

Body System/Adverse Reactions	PERTUZUMAB + trastuzumab + paclitaxel following ddAC n=199 n (%)		PERTUZUMAB + trastuzumab + docetaxel following FEC n=198 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
General disorders and administration site conditions				
Fatigue	116 (58.3)	2 (1.0)	76 (38.4)	9 (4.5)
Asthenia	37 (18.6)	3 (1.5)	82 (41.4)	0
Mucosal inflammation	43 (21.6)	2 (1.0)	74 (37.4)	7 (3.5)
Pyrexia	30 (15.1)	0	35 (17.7)	0
Edema peripheral	18 (9.0)	0	24 (12.1)	2 (1.0)
Skin and subcutaneous tissue disorders				
Alopecia	124 (62.3)	0	116 (58.6)	0
Rash	28 (14.1)	0	21 (10.6)	0
Dry skin	27 (13.6)	0	19 (9.6)	0
Nail discoloration	29 (14.6)	0	3 (1.5)	0
Palmar-Plantar Erythrodysaesthesia Syndrome	11 (5.5)	0	20 (10.1)	1 (0.5)
Gastrointestinal disorders				
Nausea	141 (70.9)	5 (2.5)	137 (69.2)	4 (2.0)
Diarrhea	133 (66.8)	6 (3.0)	137 (69.2)	20 (10.1)
Constipation	69 (34.7)	1 (0.5)	76 (38.4)	1 (0.5)
Vomiting	45 (22.6)	4 (1.0)	69 (34.8)	8 (4.0)
Stomatitis	49 (24.6)	0	54 (27.3)	10 (5.1)
Dyspepsia	38 (19.1)	0	32 (16.2)	0
Abdominal pain upper	12 (6.0)	0	26 (13.1)	0
Abdominal pain	10 (5.0)	0	20 (10.1)	0
Gastroesophageal reflux disease	23 (11.6)	0	4 (2.0)	0
Blood and lymphatic system disorders				
Anemia	54 (27.1)	6 (3.0)	60 (30.3)	5 (2.5)
Neutropenia	44 (22.1)	24 (12.1)	32 (16.2)	17 (8.6)
Febrile neutropenia	14 (7.0)	14 (7.0)	34 (17.2)	34 (17.2)
Nervous system disorders				
Headache	60 (30.2)	1 (0.5)	28 (14.1)	1 (0.5)
Dysgeusia	39 (19.6)	0	38 (19.2)	1 (0.5)
Neuropathy peripheral	85 (42.7)	6 (3.0)	41 (20.7)	1 (0.5)
Paresthesia	29 (14.6)	0	18 (9.1)	0
Dizziness	23 (11.6)	0	15 (7.6)	0
Musculoskeletal and connective tissue disorders				
Myalgia	40 (20.1)	0	66 (33.3)	2 (1.0)
Arthralgia	39 (19.6)	0	42 (21.2)	2 (1.0)
Back pain	20 (10.1)	0	17 (8.6)	0
Pain in extremity	20 (10.1)	0	15 (7.6)	0
Bone pain	23 (11.6)	1 (0.5)	9 (4.5)	0
Infections and infestations				
Urinary tract infection	21 (10.6)	2 (1.0)	4 (2.0)	0

Respiratory, thoracic, and mediastinal disorders				
Epistaxis	50 (25.1)	0	37 (18.7)	0
Dyspnea	29 (14.6)	1 (0.5)	29 (14.6)	1 (0.5)
Cough	40 (20.1)	1 (0.5)	17 (8.6)	0
Oropharyngeal pain	20 (10.1)	0	15 (7.6)	1 (0.5)
Metabolism and nutrition disorders				
Decreased appetite	39 (19.6)	0	45 (22.7)	0
Eye disorders				
Lacrimation increased	18 (9.0)	0	36 (18.2)	0
Psychiatric disorders				
Insomnia	37 (18.6)	0	25 (12.6)	0
Vascular disorders				
Hot flush	38 (19.1)	0	26 (13.1)	0
Investigations				
White blood cell count decreased	21 (10.6)	8 (4.0)	5 (2.5)	4 (2.0)
Injury, poisoning and procedural complications				
Infusion related reaction	31 (15.6)	2 (1.0)	25 (12.6)	2 (1.0)

Source: Reviewer Analysis from aae.xpt

Reviewer Comments: Toxicities during the neoadjuvant period were similar between the two arms with the exception of increased diarrhea in Cohort B, which is likely due to the difference in taxane therapy and increased risk of GI toxicity with docetaxel as compared to paclitaxel. Peripheral neuropathy was worse in Cohort A. These differences suggest that the taxane choice affects the adverse event profile with the addition of pertuzumab. These data further support the differences demonstrated in the APHINITY study based on taxane choice as well as anthracycline/non-anthracycline based regimen.

Laboratory Findings

APHINITY

In APHINITY, laboratory parameters (CBC, Chemistries, Liver function tests [LFTs]) were to be monitored at baseline and repeated within 3 days of the beginning of each cycle of adjuvant therapy and at 28 days after therapy completion (except LFTs were not required weeks 19 and 22 of targeted therapy). Baseline laboratory values were within normal limits for most parameters. Shifts in hematologic parameters were most common, and occurred in both treatment arms. Low calcium, magnesium, and potassium were more common in the PTZ arm than the PL arm, mainly due to small differences in the incidence of grade 1-2 abnormalities.

BERENICE

Laboratory studies including CBC, serum chemistries and electrolytes, were evaluated in the BERENICE study at baseline and at the beginning of each chemotherapy cycle, every 2 weeks for Cohort A during ddAC and every 3 weeks during the taxane and targeted therapy period. For Cohort B, these were obtained every 3 weeks during the neoadjuvant period. Laboratory studies were obtained per local site protocol for obtaining laboratory studies while on

trastuzumab.

Shifts in hematological parameters were common with shifts from Grade 0 to Grade 4 seen in patients in both arms for absolute neutrophil count (n=60) and absolute lymphocyte count (n=23).

The most common non-hematological grade 3 or 4 laboratory abnormalities were elevated uric acid seen in 60 total subjects (Cohort A n=31 and Cohort B n=29). All other grade 3-4 laboratory abnormalities were reported in ≤4% of patients in either cohort. No grade 3 or greater chemistry abnormalities were reported during the adjuvant period.

Reviewer Comments: Laboratory abnormalities were similar between the two treatment arms. Given that this is not a placebo controlled study, it is difficult to isolate the effect of pertuzumab on laboratory values.

Vital Signs

For the APHINITY trial, there were no major differences between the treatment arms for blood pressure (mean, median, change from baseline), heart rate or other vital sign parameters. For the BERENICE study, there were no major changes in median or mean blood pressure, pulse rate over time or body temperature throughout the study.

Electrocardiograms (ECGs)

In the APHINITY trial, ECGs were required at baseline, after completion of therapy or at week 52, and as clinically indicated. For BERENICE, ECGs were collected at screening and after completion of the anthracycline portion of the neoadjuvant regimen. No significant findings were reported.

QT

A QT study was not conducted.

Immunogenicity

The development of anti-therapeutic antibodies (ATAs) was not addressed in the APHINITY trial. Data were presented in the BERENICE and CLEOPATRA trials, and the incidence of anti-pertuzumab antibody levels was low. (See the Clinical Pharmacology review for additional comment, section 6.)

8.2.5. Analysis of Submission-Specific Safety Issues

APHINITY

For the APHINITY trial, the applicant prospectively identified "Events to Monitor" based on the known Adverse Event profile of PTZ. Cardiac events, also of special interest, were discussed in section 8.2.4 of this review under the subheading "Significant Adverse Events." The following AEs of particular interest for the application, pre-defined by the applicant, will be discussed in this section:

- Diarrhea
- Rash
- Hypersensitivity and Anaphylaxis
- Infusion-related reactions
- Mucositis
- Leukopenia
- Febrile neutropenia
- Interstitial lung disease.

The applicant used standardized MedDRA Queries (SMQs) for analysis when available. When SMQs were not available for the "Events to Monitor," baskets of Roche Standard MedDRA Adverse Events Group Terms (AEGTs) were used. AEGTs were used for Rash, Hypersensitivity and Anaphylaxis, and Mucositis. Infusion-related reactions were analyzed by SMQ and Roche AEGTs (see below). Febrile neutropenia was defined by a single preferred term, and was also reported in the main AE tables.

8.2.5.1 **Diarrhea**

In APHINITY and BERENICE, diarrhea was among the most common causes of TEAEs, both all grade and grade 3-4, and non-fatal SAEs. Diarrhea has been discussed in other sections of this review, including section 8.2.4 (subsections entitled: SAEs, TEAEs, AEs by Treatment Phase) and section 8.2.7 (Demographic subgroups).

On November 9, 2017, the applicant responded to an FDA Information Request intended to better characterize whether diarrhea typically was persistent or intermittent, whether diarrhea was more highly associated with different treatment phases or the choice of chemotherapy regimen, and the incidence of hospitalization for diarrhea by treatment group.

The incidence of diarrhea, all grades, was higher when chemotherapy was administered with targeted therapy (61% in the PTZ-treated group vs. 34% in the PL-treated group), and was higher when administered with non-anthracycline based therapy (85% in the PTZ-treated group vs. 62% in the PL-treated group) than with anthracycline based therapy (67% in the PTZ-treated group vs. 41% in the PL-treated group). The incidence of diarrhea during the period that targeted therapy was administered without chemotherapy was 18% in the PTZ-treated group vs. 9% in the PL-treated group. The median duration of all grades diarrhea was 8 days (range 1-811) for the PTZ-treated group vs. 6 days (range 1-1022) for the PL-treated group. The median duration of Grade ≥3 diarrhea was 20 days for the PERJETA-treated group vs. 8 days for the

placebo-treated group. More patients required hospitalization for diarrhea as a serious adverse event in the PTZ-treated group (2.4%) than in the PL-treated group (0.7%).

8.2.5.2 **Rash**

In APHINITY, rash was analyzed by a Roche standard AEGT, "EGFR Associated Rash." More patients in the PTZ treatment arm experienced rash than in the PL treatment arm, 51.9% and 41.7%, respectively, predominantly grade 1-2. Grade 3-4 rash events occurred in 10 patients (0.4%) in the PTZ group and 6 patients (0.2%) in the PL group. There were no fatal events. SAE of rash as a preferred term was reported in 5 patients (0.4%) in the PTZ group and 1 (0.1%) in the PL group.

8.2.5.3 **Hypersensitivity and Anaphylaxis**

For APHINITY, Hypersensitivity and Anaphylaxis AEs occurred in 116 patients (4.9%) in the PTZ arm and 86 patients (3.6%) in the PLA arm during the treatment period. The most common PT events in this category were hypersensitivity (3.4 vs. 2.9%) and drug hypersensitivity (1.3% vs. 0.5%). Grade 3-4 AEs were reported in 0.8% and 0.7%, respectively, in the PTZ vs. PL arm, with no fatal AEs. Withdrawal from PTZ/PL occurred in 6 patients (0.3%) in the PTZ arm and 2 patients (<0.1%) in the PL arm.

The highest incidence of Anaphylaxis and Hypersensitivity AEs occurred during the targeted therapy and taxane treatment (TTTT) period. The overall incidence of Hypersensitivity and Anaphylaxis AEs was higher in the PTZ group for patients who were treated with the non-anthracycline-based chemotherapy regimen (TCH) than the anthracycline-based regimen.

8.2.5.4 **Infusion-related reactions**

For APHINITY, the applicant analyzed Infusion-related reactions (IRRs) that occurred on the day of Pertuzumab/Placebo infusion, utilizing the SMQ "Anaphylactic reaction (wide)" and Roche Standard AEGTs "Anaphylaxis and Hypersensitivity" and "Hypersensitivity Infusion Related." IRRs occurred in 1293 patients (54.75) in the PTZ group and 1199 patients (51.3%) in the PL group. Most of these IRRs were grade 1-2, with grade3-4 IRR in 2.7% of PTZ patients and 2.1% of PL patients, with no fatal events. The most common of the IRRs on the day of PTZ/PL infusion were fatigue (9.2% PTZ treatment arm vs. 8.3% PL treatment arm), arthralgia (7.7% PTZ vs. 9.1% PL), hot flush (6.6% PTZ vs. 6.3% PL), myalgia (5.1% PTZ vs. 6.2% PL, and dysgeusia (5% vs. 4.3%). IRRs leading to withdrawal of any study treatment did not occur in the PTZ arm but occurred in 5 patients (0.2%) in the PL arm. IRR SAEs were reported in 3 and 1 patient, respectively, in the PTZ and PL arms.

For Cycle 1, the incidence of all Grade IRRs on the day of PTZ/PL infusion was 20.9% of patients in the PTZ arm vs. 18.0% of patients in the PL arm. For Cycle 2, the incidence was 13.3% vs.

12.6% of patients, for the PTZ and PL arms, respectively. The highest incidence of IRRs occurred during the targeted therapy + taxane chemotherapy period.

8.2.5.5 **Mucositis**

Mucositis was analyzed in APHINITY using Roche AEGT "Mucositis of the gastrointestinal tract," which included selected Gastrointestinal disorders (9 Preferred Terms [PTs]), General Disorders and Administration Site Conditions (5 PTs), and 1 PT under Respiratory, Thoracic and Mediastinal Disorders (pharyngeal inflammation). The applicant reported TEAEs of AEGT mucositis in 1348 patients (57.0%) in the PTZ arm and 1180 (49.1% in the PL arm. The most commonly reported events (PTs) were stomatitis (28.4% vs. 23.8%), mucosal inflammation (23.4% vs. 18.6%), pharyngitis (4.2% vs. 3.5%) and mouth ulceration (2.9% vs. 3.1%). There were 4.9% of patients in the PTZ arm and 2.3% in the PL arm who experienced grade3-4 events, and there were no fatal events of mucositis reported.

Reviewer Comments: *Overall the incidence of mucositis is higher for the PTZ treatment group. However, the occurrence of mucositis was reported to occur more frequently during the targeted therapy plus taxane period, somewhat less during the anthracycline treatment period, with a decrease to 2% in each arm during the post chemotherapy period of targeted therapy. Some of the differences appear likely due to interaction with different drugs in the chemotherapy backbone.*

8.2.5.6 **Leukopenia and Febrile neutropenia**

A high number of patients in each arm of APHYNITY experienced at least one leukopenic AE (PTZ 49.8%) vs. (PL 48.1%) during the treatment period. Grade ≥3 events were reported in 881 patients (37.3%) in the PTZ arm and 841 patients (35%) in the PL arm. Febrile neutropenia was reported in 12.1% and 11.1%, respectively. SAE neutropenia was reported in 208 (8.8%) of patients in the PTZ group vs. 196 in the PL group (8.1%). One death occurred on study day 65, following 3 cycles of docetaxel, carboplatin, pertuzumab and trastuzumab.

8.2.5.7 **Interstitial lung disease**

In APHINITY, the number of patients who experienced interstitial lung disease (ILD) AEs was 19 (0.8%) in the PTZ arm and 22 (0.9%)in the PL arm. The incidence of grade ≥3 ILD AEs was 5 patients in the PTZ arm (0.2%) and 4 patients in the PL arm (0.2%). There were 4 ILD SAEs in the PTZ arm and 19 ILD SAEs in the PL arm, with one death in each treatment arm.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Patient-Reported Outcomes (PRO) were assessed in the APHINITY Trial using the three instruments: EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D-3L. The EORTC QLC-C30 questionnaire is a standardized cancer-specific instrument for measuring health status

consisting of 30 items and 5 domains: physical, role, emotional, cognitive, and social function. Each domain is measured on a 4-point scale, with 4 being the worst health status. The EORTC QLQ-BR23 is an extension of QLQ-C30 with breast cancer module. The BR23 disease module contains questions related to body image, sexual function, symptoms related to upper extremity dysfunction and localized symptoms likely more related to post-surgical changes, though there are several questions related to the effects of systemic therapy as well. The EQ-5D-3L is a two-part general instrument that captures 5 descriptors of current health status as well as a general health status as measured by a visual analog scale. This is a generic health assessment tool that is typically used to generate a health utility index for economic analyses and has not been validated as a tool with content validity for use in estimating clinical benefit.

Responses to all three instruments were to be collected at screening/baseline, end of anthracycline (only for patients who received anthracycline regimen), end of taxane (week 10, 13, or 19 depending on the chemotherapy regimen), week 25, end of study treatment, follow-up month 18, follow-up month 24, and follow-up month 36. The completion rates on both arms were higher than or close to 85% at all scheduled assessments.

The mean of change from baseline for functional domains and relevant symptoms of EORTC QLQ-C30 were evaluated. Although the study was not adequately statistically designed to compare treatment arms with respect to these outcomes, the results suggested that patients in both treatment groups reported a comparable decline in physical function from baseline while on chemotherapy. Average physical function scores during anti-HER2 therapy alone approached baseline levels (assessed after surgery) in both arms after completion of therapy, however they did not return to baseline until the follow up period where patients were off treatment. There were no notable differences in physical function scores between the two treatment arms throughout the course of the study.

(b) (4)

(b) (4)

The Agency's review of the data found that though the applicant had collected high quality data with little missing data, there remained several issues when considering (b) (4)

(b) (4)

Similar to clinician reports, during the treatment period, the observed rate of patient-reported diarrhea was greater in the pertuzumab arm than in the placebo arm. At the end of taxane treatment, of the patients who had a baseline PRO assessment and an end of taxane PRO assessment, 50% of patients in the pertuzumab arm and 29% of patients in the placebo arm reported worse diarrhea compared to baseline. At the end of treatment, of the patients who had a baseline PRO assessment and an end of treatment assessment, 30% of patients in the pertuzumab arm and 14% of patients in the placebo arm reported worse diarrhea compared to baseline.

The Agency also reviewed the symptomatic adverse events that increased with the addition of pertuzumab such as rash, pruritus, and mucositis and found that the instruments used did not assess these symptomatic adverse events.

A complete assessment of the FDA analysis of patient reported outcomes is presented in Appendix, Section 19.5, "Additional Clinical Outcomes Assessment Analyses."

8.2.7. Safety Analyses by Demographic Subgroups

APHINITY
The applicant provided an analysis of adverse events for each of the following demographic subgroups:

- Gender (Female, male)
- Race (White, Asian, Black, Other)
- Age (<40, 40-64, < 65 and ≥65 years).

Gender

There were 11 patients (0.2%) who were male, and 4793 patients (99.8%) were female in the trial. There were 3 patients randomized to PTZ and 8 patients randomized to PL. Due to the small number of male patients in the trial, no meaningful comparisons can be made.

Race

The applicant categorized patients by race as follows:

- White: 1680 patients (71.2%) in the PTZ arm and 1691 (70.4%) in the PL arm
- Asian: 580 patients (24.6%) in the PTZ arm and 605 (25.2%) in the PL arm
- Black: 32 (1.4%) in the PTZ arm and 39 (1.6%) in the PL arm
- Other: 66 patients (2.8%) in the PTZ arm and 68 patients (2.8%) in the PL arm.

A similar pattern of AEs was seen across racial subgroups as in the overall population, except there appeared to be a greater difference in incidence of diarrhea between the treatment arms for Black patients (87.5% in the PTZ arm vs. 48.7% in the PL group) than for other groups.

However, the small number of Black subjects in the trial does not allow meaningful comparisons.

For febrile neutropenia, the incidence was higher for Asian patients, as was the difference between treatment arms, compared with other groups. For Asians, the incidence of febrile neutropenia was 15.9% in the PTZ arm vs. 9.9% in the PL arm, compared to White patients (11.1% vs. 11.6%, respectively), the group with the next highest incidence of febrile neutropenia.

Age

The applicant categorized patients by age into 3 groups:

- <40 years
- 40-64 years
- ≥65 years.

Since the number of patients age ≥75 was small (56 patients =1.2%), the applicant did not analyses these oldest patients separately in the CSR. Almost all patients experienced AEs, with a similar profile of AEs, generally, for each group compared to the overall population. Patients age ≥65 had a higher incidence of diarrhea and anemia in both treatment arms compared with younger patients, with a greater difference by age in the PTZ treatment arm. The next table summarizes the FDA analysis of key safety events by age (<65 vs. ≥65 year of age) and treatment arm.

Table 49: APHINITY FDA Analysis of Key Safety Events by Age and Treatment Arm

	PTZ + Trastuzumab + Chemotherapy (N=2364)			**PL+ Trastuzumab + Chemotherapy (N=2405)**		
	Age <65 (N=2062)	Age ≥65 (N=302)	Total (N=2364)	Age <65 (N=2112)	Age ≥65 (N=293)	Total (N=2405)
TEAE	2059 (99.9%)	302 (100%)	2361 (99.9%)	2101 (99.5%)	291 (99.3%)	2392 (99.5%)
Grade 3-4 TEAE	1296 (62.9%)	219 (72.5%)	1515 (64.1%)	1183 (56.0%)	189 (64.5%)	1372 (57.0%)
SAE	560 (27.2%)	132 (43.7%)	692 (29.3 %)	479 (22.7%)	106 (36.2%)	585 (24.3 %)
Deaths	54 (2.6 %)	19 (6.3 %)	73 (3.1%)	74 (3.5 %)	21 (7.2 %)	95 (4.0%)
Deaths due to AEs	11 (0.5 %)	7 (2.3 %)	18 (0.8%)	12 (0.6 %)	8 (2.7 %)	20 (0.8%)
Diarrhea	1450 (70.3%)	233 (77.2 %)	1683 (71.2%)	940 (44.5 %)	146 (49.8%)	1086 (45.2%)
Grade 3-4 Diarrhea	184 (8.9 %)	48 (15.9 %)	232 (9.8%)	70 (3.3 %)	20 (6.8 %)	90 (3.7%)

Overall there was a higher percentage of patients in the PTZ arm compared with the PL arm who experienced grade 3-4 TEAE, SAEs, diarrhea of all grades and grade 3-4 diarrhea. Within each treatment arm, the incidence (%) was greater for patients ≥65 years of age compared with those < age 65 for grade 3-4 TEAEs, SAEs, deaths, deaths due to AEs, all grades of diarrhea, and for grade 3-4 diarrhea.

The next table summarizes the FDA analysis of Primary and Secondary Cardiac Events by age and treatment arm. (See this review, Section 8.2.4 for definitions and discussion of Primary and Secondary Cardiac Events.)

Table 50: APHINITY FDA Analysis of Primary and Secondary Cardiac Events by Age and Treatment Arm

	PTZ + Trastuzumab + Chemotherapy (N=2364)			**PL + Trastuzumab + Chemotherapy (N=2405)**		
	Age <65 (N=2062)	**Age ≥65 (N=302)**	**Total (N=2364)**	**Age <65 (N=2112)**	**Age ≥65 (N=293)**	**Total (N=2405)**
Primary Cardiac Event	8 (0.4%)	9 (3.0%)	17 (0.7%)	5 (0.2%)	3 (1.0%)	8 (0.3%)
***Heart Failure**	8 (0.4%)	7 (2.3%)	15 (0.6%)	4 (0.2%)	2 (0.7%)	6 (0.2%)
Cardiac Death	0 (0.4)	2 (0.7%)	2 (0.1%)	1 (0.05%)	1 (0.3%)	2 (0.1%)
****Secondary Cardiac Event**	52 (2.5%)	12 (4.0%)	64 (2.7%)	51 (2.4%)	16 (5.5%)	67 (2.8%)

* Heart failure: NYHA Class III/IV and LVEF↓≥10 EF points from baseline & to <50%

**Secondary Cardiac Event: Asymptomatic or minimally symptomatic LVEF↓≥10 points from baseline & to <50%, confirmed ≤3 weeks/or adjudicated by Cardiac Advisory Board

The incidence of Primary Cardiac Events in the trial was low overall, with a numerically higher incidence of Heart Failure (a protocol-defined Primary Cardiac Event) in the PTZ treatment arm compared with the PL arm (0.6% vs. 0.2%). The incidence of Secondary Cardiac Events was 2.7% in the PTZ arm and 2.8% in the PL arm, with a slightly higher incidence for the older age group compared with the younger age group in each treatment arm.

Reviewer Comments: *The number of Primary and Secondary Cardiac Events in the subgroups is low overall, requiring caution in trying to make meaningful comparisons.*

Applicant's Pooled Analysis of Safety and Efficacy from Multiple Pertuzumab Trials by Age

In response to an FDA Information Request, the applicant provided a pooled analysis of geriatric data from the 5 breast cancer studies referenced within the USPI for Pertuzumab:

- TRYPHAENA – Neoadjuvant
- APHINITY - Adjuvant
- NEOSPHERE –Neoadjuvant
- CLEOPATRA – First-line metastatic.
- BERENICE – Neoadjuvant

The following table lists the number of patients aged ≥65 years and ≥75 years exposed to PTZ by study.

Table 51: Applicant's Analysis of the Number of Patients Aged ≥ 65 Years and ≥ 75 Years Exposed to PTZ in Five Pertuzumab Breast Cancer Trials

Study number (Study name)	Aged ≥65 years	Aged ≥75 years
BO22280 (TRYPHAENA)	26	4
BO25126 (APHINITY)	302	30
WO20697 (NEOSPHERE)	22	2
WO20698 (CLEOPATRA)	68	5
WO29217 (BERENICE)	46	6

Adverse events reported during the overall treatment period were determined, except for the TRYPHAENA and NEOSPHERE studies. For these two trials, only AEs that started during the neoadjuvant period were included. In the pooled analysis, there were 464 patients who were age ≥ 65 years of age, of whom 47 were ≥75 years of age. The most common (≥10%) grade 3-4 AEs in both older age groups were neutropenia (22% for age ≥65 vs. 23% for age ≥75), febrile neutropenia (12% vs. 13%), diarrhea (15% vs. 17%), and the incidence of anemia was 15% for patients ≥75 years of age.

There was at least a 5% higher incidence of the following all grade AEs for patients aged ≥65 years of age, compared to patients <65 years of age: Decreased appetite (13% higher), anemia (7% higher), weight decreased (7% higher), asthenia (7% higher), dysgeusia (7% higher), neuropathy peripheral and hypomagnesemia (each, 5% higher).

No overall differences in efficacy were reported in patients aged ≥ 65 years compared with patients aged <65 years of age. There were too few patients aged ≥75 years of age (n=47) to draw conclusions regarding comparative efficacy.

Reviewer Comments: *In the APHINITY trial there were 302 patients ≥65 years of age treated with pertuzumab. Compared with those <65 years of age, the older patients had a higher incidence of grade 3-4 TEAEs, SAEs, deaths, deaths due to AEs, all grades of diarrhea, and grade 3-4 diarrhea. There were 30 patients in APHINITY ≥75 years of age in the pertuzumab treatment arm. In view of the enhanced toxicity observed for patients age ≥65 years of age, and very limited data for patients age ≥75 years, caution is indicated. Black patients are another subgroup which is under-represented in the APHINITY TRIAL, with only 32 Black patients*

exposed to pertuzumab.

8.2.8. Specific Safety Studies/Clinical Trials

The BERENICE Trial (WO29127) has been discussed elsewhere in this review (clinical study report submitted as supplement 113). BERENICE was designed to evaluate cardiac safety for PTZ in combination with anthracycline-based chemotherapy regimens in the neoadjuvant setting, with continuation of PTZ plus trastuzumab in the adjuvant setting for patients with early breast cancer.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Human Reproduction and Pregnancy

The pertuzumab product label (USPI) contains a Boxed Warning, "Embryo-fetal Toxicity: Exposures to Pertuzumab can result in embryo-fetal deaths and birth defects. Advise patients of these risks and the need for effective contraception." Section 5.2 of the USPI states, "Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy. In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at exposures of 2.5 to 20 times the exposure in humans at the recommended dose, based on Cmax… Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of pertuzumab in combination with trastuzumab."

There is no information regarding the presence of pertuzumab in human milk or the effects on the breastfed infant.

Since initial approval in 2012, Genentech has maintained a pregnancy registry that monitors pregnancy outcomes in women exposed to pertuzumab during pregnancy or within 7 months prior to conception (MotHER Pregnancy Registry). There is also a pregnancy pharmacovigilance program for pertuzumab for health care providers and patients to report exposures to Genentech.

In the APHINITY trial, female patients and partners were required to use strict contraceptive measures during and up to 7 months after the last dose of study medication. Nine ongoing pregnancies were reported as of the time of the primary data cut-off date (December 19, 2016) and an additional 2 ongoing pregnancies were reported as of the 3-Month Study Update Report. Updates were provided for the initial 7 pregnancies, 4 in the PTZ arm and 3 in the PL arm. All 7 delivered live infants, without delivery complications or congenital defects. The pregnancies appear to have been conceived after completion of study therapy.

Pediatrics and Assessment of Effects on Growth

Pertuzumab has not been studied in children.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdoses have not been reported for pertuzumab. There is no abuse potential and withdrawal considerations are not relevant.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Genentech reports that as of June 7, 2017, an estimated cumulative total of (b) (4) patients have been treated with pertuzumab in the marketing setting. The following table, from the 3-Month Safety Update Report, summarizes the System Organ Classes (SOCs) of the most frequently reported AEs for pertuzumab from post-Market Data.

Table 52: SOCs of Most Frequently Reported AEs for Pertuzumab (8 June 2012 – 7 June 2017) (Applicant Table)

SOC	Spontaneous, including health authority (worldwide) and literature		Non-interventional post-marketing study and reports from other solicited sources**
	Serious	Non-Serious	Serious
General Disorders and Administration Site Conditions	507	1627	688
Gastrointestinal Disorders	570	1231	268
Skin and Subcutaneous Tissue Disorders	258	1192	25

Source: Appendix 2b of the PBRER 1078884: Cumulative and interval summary tabulations of serious and non-serious adverse reactions from postmarketing data sources

*Non-interventional studies (including post-authorization safety studies), reports from other solicited sources, and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, health authorities [worldwide], and scientific literature)

** This does not include interventional clinical trials

cum = cumulative; SOC = system organ class

The following table, from the 3-Month Safety Update Report, shows the cumulative exposure to pertuzumab from Marketing Experience.

Table 53: Pertuzumab Cumulative Exposure from Marketing Experience (Applicant Table)

Indication	Sex			Age (years)				Region				Total
	M	F	Unk	0 to ≤ 16	> 16 to ≤ 65	> 65	Unk	EEA	U.S.	RoW	Japan	
EBC	(b) (4)											
MBC												
Total												
Grand Total												

EBC = early breast cancer; EEA = European Economic Area; F = female; M = male; MBC = metastatic breast cancer; n/a = Not applicable; RoW = Rest of World; Unk = unknown.

Expectations on Safety in the Postmarket Setting

In view of extensive market exposure since the initial approval of Pertuzumab (PERJETA®) in 2012, the safety profile is well known. It appears unlikely that significant new safety concerns will occur.

8.2.11. Integrated Assessment of Safety

APHINITY was a large, phase 3, randomized, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus PTZ vs. chemotherapy plus trastuzumab plus placebo (PL) in the adjuvant setting. The chemotherapy was either a standard anthracycline-based regimen or non-anthracycline based regimen (carboplatin plus docetaxel). In APHINITY, there were 4769 patients in the safety population (2364 randomized to PTZ and 2405 randomized to PL).

BERNICE was a non-randomized trial designed to evaluate cardiac safety for PTZ in combination with anthracycline-based chemotherapy in the neoadjuvant setting, with continuation of PTZ plus trastuzumab in the adjuvant setting for patients with early breast cancer. Cohort A enrolled 199 patients (dose dense AC followed by weekly paclitaxel) and 202 were enrolled in Cohort B (FEC followed by docetaxel).

No new safety signals were identified in either study and the safety profile was consistent. In this overview, the emphasis will be on the safety results from the larger, randomized, placebo-controlled APHINITY trial. See sections 8.2.4, 8.2.5, and 8.2.7 for details.

In APHINITY, disease recurrence was the most common cause of deaths. The next most common cause of deaths was Adverse Events. Deaths due to AEs any time during the study period occurred in 18 patients (0.8%) in the PTZ arm and 20 patients (0.8%) in the PL arm, with 1 death in each arm attributed to study therapy (including 1 tongue cancer). Among the fatal AEs, there were 9 and 8 Second Primary Non-Breast Cancers (SPNBC) in the PTZ and PL treatment arms, respectively.

In APHINITY, the incidence of non-fatal SAEs for the period including 28 days after the last dose of any study treatment was higher in the PTZ arm (29.3%) compared with the PL arm (24.3%). There were 208 patients (8.8%) in the PTZ arm and 196 patients (8.1%) in the PL arm who experienced SAE febrile neutropenia. There were 58 patients (2.5%) in the PTZ arm and 18 patients (0.7%) in the PL arm who experienced SAE diarrhea. Almost all diarrhea SAEs required hospitalization and occurred when targeted therapy was administered in combination with chemotherapy. No patients on PTZ arm required hospitalization for diarrhea during the targeted therapy alone treatment phase.

AE-related discontinuation of any study medication occurred in 309 (13.1%) patients in the PTZ treatment arm and in 277 (11.5%) patients in the PL treatment arm of APHINITY. More patients were discontinued from the PTZ arm than the PL arm for diarrhea (1.6% PTZ arm patients vs. 0.3% PL arm patients) and cardiac failure (1.2% PTZ arm patients vs. 0.6% PL arm patients), but not for ejection fraction decreased (1.8% PTZ arm patients vs. 2.5% PL arm patients). The % of patients discontinued for peripheral neuropathy was similar (1.5% vs. 1.6%). AE-related discontinuation of PTZ or PL occurred in 7.0% and 5.8% of patients, respectively. More patients were discontinued from PTZ than from PL for AEs cardiac failure (PTZ 1.8% vs. PL 0.6%) and diarrhea (PTZ 0.8% vs. PL 0.1%), but not for AE “ejection fraction decreased (PTZ 1.8% vs. 2.5% PL).”

The number of APHINITY Primary Cardiac Events was low in each treatment arm (PTZ 0.7% and PL 0.3 %), predominantly heart failure events rather than cardiac deaths of which there were 2 in each group. Recovery of LVEF dysfunction occurred in 7/15 (46.7%) and 4/6 (66.7%) of patients treated with PTZ or PL, respectively. Secondary Cardiac Events occurred in 2.7% of PTZ-treated patients vs. 2.8% of PL-treated patients, with LVEF recovery occurring in 79.7% and 80.6%, respectively. Most Secondary Cardiac Events (87.8%) occurred in patients treated with anthracyclines. The cardiac risk for the addition of PTZ to standard trastuzumab and chemotherapy appears acceptable.

In APHINITY, when pertuzumab was administered with trastuzumab and chemotherapy, the most common treatment emergent adverse events (>30%) were diarrhea, nausea, alopecia, fatigue, peripheral neuropathy, and vomiting. The most common grade 3-4 adverse events (≥2%) were neutropenia, febrile neutropenia, diarrhea, leukopenia, anemia, fatigue, nausea, and stomatitis. More patients in the PTZ arm (71%) experienced all grade diarrhea than in the PL arm (45%). Grade 3-4 diarrhea was also higher (PTZ 9.9% vs. PL 3.7%). For the treatment phase when only targeted therapy was administered, the incidence of all grade diarrhea in both arms was less than when administered with chemotherapy, but there was still a difference between treatment arms (PTZ 18.1% vs. PL 9.2%)

The safety profile of pertuzumab added to standard chemotherapy and trastuzumab is acceptable for appropriately selected patients with early breast cancer, and no new safety signals were identified in APHINITY or BERENICE. The Primary Cardiac Event rates were low. The

Secondary Cardiac Event rates were low and similar between the APHINITY treatment arms. In APHINITY, the incidence of diarrhea, all grades, was higher for PTZ than PL when chemotherapy was administered with targeted therapy and was highest when administered with non-anthracycline-based chemotherapy. More patients required hospitalization for diarrhea in the PTZ treatment group than the PL treatment group. Compared with patients younger than age 65, patients *≥65* years of age had a higher incidence of grade 3-4 TEAEs, SAEs, deaths, deaths due to AEs, all grades of diarrhea, and grade 3-4 diarrhea. The label will be updated to include safety data from both trials. The Limitations of Use statements regarding safety of Perjeta as part of an anthracycline containing regimen and safety of administration for greater than 6 cycles in early breast cancer will be revised.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

There are no major statistical issues with the efficacy results of the pivotal study APHINITY. The study met its primary objective of IDFS and the results appeared consistent across sensitivity analyses. A high-risk subgroup was not a pre-specified subgroup and analyses in such subgroups are generally considered exploratory. However, it was determined by the clinical team that the benefit to risk ratio was favorable in patients at high-risk of recurrence.

8.4. Conclusions and Recommendations

The APHINITY study met its primary endpoint of improving IDFS for patients with operable HER2 positive breast cancer. The results of the study were statistically significant for the overall study population, and most clinically significant for patients at high risk of disease recurrence such as those patients with hormone receptor negative disease and/or evidence of lymph node involvement.

The addition of pertuzumab to chemotherapy and trastuzumab did increase the incidence of adverse events, including diarrhea, fatigue, anemia, and rash. The incidence of grade 3-4 adverse events was similar in the treatment arms except for diarrhea (10% vs. 4%). More patients required hospitalization for diarrhea in the pertuzumab treatment arm. The choice of the chemotherapy backbone (anthracycline vs. non-anthracycline) had an impact on the safety profile, including the types and severity of adverse events.

Given the increased risk associated with the addition of pertuzumab to standard chemotherapy and trastuzumab, we agree with the applicant's proposed indication of addition of pertuzumab to standard regimens for those at high risk of disease recurrence. These patients are most likely to have a favorable benefit-risk with the addition of pertuzumab. Due to multiple patient and tumor characteristics resulting in breast cancer at high risk of recurrence, the determination of high risk is not defined specifically in the indication, although certain high-risk subgroups such as lymph-node positive, and ER negative disease may benefit more from the addition of pertuzumab.

In conclusion, pertuzumab demonstrated a statistically significant improvement in IDFS in a large, randomized, double-blind clinical study. Despite immature OS data, in patients with high risk HER2-positive EBC, this IDFS improvement represents a clinically meaningful benefit. The safety profile is acceptable in the intended population. Appropriate labeling for Left ventricular dysfunction, embryo-fetal toxicity, infusion related reactions, and hypersensitivity in Warnings and Precautions identifies these concerns to prescribers and assists with appropriate management.

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9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting or other external consultations were required for this supplemental BLA.

10 Pediatrics

On April 30, 2013, Genentech submitted an initial Pediatric Study Plan (iPSP) with a request for a waiver from all requirements of the Pediatric Research Equity Act (PREA) for pertuzumab for the treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (BLA 125k408/051, Serial # 0112). In the sBLA Accelerated Approval Letter, dated, September 30, 2013, FDA waived the pediatric study requirement for the application. On October 21, 2016, Genentech requested clarification if the waiver would apply to (b) (4) . On October 31, 2016, FDA communicated that since the waiver was granted for the disease, a full waiver request could be submitted with the new supplement

In section 1.9.1 of the supplemental BLA under review, (#118) Genentech requested a Waiver of Pediatric Studies, requesting a disease-specific waiver for the treatment of breast cancer in adults.

S118 and S113 are both treatment of early breast cancer, already covered under the 2013 PSP, which PeRC has already reviewed, and for which the waiver was granted.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The table below summarizes significant changes to the proposed prescribing information made by FDA and the applicant. This labeling was under negotiation at the time of this review. See the final approved prescribing information for Perjeta (pertuzumab) accompanying the sBLA 125409 approval letter for complete details.

Summary of Significant Labeling Changes *(As of December 7, 2017)*		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights		
Indications and Usage	*See Full Prescribing Information, Indications and Usage*	*See Full Prescribing Information, Indications and Usage for corresponding revisions*
Dosage and Administration	*See Full Prescribing Information, Dosage and Administration*	FDA added the following: "• HER2 testing: Perform using FDA-approved tests by laboratories with demonstrated proficiency. (2.1)" *For other revisions, see Full Prescribing Information, Dosage and Administration for corresponding new recommended doses.*
Warnings and Precautions	…	The following was removed since this information is included in the Highlights, Boxed Warning and doesn't require repetition under this heading: "Left Ventricular Dysfunction: Monitor LVEF and withhold dosing as appropriate. (5.1, 6.1)" FDA also removed the HER2 testing information under this heading since now in Highlights, Dosage and Administration.
Adverse Reactions	…	The most common adverse reaction statements were added for neoadjuvant treatment of breast cancer for PERJETA in combination with trastuzumab and paclitaxel, PERJETA in combination with trastuzumab and docetaxel; and for adjuvant treatment of breast cancer in

		combination with trastuzumab and chemotherapy.
Full Prescribing Information		
1. Indications and Usage	1.2 Early Breast Cancer …	The subsection 1.2 heading was revised from "Neoadjuvant Treatment of Breast Cancer" to "Early Breast Cancer". The neoadjuvant indication was revised for use in combination with "trastuzumab and docetaxel" to "trastuzumab and chemotherapy". The following information was removed from 1.2: "This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival." The indication for (b) (4) [redacted] The Limitations of Use statements related to the safety of PERJETA as part of a doxorubicin containing regimen and the safety of PERJETA administered for greater than 6 cycles of early breast cancer were removed. *See Section 1.2 and 1.3 of this review for more information.*
2. Dosage and Administration	2.1 Patient Selection …	The "Patient Selection" information related to HER2 protein overexpression was moved from the

		Warnings and Precautions (5.5) to the Dosage and Administration subsection (2.1) to be consistent with current best labeling practices for companion diagnostic devices. FDA revised this information to be consistent with HER2 testing experience and with other products with HER2 companion diagnostic devices.
	2.2 Recommended Doses and Schedules …	The neoadjuvant treatment of breast cancer dosing information was updated to incorporate the BERENICE study experience and to add the following treatment regimen: "Four preoperative cycles of dose-dense doxorubicin and cyclophosphamide (ddAC) alone followed by 4 preoperative cycles of PERJETA in combination with paclitaxel and trastuzumab as given in BERENICE". FDA clarified that following surgery, up to 18 cycles may be required to complete one year of treatment. FDA removed "There is insufficient evidence to recommend continued use of PERJETA for greater than 6 cycles for early breast cancer. There is insufficient evidence to recommend concomitant administration of an anthracycline with PERJETA, and there are no safety data to support sequential use of doxorubicin with PERJETA." The following was added: "PERJETA should be administered in combination with trastuzumab every 3 weeks for a total of 1 year (up to 18 cycles) or until disease recurrence or

		unmanageable toxicity, whichever occurs first, as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy as given in APHINITY. PERJETA and trastuzumab should start on Day 1 of the first taxane-containing cycle [*see Clinical Studies (14.3)*]."
	2.3 Dose Modifications	FDA agreed to delete redundant information also included in the Warnings and Precautions (5.1) for Left Ventricular Ejection Fraction (LVEF) dose modifications. FDA consolidated the dose modifications (b) (4) to be consistent with FDA labeling guidance and current best labeling practices.
3. Dosage Forms and Strengths	…	To be consistent with FDA labeling requirements and to include the dosage form, FDA revised this section to the following: Injection: 420 mg/14 mL (30 mg/mL) in a single-dose vial
5. Warnings and Precautions	5.1 Left Ventricular Dysfunction …	FDA revised this section to increase the prominence of the LVEF monitoring and management information by consolidating and moving the following information to the first paragraph of this subsection: "Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within normal limits. If the LVEF declines and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and trastuzumab should be strongly considered [*see Dosage and Administration (2.3)*]."

		The LVEF information from the BERENICE study was added. FDA required the addition of heart failure and LVEF decline information from the APHINITY study that included patients treated with anthracyclines. *See 8.2.4 and 8.2.7 of this review for more information.*
	5.5 HER2 Testing …	FDA removed this subsection. *See 2.1 above for more information.*
6. Adverse Reactions	6.1 Clinical Trials Experience …	FDA added the clinical trial names (e.g., BERENICE, APHINITY, etc.) throughout labeling to be consistent with current best labeling practices. For all the studies described in 6.1, FDA revised the information for the adverse reactions (ARs) that led to permanent discontinuation, to retain the permanent discontinuation rates for each treatment regimens, and to list the most common ARs resulting in permanent discontinuation of PERJETA (where possible). Other formatting revisions (e.g., table titles, column headings, rounding, etc.) were made to all AR tables to be internally consistent in format and consistent with OHOP best labeling practices. The "Neoadjuvant Treatment of Breast Cancer (BERENICE)" subsection was added. Key revisions to the applicant's proposed labeling included: • Addition of peripheral neuropathy to the most common ARs. • Addition of peripheral neuropathy and alanine

		aminotransferase increased to the most common Grade 3-4 ARs. The "Adjuvant Treatment of Breast Cancer (APHINITY)" subsection was added. Key revisions to the applicant's proposed labeling included: • Addition of peripheral neuropathy to the most common ARs. • Addition of a paragraph to characterize diarrhea ARs related to PERJETA. • For ARs occurring in patients receiving PERJETA and trastuzumab after discontinuation of chemotherapy, FDA removed the following general unsupported claims: "(b) (4) ".
	6.2 Immunogenicity …	FDA removed a redundant paragraph related to immunogenicity data limitations.
7. Drug Interactions	…	FDA agreed to add paclitaxel and carboplatin to the no drug-drug interactions statement for pertuzumab.
8. Use in Specific Populations	8.5 Geriatric Use …	FDA revised the proposed information to pool PERJETA experience in older patients and provide clinically relevant information per OHOP best labeling practices. This section was revised to the following: "In studies in the indicated populations, CLEOPATRA, NeoSphere, TRYPHAENA, BERENICE,

		and APHINITY, 464 patients who received PERJETA were ≥ 65 years of age and 47 were ≥ 75 years of age. The most common (≥ 10%) Grade 3-4 adverse reactions in both age groups were neutropenia (22% ≥ 65 years, 23% ≥ 75 years), febrile neutropenia (12% ≥ 65 years, 13% ≥ 75 years), diarrhea (15% ≥ 65 years, 17% ≥ 75 years) and anaemia (15% ≥ 75 years). The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥ 65 years of age, compared to patients aged <65 years of age: decreased appetite (13% higher), anaemia (7% higher), weight decreased (7% higher), asthenia (7% higher), dysgeusia (7% higher), neuropathy peripheral and hypomagnesaemia (both 5% higher). No overall differences in efficacy of PERJETA were observed in patients aged ≥ 65 and <65 years of age. There are too few patients aged ≥ 75 years to draw conclusions on efficacy in this age group. Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of pertuzumab between patients < 65 years (n=306) and patients ≥ 65 years (n=175)."
14. Clinical Studies	…	FDA added the study names and NCT#s to be consistent with current best labeling practices. Arbitrary terms such as "(b) (4)" were also removed from the trial descriptions.
	14.2 Neoadjuvant Treatment of Breast Cancer	The BERENICE study subsection was added. Key revisions to the applicant's proposed labeling

	…	included: • Adding bullets to clearly differentiate the treatment regimens used in this trial • Adding ECOG performance status to the demographic information.
	14.3 Adjuvant Treatment of Breast Cancer	FDA agreed to add this new subsection. Key revisions to the applicant's proposed labeling included: • Addition of the stratification factors to the study description (i.e., region, nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen) • Addition of the doses and schedules utilized for the chemotherapy regimens in this trial; and removal of (b) (4) " • Addition of ECOG performance status to the demographic information. • Revision of HRs and p-values based on FDA statistical reviewer findings. • Removal the (b) (4) • Removal of the (b) (4) • FDA removed text statements

		related to the (b) (4) such as: (b) (4) • FDA removed (b) (4) • FDA removed (b) (4)

William Pierce
Associate Director for Labeling DOP1

12 Risk Evaluation and Mitigation Strategies (REMS)

There are no safety issues related to this agent that warrant consideration of a REMS.

13 Postmarketing Requirements and Commitment

PMC 3312-1
Submit the overall survival (OS) data and analysis with a final report from the clinical trial APHINITY BIG 4-11/BO25126/TOC4939g clinical trial entitled "A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer."

Draft Protocol Submission:	06 /2011
Final Protocol Submission:	02 /2015
Trial Completion:	12 /2023
Final Report Submission:	06 /2024

14 Division Director (OB)

Rajeshwari Sridhara, PhD
Division Director, Division of Biometrics V

15 Division Director (Clinical)

Julia Beaver, MD
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16 Appendices

16.1. References

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16.2. Financial Disclosure

Please see section 8.1.3 regarding financial disclosures for both the APHINITY and BERENICE studies. Additional information regarding financial disclosures for the APHINITY study is included below.

Covered Clinical Study (Name and/or Number): APHINITY BO25126

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4728		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 12		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator 9 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 71		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

Please see the Pharmacology/Toxicology review by Dr. Kimberly Ringgold in the original BLA 125409 review.

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

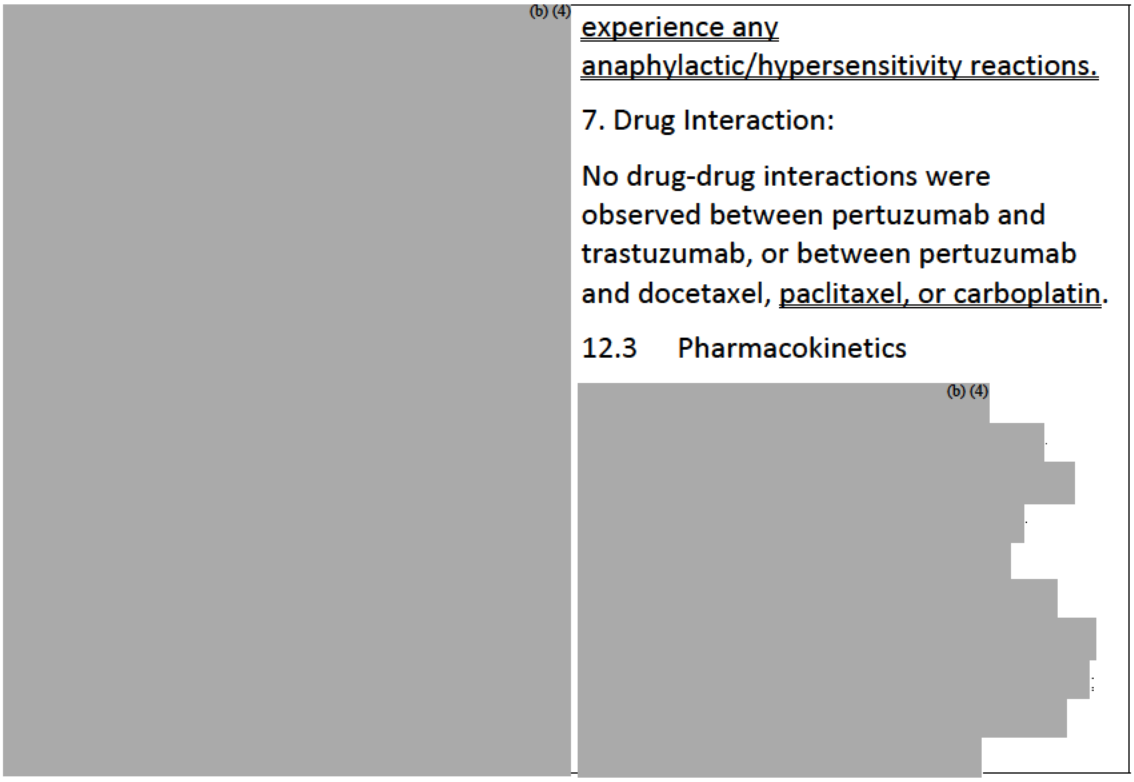
The Question Based Clinical Pharmacology Review regarding the labeling changes is appended below:

16.4.1. Are the Applicant's proposed labeling updates acceptable?

Yes. The proposed labeling updates are generally acceptable from a clinical pharmacology perspective, based on review on the submitted PK results.

The Applicant proposed the following labeling changes as indicated as the content, and the ~~content~~ is the Agency's deletion:

Applicant's Proposal	Agency's Counter-Proposal
(b) (4)	6.2 Immunogenicity: Patients in (b) (4) CLEOPATRA were tested at multiple time-points for antibodies to PERJETA. (b) (4) (b) (4) 3 (b) (4)% (13 (b) (4)/389 (b) (4)) of patients in the PERJETA-treated group and (b) (4) 7 (b) (4)% (25 (b) (4) 372) of patients in the placebo-treated group tested positive for anti-PERJETA antibodies. Of these 38 (b) (4) patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to the anti-therapeutic antibodies (ATA). The presence of pertuzumab in patient serum at the levels expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-pertuzumab antibody development. In the neoadjuvant period of BERENICE (b) (4), 0.3% (1/383) of patients treated with PERJETA tested positive for anti-PERJETA antibodies. This patient did not



16.4.1.1. Background

The purpose of the current efficacy supplement submission (S-113; S-118) is to support use of (b) (4) based on data from the randomized Phase 3 pivotal Trial BO25126 (APHINITY).

Study BO25126 (APHINITY) was a randomized, multicenter, double-blind, placebo-controlled comparison of placebo plus Trastuzumab plus chemotherapy (Pla+H+chemo) versus Pertuzumab plus Trastuzumab plus chemotherapy (Ptz+H+chemo) as adjuvant therapy in patients with operable HER2-positive primary breast cancer. Patients were randomized 1:1 to receive Trastuzumab and Pertuzumab or placebo for 52 weeks. Pertuzumab was administered as a loading dose of 840 mg intravenously followed by 420 mg every 3 weeks (q3w). Trastuzumab was administered as a loading dose of 8 mg/kg IV followed by 6 mg/kg q3w.

A PK substudy was conducted to address four primary objectives:

- To characterize the steady-state PK of pertuzumab in patients with HER2+ EBC;
- To characterize the potential PK DDI of trastuzumab on the PK of pertuzumab;
- To characterize the potential PK DDI of pertuzumab on the PK of trastuzumab;
- To characterize the potential PK DDI of pertuzumab on the PK of paclitaxel and carboplatin, in patients with EBC.

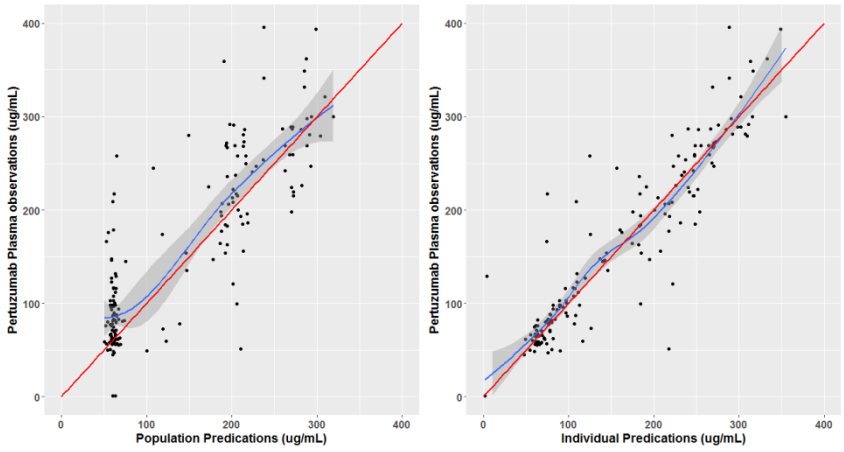
The PK Substudy included 72 patients of whom 38 were in the Ptz+H+chemo treatment arm and 34 contributed pertuzumab concentration data for the PopPK analysis.

The potential effect of trastuzumab on the PK of pertuzumab was assessed by comparing the pertuzumab observed PK in APHINITY with the PopPK model predictions. If the pertuzumab observations in APHINITY were adequately predicted by the historical model built with the majority of the data (>95%) from study in which pertuzumab was utilized without concomitant trastuzumab treatment, it suggests no impact of trastuzumab on the PK of pertuzumab. The potential effect of pertuzumab on the steady state PK of trastuzumab was assessed by comparing the serum concentrations at pre-dose ($C_{min;ss}$) and post-infusion ($C_{max;ss}$) in Cycles 10 and 15 in the Ptz+H+chemo and Pla+H+chemo treatment arms. Similarly, the potential effect of pertuzumab on the PK of paclitaxel (and its metabolite 6-alpha-hydroxy-paclitaxel) and carboplatin was assessed by comparing the plasma maximum concentration (C_{max}) and area under the concentration vs. time curve over all concentration measurements (AUC_{last}) in Cycle 1 in the Ptz+H+chemo and Pla+H+chemo treatment arms.

16.4.1.2. Population PK Analysis

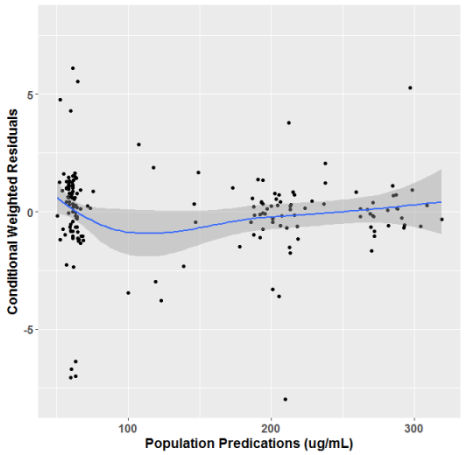
Pertuzumab PK prediction were obtained via post-hoc Bayesian forecasting by fixing the parameters in the structural and variance model to the parameter estimates in the historical validated PopPK model developed based on pertuzumab without concomitant trastuzumab treatment. Individual PK parameters was carried out using first order conditional estimation with Interaction (FOCE-I). In the historical PopPK model, LBW and baseline serum albumin were identified as statistically significant covariates. Albumin levels were not measured in APHINITY. The median observed albumin level in another EBC study (study BO22227) of 4.3 g/dL was adopted for prediction. The adequacy of PK model to fit the data was determined by graphical assessment of the match between observed and model predicted pertuzumab concentrations, conditional weighted residuals, as well as VPC check (Fig.1, Fig. 2 and Fig. 3). The results suggested that the previously developed and validated PopPK model appropriately described the pertuzumab PK data from the APHINITY Global PK substudy.

Figure 1. Observed Versus Model-Simulated Pertuzumab Serum Concentrations



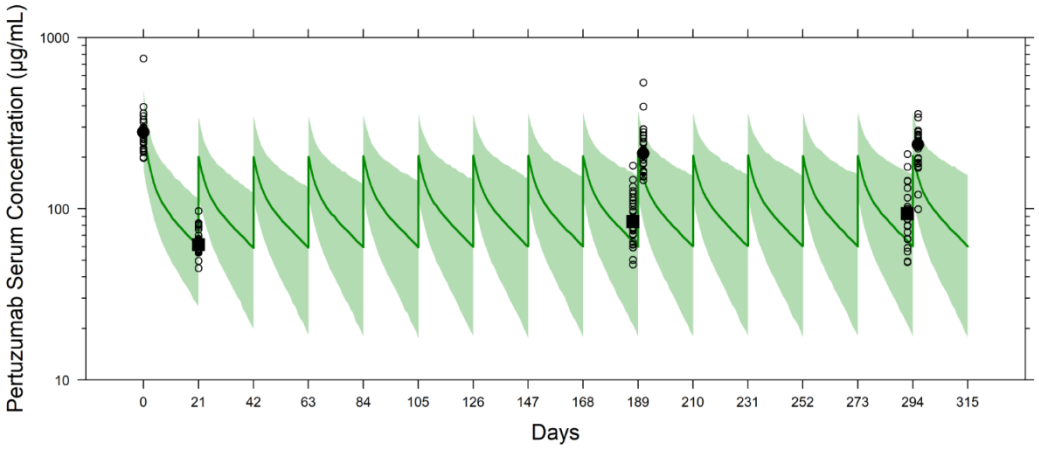
Source: Reviewer's analysis

Figure 2. Conditional Weighted Residuals versus Population Predictions



Source: Reviewer's analysis

Figure 3. Visual Predictive Check - PK Substudy



Source: Applicant's study report 1080205, Page 38, Figure 5

16.4.1.3. Drug-drug Interaction (DDI) Evaluations

16.4.1.3.1. DDI of trastuzumab on the PK of Pertuzumab

No noticeable impact of trastuzumab on the PK of pertuzumab was observed. Pertuzumab concentrations in APHINITY Global PK Substudy were similar to those predicted by the PopPK model with PK data from pertuzumab without concomitant trastuzumab (Figure 1, 2, 3).

16.4.1.3.2. DDI of Pertuzumab on the PK of Trastuzumab

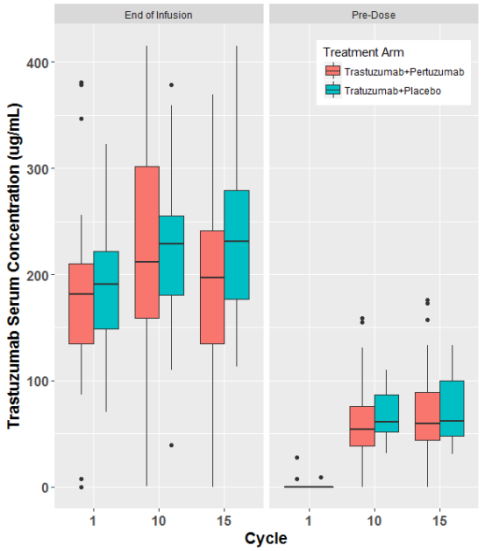
The potential effect of pertuzumab on the steady state PK of trastuzumab was assessed by comparing the serum concentrations at pre-dose ($C_{min;ss}$) and post-infusion ($C_{max;ss}$) in Cycles 10 and 15 in the Ptz+H+chemo and Pla+H+chemo treatment arms. The result shows no evidence of a significant impact of pertuzumab on Trastuzumab serum Cmin or Cmax (Table 1 and Fig. 4).

Table 1. Summary of C_{min} and C_{max} of Trastuzumab with or without Pertuzumab

	Ptz+H+chemo		Pla+H+chemo		
TimePoint	mean (±SD)	n	mean (±SD)	n	Mean Ratio* (90% CI)
Cycle 1 C_{max}	179.1 (±69.1)	34	189.9 (±51.6)	33	0.873 (0.713-1.07)
Cycle 1 C_{min}	30.8 (±11.3)	31	34.1 (±11.4)	31	0.874 (0.745-1.03)
Cycle 10 C_{max}	226.3 (±87.4)	32	224.5 (±70.7)	27	0.978 (0.797-1.2)
Cycle 10 C_{min}	67.0 (±38.5)	32	68.4 (±23.0)	26	0.878 (0.711-1.09)
Cycle 15 C_{max}	195.1 (±88.6)	24	233.6 (±73.5)	21	0.765 (0.605-0.968)
Cycle 15 C_{min}	75.7 (±44.6)	26	71.0 (±30.4)	22	0.967 (0.737-1.27)

Source: Applicant's study report 1080205, Page 39, Table 8.

Figure 4. Summary of C_{min} and C_{max} of Trastuzumab with or without Pertuzumab

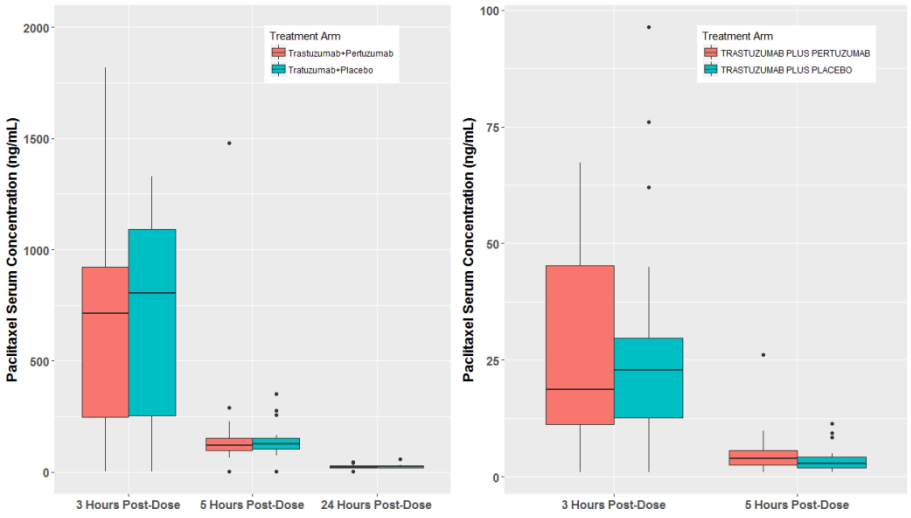


Source: Reviewer's analysis

16.4.1.3.3. DDI of Pertuzumab on the PK of paclitaxel and carboplatin

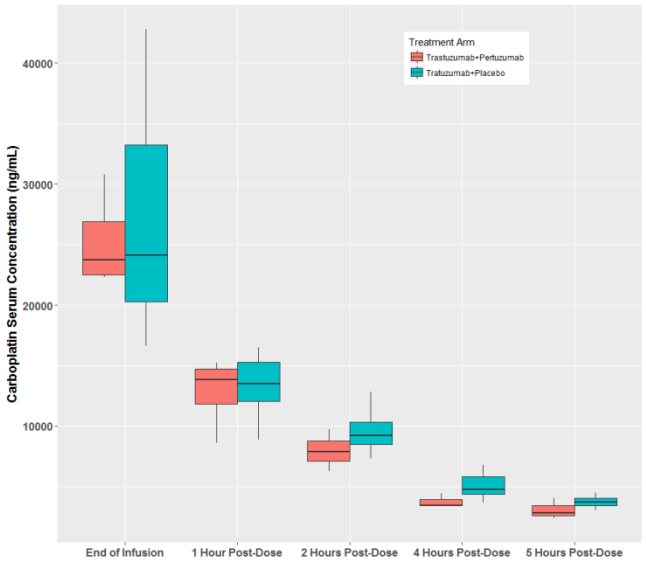
No evidence of significant impact of pertuzumab (in combination with Trastuzumab) on paclitaxel or 6-alpha-hydroxy-paclitaxel PK, or on carboplatin PK based on the graphical assessment (Fig. 5 and 6).

Figure 5. Paclitaxel and Metabolite Concentrations in Cycle 1 with/without Pertuzumab



Source: Reviewer's analysis

Figure 6. Carboplatin Concentrations in Cycle 1 with/without Pertuzumab



Source: Reviewer's analysis

16.4.1.3.4. PK of Pertuzumab in EBC vs. MBC

To compare pertuzumab exposure in patients with EBC and MBC, pertuzumab PK data from APHINITY was compared to the observed pertuzumab data from the previous MBC trial CLEOPATRA. It was found that serum C_{min} and C_{max} in APHINITY (Cycles 1, 10, and 15) are comparable to PK data from study CLEOPATRA (Table 2).

Table 2. Summary of Pertuzumab PK in Patients with EBC and MBC

APHINITY (EBC)					CLEOPATRA (MBC)				
Cycle	C_{min} $(\mu g/mL)$	n	C_{max} $(\mu g/mL)$	n	Cycle	C_{min} $(\mu g/mL)$	n	C_{max} $(\mu g/mL)$	n
1	65.9±12.4	30	291.2±99.1	30	3	63.4±48.1	18	183±33.5	18
10	91.0±30.9	30	229.8±83.4	28	9	75.5±22.1	16	196±66.3	14
15	98.4±39.6	24	232.8±64.6	21	15	94.1±30.6	11	221±32.0	9

Source: Applicant's study report, Page 46, Table 12.

16.4.1.4. Immunogenicity of Pertuzumab

Immunogenicity of pertuzumab were evaluated in trials CLEOPATRA and BERENICE. The updated data show that 3.3% (13/389) of patients in the pertuzumab-treated group and 6.7% (25/372) of patients in the placebo group in CLEOPATRA (Table 3), and 0.3% (1/383) of patients treated with pertuzumab in BERENICE (Table 4) were tested positive for anti-PERJETA antibodies.

Table 3. Immunogenicity of Pertuzumab in Trial CLEOPATRA

	Pla+T+D arm		Ptz+T+D arm	
Cutoff Date	13 May 2011	14 May 2012	13 May 2011	14 May 2012
Post-baseline samples available	372	372	386	389
No. of patients positive at baseline (regardless of post-baseline result)	7	8	5	5
No. of patients positive at baseline, negative post-baseline	1	2	4	4
No. of patients positive at baseline, positive post-baseline	6	6	1	1
No. of patients negative at baseline, positive post-baseline	15	17	10	12
No. of patients baseline unknown, positive post-baseline	2	2	0	0
Total no. of patients positive post-baseline [1]	**23**	**25**	**11**	**13**

Source: CLEOPATRA CSR in submission supplement-32 SDN345 on 12/13/2012

Table 4. Immunogenicity of Pertuzumab in Trial CLEOPATRA

	COHORT A (N=199)	COHORT B (N=201)	All Patients (N=400)
Baseline Prevalence of ATAs			
Baseline evaluable patients	189	188	377
Patients with a positive sample at baseline	2 (1.1%)	0 (0.0%)	2 (0.5%)
Patients with no positive samples at baseline	187	188	375
Post-Baseline Incidence of ATAs			
Post-baseline evaluable patients	186	197	383
Patients positive for ATA	0 (0.0%)	1 (0.5%)	1 (0.3%)
Treatment-induced ATA	0	1	1
Treatment-enhanced ATA	0	0	0
Patients negative for ATA	186	196	382
Treatment unaffected	2	0	2

Source: BERENICE CSR in submission SDN931 on 02/28/2017

In conclusion, based on the clinical pharmacology reviewer's finding, it was concluded that the proposed labeling updates are acceptable from a clinical pharmacology perspective.

16.5. Additional Clinical Outcome Assessment Analyses

Patient reported outcomes (PRO) data were collected in the APHINITY study. The Applicant used three instruments, i.e., EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D-3L, to assess patients' health status and outcomes.

Instruments

EORTC QLQ -C30

The EORTC QLQ -C30 is a 30-item questionnaire that is composed of the following:

- A global quality of life domain
- 5 multi-item functional domains that include physical, role, emotional, cognitive and social functioning
- 3 multi-item symptom domains that include fatigue, nausea/vomiting, and pain
- 6 single item symptom questions that assess other cancer-related symptoms which includes dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact of cancer

The questionnaire has 28 items with 4-point responses from "Not at all" to "Very much" which are used to assess functioning and symptoms, and 2 items that use 7-point scales for assessing global health and overall quality of life. The EORTC QLQ-C30 measures were scored per the EORTC Scoring Manual. If more than 50% of the constituent items were completed for a multi-item domain in the EORTC QLQ-C30, a transformed score was computed, and for domains with less than 50% of the items completed, the domain was considered missing as stated in the manual. The transformed score for each domain ranges from 0 to 100. For functional domains, higher transformed scores indicate better status; and for symptom domains, higher transformed scores indicate more severe symptoms.

Reviewer Comments: *The EORTC QLQ-C30 instrument assesses a variety of factors that affect patients on treatment. This instrument does not isolate the effect the study treatment from a patient's report, and a decreased quality of life or lower scores in a specific domain may be due to post-surgical issues, recurrent disease that is developing, study treatment, an unrelated co-morbidity, or an entirely new disease process. The 30 items do encompass a reasonable amount of issues that are pertinent to a patient's daily level of functioning, but this questionnaire is limited in its ability to ascertain the cause of any decreased level of functioning or quality of life for an individual patient.*

EORTC QLQ-BR23

QLQ-BR23 is an extension of QLQ-C30 with breast cancer module. The BR23 disease module contains questions related to body image, sexual function, symptoms related to upper extremity dysfunction and localized symptoms likely more related to post-surgical changes.

Reviewer comments: *Many symptoms collected in the BR23 disease module are likely more related to the effects of surgical intervention and radiation intervention that are not related to the systemic treatments which were the focus of the study.*

EQ-5D-3L

The EQ-5D-3L instrument is self-administered and consists of 2 parts. The first part is comprised of 5 descriptors of current health state including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The patient rates each state on a 3-level scale (1=no problem, 2=some problem, 3=extreme problem). Published weights are used to create a single summary score from these responses, which is called the EQ-5D index. Lower scores in this index represent a higher level of dysfunction and 1 is assigned as a score for perfect health.

The second part of this instrument assesses general health status, and is measured by a visual analog scale called the EQ-5D VAS. This scale measures the patient's self-rated health status on a scale from 0 (worse imaginable health state) to 100 (best imaginable health state).

Reviewer Comments: *The EQ-5D-3L is a composite that incorporates self-reported ability to function, pain, and general health status as filled out by the patient. This instrument Is a generic preference based measure intended to provide a health utility index value for use in economic analyses* (b) (4) .

Schedule of Assessments

Patients were to complete the measures at screening until recurrence or until 36 months after randomization. All three instruments were to be collected at screening/baseline, end of anthracycline (only for patients who received anthracycline regimen), end of taxane (week 10, 13, or 19 depending on the chemotherapy regimen), week 25, end of study treatment, follow-up month 18, follow-up month 24, and follow-up month 36.

Reviewer Comments: *Based on the schedule of assessments, the degree to which the combination therapy may have affected the patient's functioning in the interval of the cycle may be missed. For example, there may be differences at day 8 of a cycle between the arms that would not be captured once the next cycle is initiated and when there is only a seven-day recall period. This may minimize any differences between arms and additive toxicity that might occur earlier in the cycle.*

Statistical Analysis Plan

Patient reported outcomes were secondary endpoints of the APHINITY study. There was no specific hypothesis testing plan, nor were there type I error adjustments for multiple comparisons. The purpose of these analyses was descriptive.

The completion rate for each PRO assessment was defined as the number of patients who completed the questionnaires at that time point, divided by the number of patients eligible to be assessed for that study visit.

The analysis of the PRO endpoints was based on the intent to treat population. Summary statistics of absolute scores of the domains of the QLQ-C30 and QLQ-BR23, and their changes from baseline were to be calculated. A 10-point threshold was used to define clinically meaningful worsening and improvement by the Applicant. EQ-5D-3L data was planned to be used for pharmaco-economic modeling purposes and not covered in this review.

Reviewer Comments:

- *As the PRO analyses were not controlled for multiple comparisons, these analyses are considered exploratory.*
- (b) (4)

(b) (4)

FDA Analyses of Patient-Reported Outcome Results

PRO Completion Rates

As shown in Table 54, per FDA's analysis, the completion rates for the EORTC QLQ-C30 were higher than or close to 85% at all scheduled assessments in both treatment arms. The primary reason for non-completion of the instrument was administrative failure. EORTC QLQ-BR23 and EQ-5D-3L had similar completion rates as EORTC QLQ-C30.

Table 54 FDA's Analysis of EORTC QLQ-C30 Completion Rates at Each Assessment, Study APHINITY

	Chemotherapy, trastuzumab and pertuzumab N=2400	**Chemotherapy, trastuzumab and placebo N=2404**
Baseline		
Evaluable patients	2400	2404
Completed ≥1 question	2338 (97%)	2343 (98%)
Completed all questions	2230 (93%)	2256 (94%)
End of Taxane		
Evaluable patients	2239	2283
Completed ≥1 question	2120 (95%)	2164 (95%)
Completed all questions	2024 (90%)	2073 (91%)
Week 25		
Evaluable patients	2187	2237
Completed ≥1 question	2096 (96%)	2124 (95%)
Completed all questions	2036 (93%)	2058 (92%)
End of Treatment		
Evaluable patients	2378	2391
Completed ≥1 question	2089 (88%)	2142 (90%)
Completed all questions	2014 (85%)	2066 (86%)
FU Month 18		
Evaluable patients	2208	2244
Completed ≥1 question	1960 (89%)	1960 (87%)
Completed all questions	1896 (86%)	1895 (84%)

FU Month 24		
Evaluable patients	2169	2189
Completed ≥1 question	1900 (88%)	1910 (87%)
Completed all questions	1842 (85%)	1846 (84%)
FU Month 36		
Evaluable patients	2094	2097
Completed ≥1 question	1859 (89%)	1831 (87%)
Completed all questions	1799 (86%)	1772(85%)

Source: CSR Table 37 and reviewer's analysis of dataset aqsc.xpt

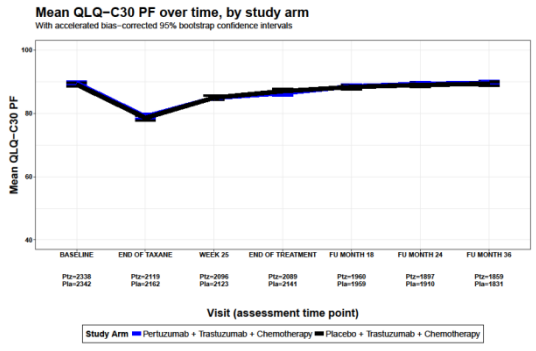
Reviewer Comments: The completion rates demonstrated that there was adequate quality data collection of patient reported outcomes. The proportion of patients that responded over time decreased slightly, however >80% of patients completed assessments at each prescribed visit.

Analysis of EORTC QLQ-C30 Scores over Time

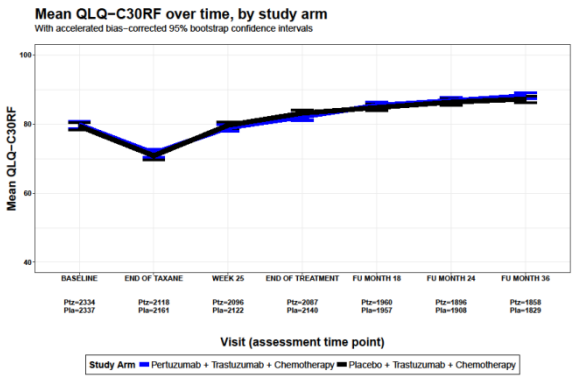
The mean score of EORTC QLQ-C30 over time is shown in Figure 5 (a) for physical function domain and (b) for role function domain, and the mean of change from baseline over time is shown in Figure 5 (c) and (d). Patients in both treatment arms reported a decline in physical and role function domains by the end of taxane treatment. The mean scores improved during the post-chemo anti-HER2 therapy period and approached baseline levels in both arms after completion of therapy.

Figure 5 FDA's Descriptive Analyses of EORTC QLQ-C30 Physical Function and Role Function over Time, Study APHINITY

(a) EORTC QLQ-C30 Physical Function Mean over Time

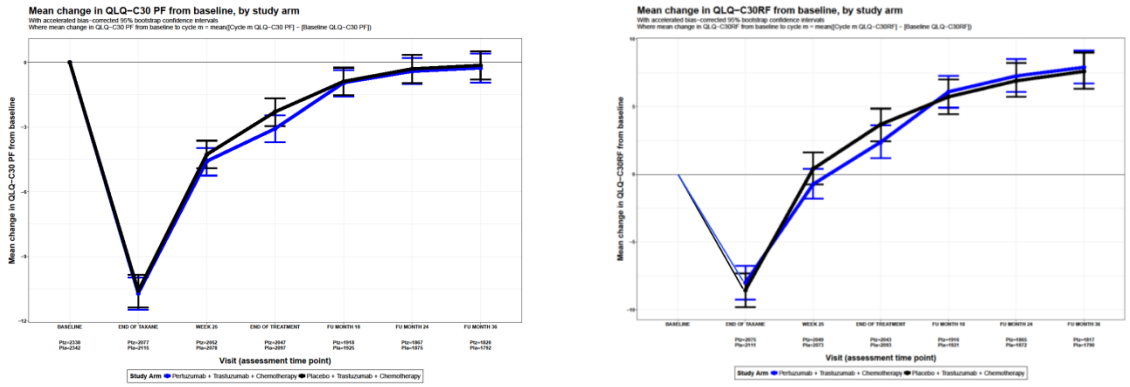


(b) EORTC QLQ-C30 Role Function Mean over Time



(c) EORTC QLQ-C30 Physical Function Mean of Change Compared to Baseline over Time

(d) EORTC QLQ-C30 Role Function Mean of Change Compared to Baseline over Time



Reviewer Comments: It has been noted that the study was not adequately designed to compare treatment arms with respect to the PRO endpoints. Figure 5 *shows no notable differences in physical or role function scores between patients on pertuzumab and patients on placebo throughout the course of the study.*

Due to the lack of a meaningful change threshold of each domain, the review team evaluated the change of physical function and role function compared to baseline at each assessment using empirical cumulative distribution function (ECDF). The ECDF curves show a continuous plot of the score change from baseline on the X-axis and the percent of patients experiencing that change on the Y-axis (Figure 6, Figure 7).

Figure 6 ECDF of EORTC QLQ-C30 Physical Function, FDA's Analysis

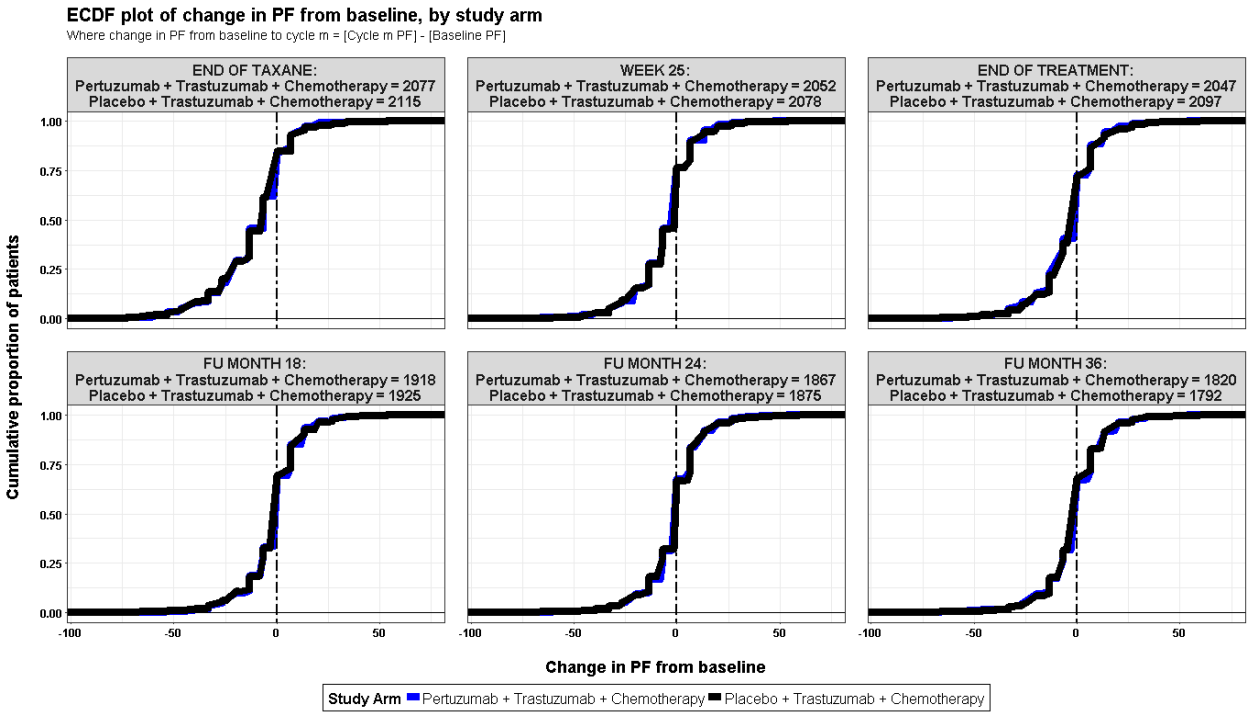
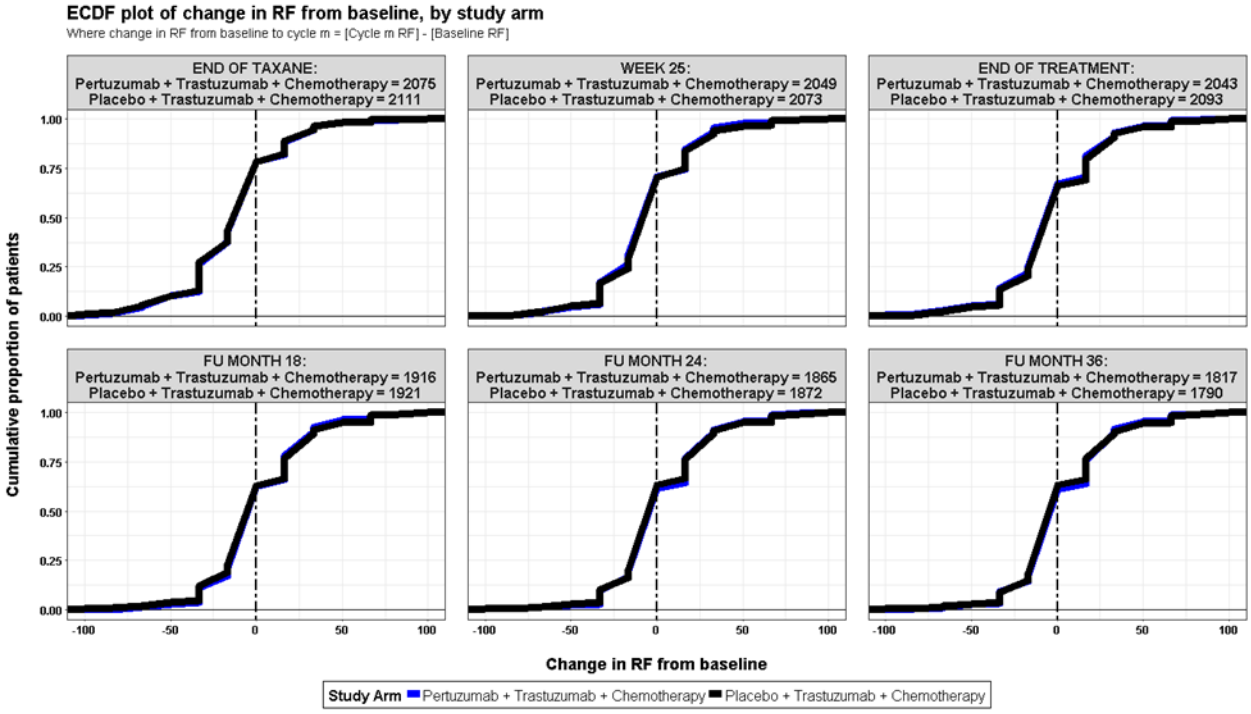


Figure 7 ECDF of EORTC QLQ-C30 Role Function, FDA's Analysis



Reviewer Comments: As shown in the ECDF curves, scores from the two treatment arms overlap indicating that there were no notable differences between the two arms.

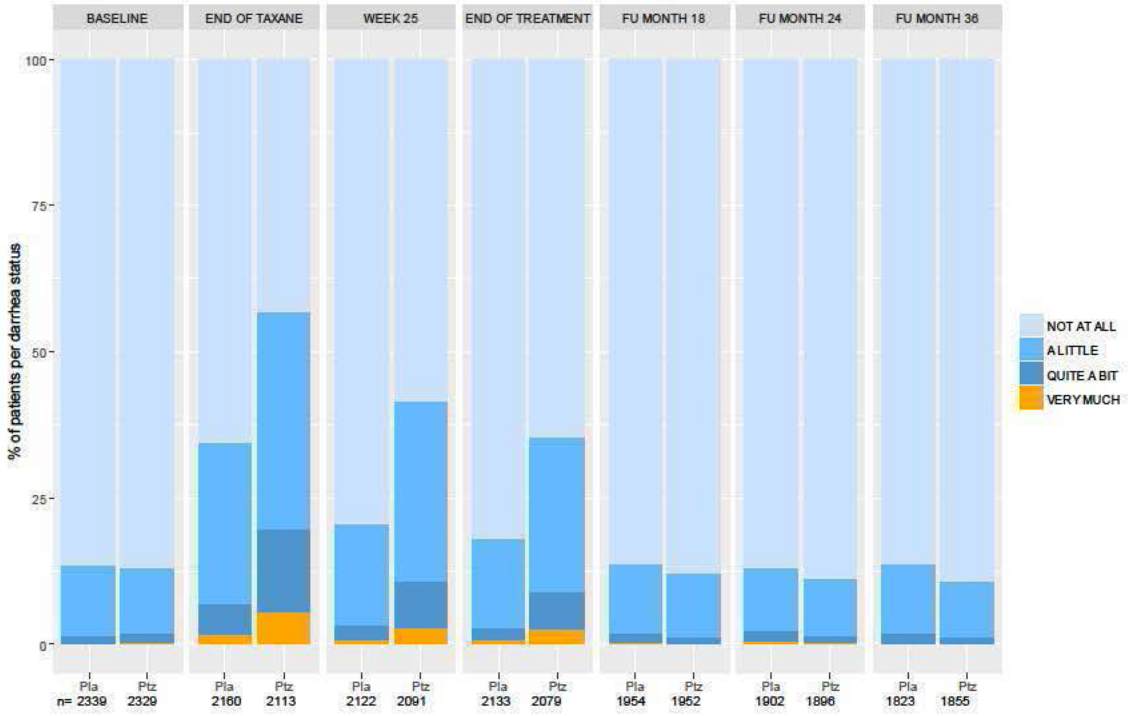
Similarly, scores from the other three functional domains of EORTC QLQ-C30, i.e., social functioning, cognitive functioning, and emotional functioning, had no notable differences between the two treatments arms over all assessments.

The review team also selected several symptoms from the EORTC QLQ-C30 instrument for further analysis based on the known adverse event profile of pertuzumab. Diarrhea was assessed by asking patients, “During the past week, have you had diarrhea?”. While on study therapy, the observed rate of patient-reported diarrhea was greater in the pertuzumab arm than in the placebo arm and the rates were not reported as similar until the post-treatment follow up period.

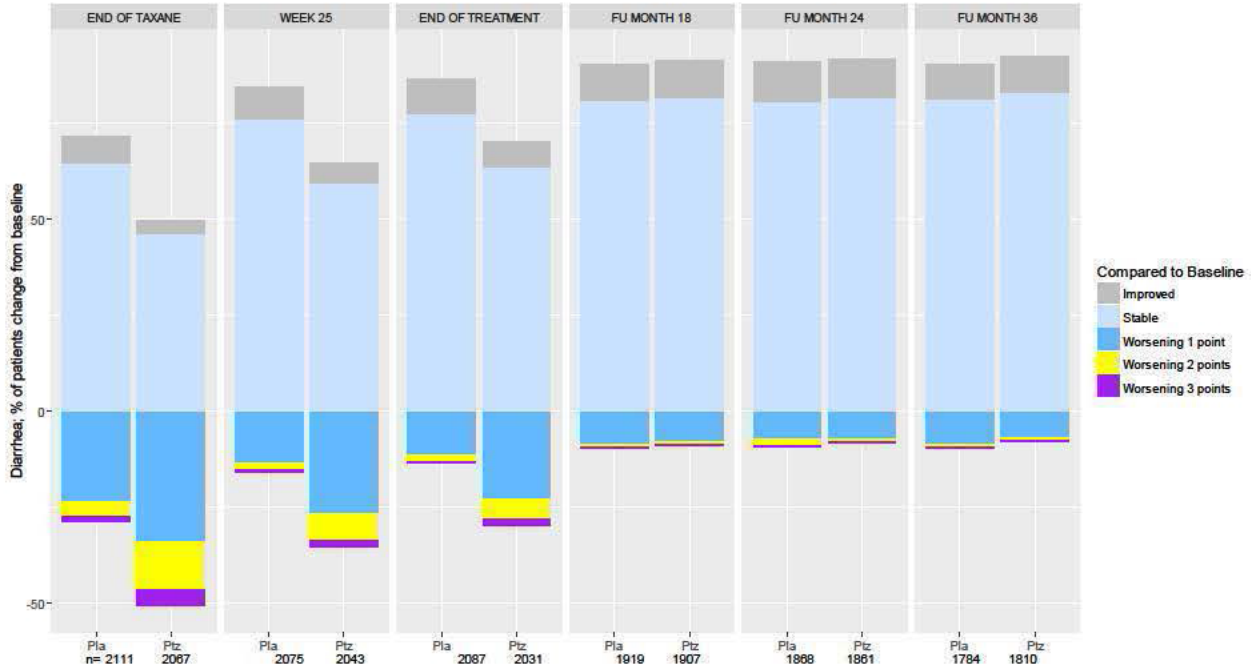
At the end of taxane treatment, of the patients who had a baseline PRO assessment and an end of taxane PRO assessment, 50% of patients in the pertuzumab arm and 29% of patients in the placebo arm reported worse diarrhea compared to baseline. At end of treatment, of the patients who had a baseline assessment and an end of treatment assessment, 30% of patients in the pertuzumab arm and 14% of patients in the placebo arm reported worse diarrhea compared to baseline.

Figure 8 Distribution of Diarrhea Score over Time

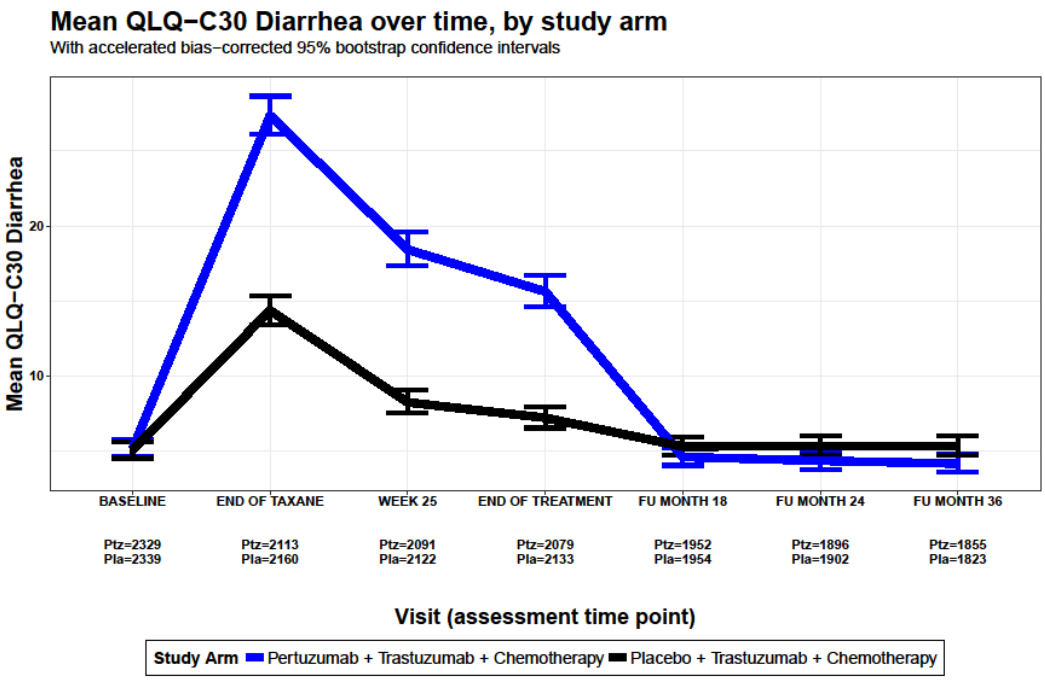
(a) Distribution of Raw Scores



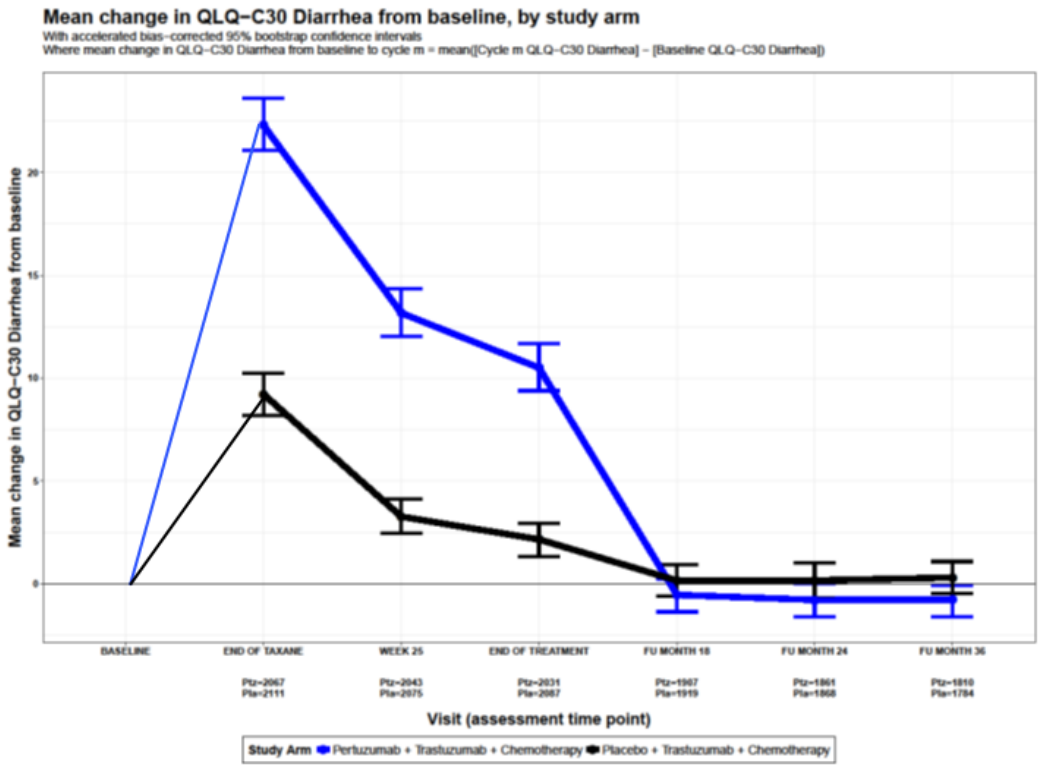
(b) Distribution of Change of Raw Scores from Baseline



(c) Mean of Transformed Scores



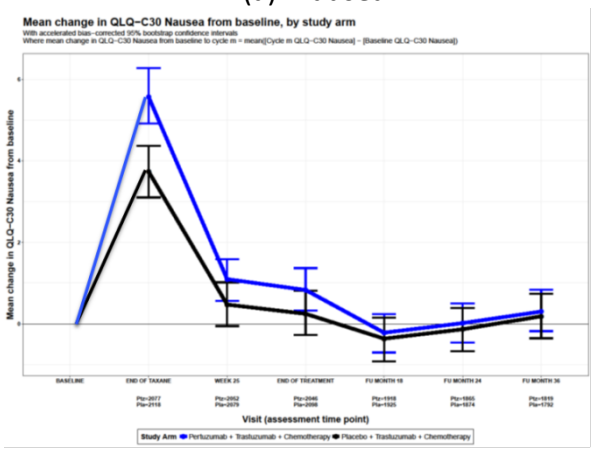
(d) Mean of Change From Baseline of Transformed Scores



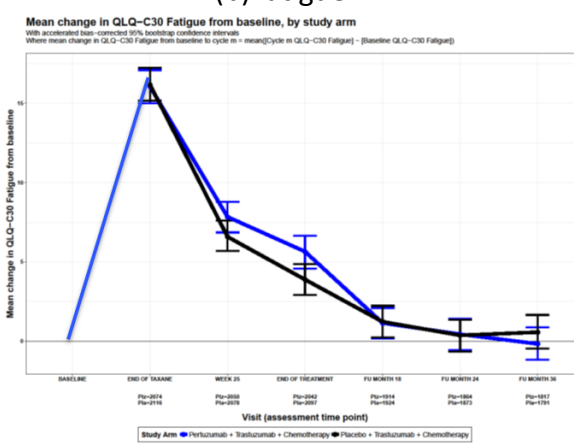
Reviewer Comments: The single item assessment of diarrhea demonstrated that there was a difference between arms in PRO data related to diarrhea, with worse diarrhea reported by those patients who received pertuzumab as compared to placebo. This was consistent with AE reporting by clinicians, though the PRO data adds additional longitudinal information revealing the trajectory and persistence of differences between the treatment arms until the post-treatment follow up period.

Figure 9: Mean of change compared to baseline per transformed scores of (a) Nausea; (b) Fatigue; (c) Pain from EORTC QLQ-C30

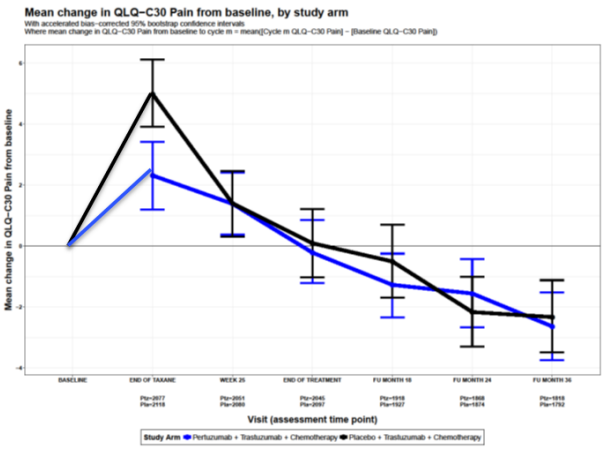
(a) Nausea



(b)Fatigue



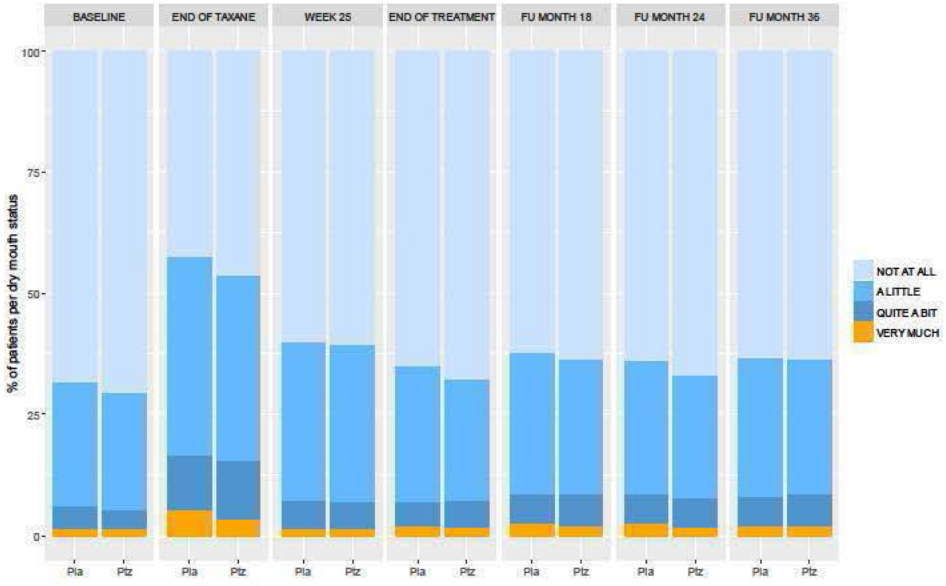
(c)Pain



Reviewer Comments: Analysis of single items assessing nausea demonstrated increase in nausea in the pertuzumab arm as compared to the placebo, though this difference decreased overtime. Patient reported assessments of fatigue were similar between treatment arms. Pain appeared to be increased in the placebo arm at the end of taxane therapy, though there were no notable differences at subsequent assessments.

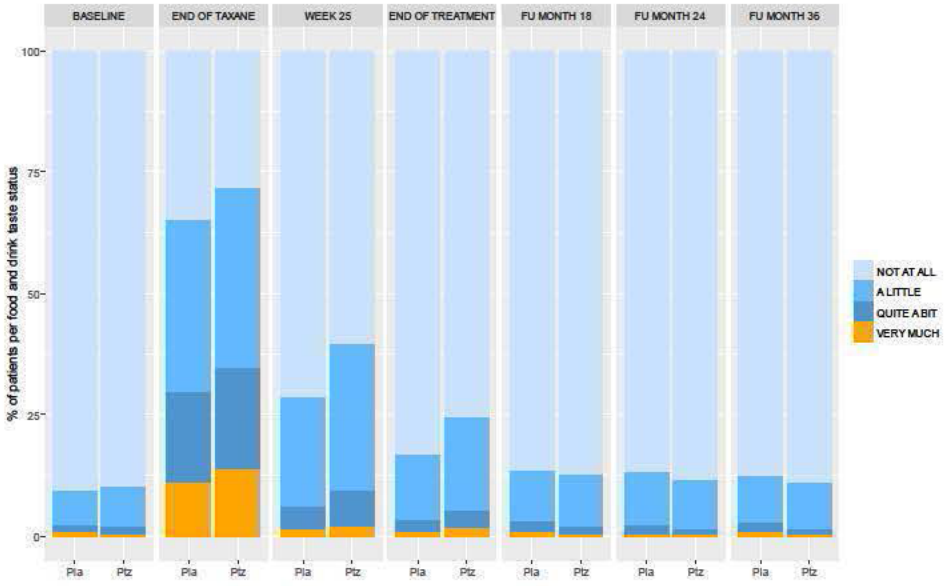
Analyses of EORTC QLQ-BR23

Q31 Do you have a dry mouth



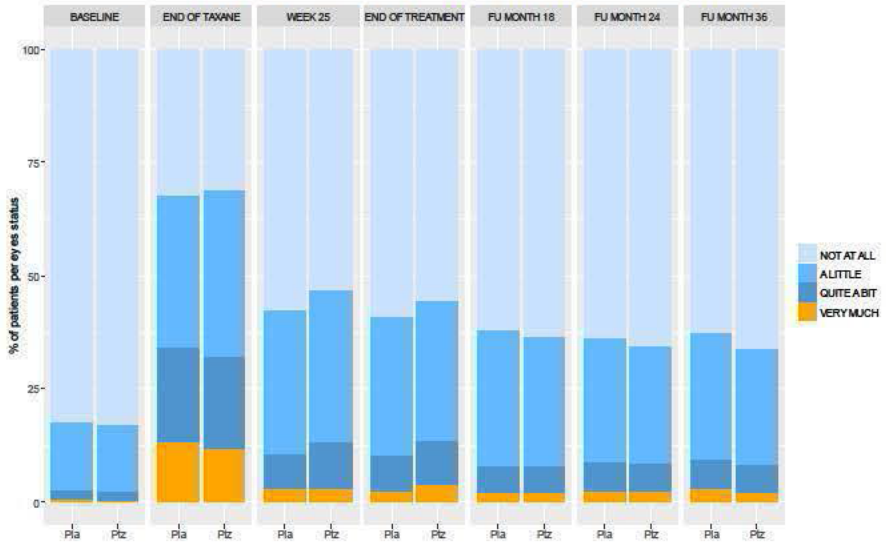
	Baseline		End of Taxane		Week 25		End of Treatment		FU Month 18		FU Month 24		FU Month 36	
	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz
N	2335	2333	2156	2112	2122	2090	2137	2083	1952	1955	1910	1897	1825	1855
Not at all	68%	70%	42%	46%	60%	61%	65%	68%	62%	64%	64%	67%	63%	64%
A little	26%	24%	41%	38%	33%	32%	28%	25%	29%	28%	27%	25%	28%	28%
Quite a bit	5%	4%	11%	12%	6%	6%	5%	5%	6%	7%	6%	6%	6%	7%
Very much	1%	2%	5%	4%	2%	2%	2%	2%	3%	2%	2%	2%	2%	2%

Q32. Did food and drink taste different than usual?



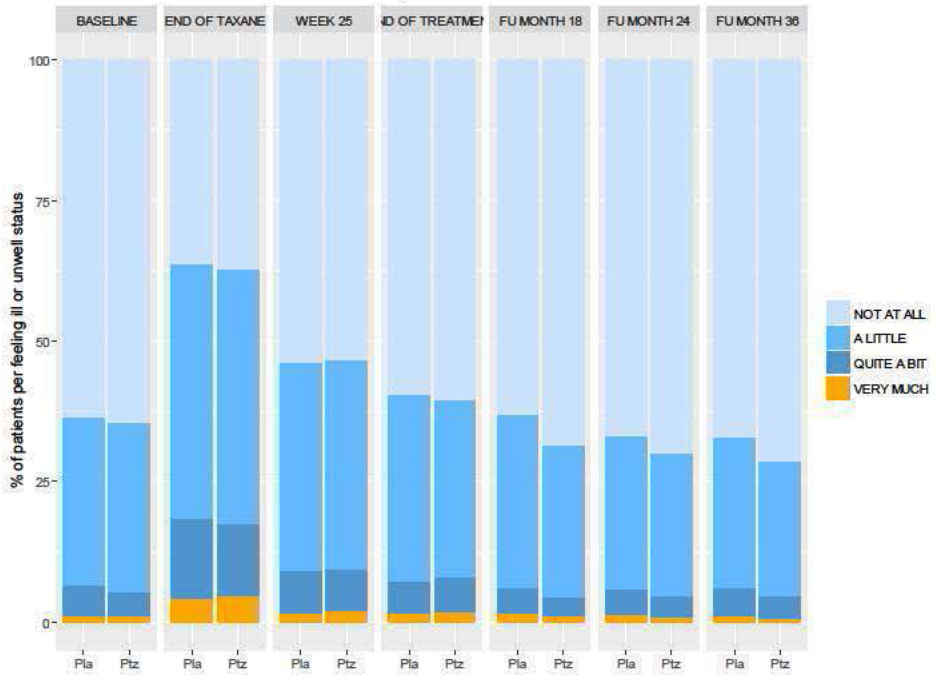
	Baseline		End of Taxane		Week 25		End of Treatment		FU Month 18		FU Month 24		FU Month 36	
	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz
N	2335	2330	2154	2111	2115	2090	2137	2082	1951	1955	1908	1895	1823	1854
Not at all	91%	90%	35%	28%	71%	60%	83%	76%	86%	87%	87%	88%	88%	89%
A little	7%	8%	36%	37%	23%	30%	13%	19%	10%	11%	11%	10%	10%	10%
Quite a bit	1%	2%	18%	20%	4%	7%	3%	4%	2%	2%	2%	1%	2%	<1%
Very much	<1%	<1%	11%	14%	2%	2%	<1%	2%	<1%	<1%	<1%	<1%	<1%	<1%

Q33. Were your eyes painful, irritated or watery?



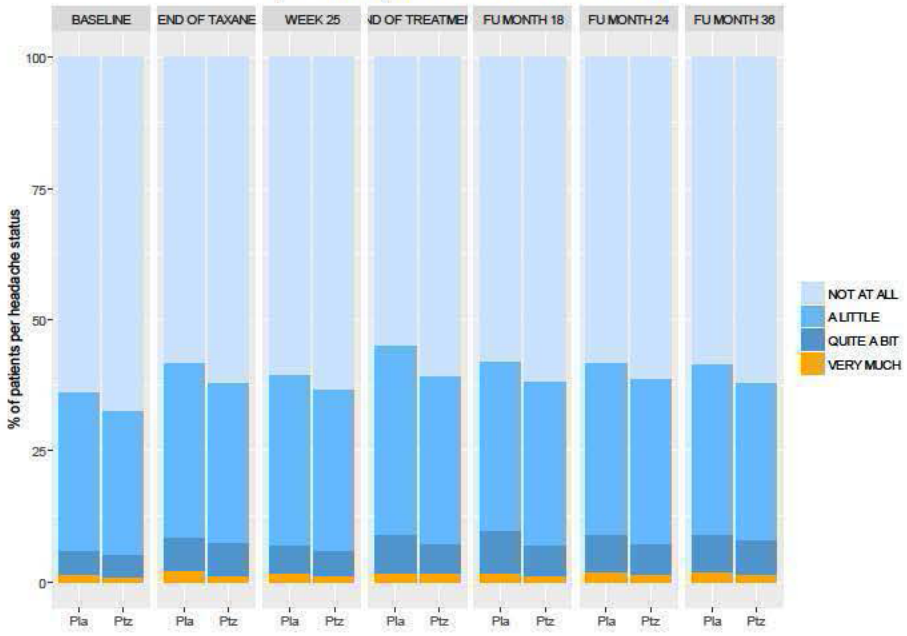
	Baseline		End of Taxane		Week 25		End of Treatment		FU Month 18		FU Month 24		FU Month 36	
	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz
N	2333	2327	2153	2113	2120	2086	2134	2082	1948	1955	1909	1896	1822	1853
Not at all	82%	83%	32%	31%	57%	53%	59%	55%	62%	63%	64%	66%	63%	66%
A little	15%	15%	34%	37%	32%	34%	31%	31%	30%	29%	28%	26%	28%	26%
Quite a bit	2%	2%	21%	20%	7%	10%	8%	10%	6%	6%	6%	6%	6%	6%
Very much	<1%	<1%	13%	12%	3%	3%	3%	4%	2%	2%	3%	2%	3%	2%

Q36. Did you feel ill or unwell?



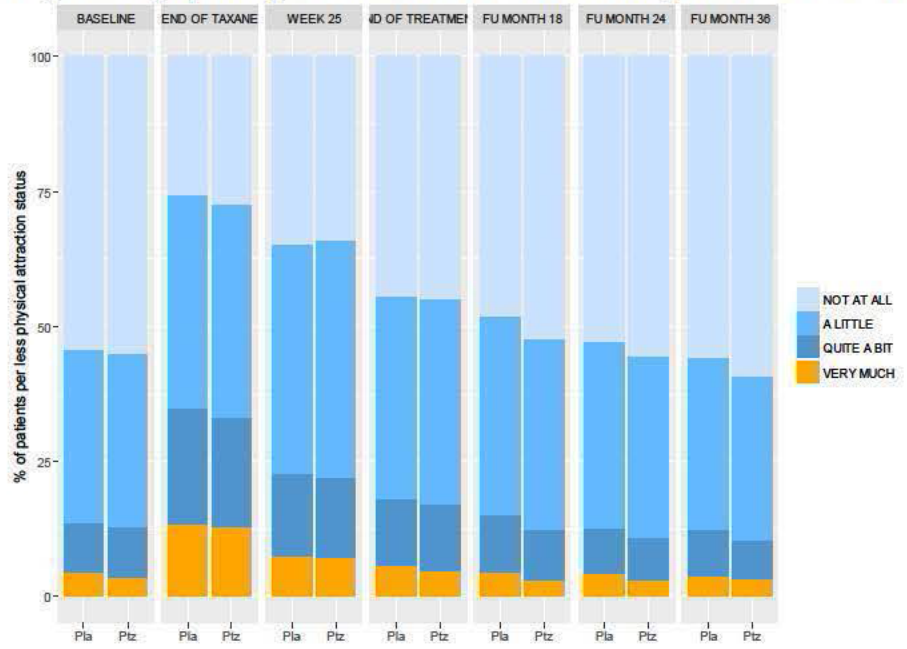
	Baseline		End of Taxane		Week 25		End of Treatment		FU Month 18		FU Month 24		FU Month 36	
	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz
N	2306	2302	2140	2088	2108	2067	2114	2058	1925	1932	1880	1869	1807	1826
Not at all	64%	65%	36%	37%	54%	53%	60%	61%	63%	68%	67%	70%	67%	71%
A little	30%	30%	45%	45%	37%	37%	33%	31%	31%	27%	27%	25%	27%	24%
Quite a bit	5%	4%	14%	13%	7%	7%	6%	6%	4%	3%	5%	4%	5%	4%
Very much	1%	1%	4%	5%	2%	2%	2%	2%	2%	1%	1%	<1%	1%	<1%

Q38. Did you have headaches?



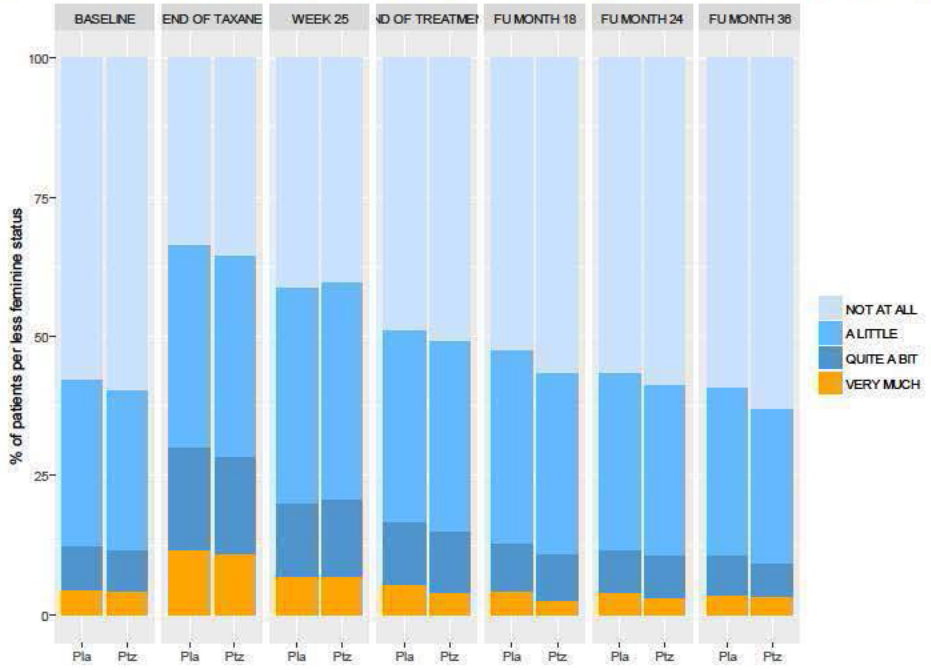
	Baseline		End of Taxane		Week 25		End of Treatment		FU Month 18		FU Month 24		FU Month 36	
	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz
N	2314	2308	2153	2105	2106	2083	2127	2073	1937	1942	1898	1883	1813	1840
Not at all	64%	67%	58%	62%	60%	63%	55%	61%	58%	62%	58%	61%	58%	62%
A little	30%	27%	33%	31%	32%	31%	36%	32%	32%	31%	33%	31%	32%	30%
Quite a bit	5%	4%	7%	6%	6%	5%	7%	6%	8%	6%	7%	6%	7%	7%
Very much	1%	1%	2%	1%	2%	1%	2%	2%	2%	1%	2%	2%	2%	1%

Q39. Have you felt physically less attractive as a result of your disease or treatment?



	Baseline		End of Taxane		Week 25		End of Treatment		FU Month 18		FU Month 24		FU Month 36	
	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz
N	2312	2307	2151	2103	2111	2081	2124	2072	1938	1946	1900	1880	1811	1835
Not at all	54%	55%	26%	27%	35%	34%	44%	45%	48%	52%	53%	55%	56%	59%
A little	32%	32%	39%	40%	42%	44%	38%	38%	37%	35%	35%	34%	32%	31%
Quite a bit	9%	9%	22%	20%	15%	15%	13%	12%	11%	9%	9%	8%	9%	7%
Very much	4%	4%	13%	13%	7%	7%	6%	5%	5%	3%	4%	3%	4%	3%

Q40. Have you been feeling less feminine as a result of your disease or treatment?



	Baseline		End of Taxane		Week 25		End of Treatment		FU Month 18		FU Month 24		FU Month 36	
	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz	Pla	Ptz
N	2305	2304	2147	2099	2105	2079	2120	2068	1938	1942	1900	1881	1807	1838
Not at all	58%	60%	34%	35%	41%	40%	49%	51%	52%	56%	56%	59%	59%	63%
A little	30%	29%	36%	36%	39%	39%	34%	34%	35%	33%	32%	31%	30%	28%
Quite a bit	8%	8%	18%	18%	13%	14%	12%	11%	9%	8%	8%	8%	7%	6%
Very much	5%	4%	12%	11%	7%	7%	5%	4%	4%	3%	4%	3%	4%	3%

Reviewer Comments: There were no notable differences between the treatment arms, though there did appear to a slight increase in the proportion of patients reporting dysgeusia in the pertuzumab arm as compared to placebo.

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

/s/

KIM J ROBERTSON
12/19/2017

HUIMING XIA
12/19/2017

PENGFEI SONG
12/19/2017

LYNN J HOWIE
12/19/2017
Clinical Reviewer Memo BLA 125409, Supplements 113 and 118
Clinical Efficacy review is complete and has been added to the sBLA Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

NANCY S SCHER
12/19/2017

LIJUN ZHANG
12/19/2017

RAJESHWARI SRIDHARA on behalf of ROBERT J SCHROEDER
12/19/2017
Signed on behalf of Dr. Schroeder

WILLIAM F PIERCE
12/19/2017

LALEH AMIRI KORDESTANI
12/19/2017

RAJESHWARI SRIDHARA
12/19/2017

JULIA A BEAVER
12/20/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s113

PRODUCT QUALITY REVIEW(S)

Memorandum of Review:

Submission Tracking Number (STN):	125409/113-S
Subject:	Immunogenicity Assay Revalidation to support use of new reagents
Stamp Date:	February 28, 2017
Date:	December 6, 2017
Primary Reviewer:	Kathryn King
Secondary Reviewer:	Wendy Weinberg
Tertiary Reviewer:	Susan Kirshner
RBPM:	Kim Robertson
Consults:	N/A
Applicant:	Genentech
Product:	Perjeta (pertuzumab)
Indication:	Early and metastatic HER2+ breast cancer
Filing Action Date:	September 11, 2017
Action Due Date:	December 28, 2017

1. Summary Basis of Recommendation:

a. Recommendation: Approval

b. Justification: In this submission, the Sponsor provided sufficient data from an assay revalidation exercise to support that their new controls (negative control, positive screening control and positive titer control), as well as their new reagents (biotin- and DIG-rhuMAB 2C4 conjugates and streptavidin coated plates) and the assay itself perform as intended.

2. Suggested Language for Action Letter:

Not applicable. This was not a CMC only submission. The immunogenicity revalidation was part of a clinical efficacy supplement managed by OND.

3. Review:

Background: The ELISA method for the detection of antibodies to pertuzumab in human serum (currently (b) (4) Method ICDIM 193) was previously known as Genentech Method BA.MET.2C4.012. The originally validated Method BA.MET.2C4.012 was reviewed in 2012 as part of the original BLA submission. It is stated that, subsequent to the approval of the BLA, the method was transferred to (b) (4) and partially validated for additional disease states including early breast cancers (b) (4), and that these data are on file at Genentech. Due to the lack of availability of critical reagent lots including the negative control, biotin and DIG conjugates, as well as a change in the streptavidin coated plate supplier, the method was revalidated for the current submission by (b) (4) as ICDIM 193. This revalidation included the following disease states: early and

metastatic breast cancer, [redacted]. Midway through the validation exercise it was determined that a new positive screening control (PSC) and positive titer control (PTC) were needed. Thus, these were added to the revalidation exercise. The current submission contains Genentech's summary of the revalidation as well as [redacted]'s Method Validation Plan, Method Validation Report, and data appendix. The following review reflects the information provided across these 4 documents.

Description of the Screening ELISA:

The qualitative method that was validated in the current submissions is a bridging ELISA to screen for the presence of anti-therapeutic antibodies (ATA), based on the same principles as the originally approved assay. For this assay, rhuMAB 2C4 conjugated to biotin (2μg/ml) and rhuMAB 2C4 conjugated to digoxigenen (DIG) (2μg/ml) are co-incubated 16-22 hours with either diluted samples or controls (negative and positive) in a 96 well microplate. Samples from the microplate are transferred to a pre-washed streptavidin coated 96 well microplate and incubated for 2 hours. After washing, a mouse anti-digoxigenin antibody conjugated with horseradish peroxidase (HRP) is added for 1h. The plates are again washed and a substrate solution, which is equal volumes of tetramethylbenzidine and peroxidase solution B, is added for color development. The reaction is stopped at 15-20 minutes by adding 1M phosphoric acid. Plates are read at 450 nm for detection and at 620 or 630nm for reference absorbance.

There are 3 analysis tiers.
Tier 1: Initial screening assay performed at a 1:20 minimum dilution. Samples producing signal above the assay cut point (determined per plate as: mean Negative Control (NC) x disease specific cut point factor) are considered potentially positive for ATA.
Tier 2: Potentially positive samples are evaluated by dilution at 1:10 in assay diluent in the presence or absence of 50ug/ml pertuzumab for 1h before performing the assay, as described above, at a final Minimum Required Dilution (MRD) of 1:20. Positive samples are identified by a percent decrease in signal ≥ the disease specific cut point.
Tier 3: Confirmed positive samples from Tier 2 are titered until a response below the titer cut point is obtained (As discussed below, for breast [redacted] this was determined to be: Mean NC + disease state titer offset cut point factor; [redacted]

Review of the Information Provided:

For ease of reference a summary of the parameters validated is provided in the table below.

Antibodies to Pertuzumab in Human Serum

(b) (4) **Project Code**	RAAL2			
(b) (4) **Method ID**	ICDIM 193			
Analyte	Antibodies to Pertuzumab (CDR hu2C4)			
Minimum Required Dilution (MRD)	1/20 in assay diluent			
Matrix	Disease-state human serum (early and metastatic breast cancers (BC), (b) (4) (b) (4)			
Method Description	ELISA			
Sample Volume	15-µL aliquot			
Sample Storage Temperature	-80 °C ± 10 °C			
PC Concentrations	5.00 and 50.0 ng/mL (PSC and PTC, respectively) of CDR hu2C4 (surrogate positive source material lot bab-07Oct13-2)			
Assay Cut Points[a]	Mean NC × Disease-specific Screening Cut Point Factor (sCPF), where • BC sCPF: 0.617 (b) (4)			
Confirmatory Cut Points (CCPs)[a]	Pertuzumab Signal Inhibition per Disease State: • BC CCP: 21.5% (b) (4)			
Titer Cut Points[a]	Mean NC + Disease-Specific Titer Offset Cut Point Factor (CPF), where • BC Titer Offset CPF: 0.0842 (b) (4)			
Precision (%CV)[b]		**PSC**	**PTC**	**NC**
	Concentration (ng/mL)	5.00	50.0	N/A
	Intra-Assay	(b) (4)		
	Inter-Assay			
PSC/CP Ratio Range[c]	2.00 to 3.27 (BC) (b) (4)			
PTC Titer Range[c]	(b) (4) (b) (4)			
Relative Sensitivity	(b) (4)			

Bioanalytical Method Validation Summary—*Continued*

Recovery	(b) (4) [redacted] **Fortified at 10.0 ng/mL (positive source material lot bab-07Oct13-2)** Early Breast Cancer: 10 out of 10 pre-screened samples screened negative, 10 out of 10 qualifying samples (100%) and the NC pool fortified at 10.0 ng/mL screened positive. Metastatic Breast Cancer: 10 out of 10 pre-screened samples screened negative, 10 out of 10 qualifying samples (100%) and the NC pool fortified at 10.0 ng/mL screened positive. (b) (4) [redacted]
Cross-Reactivity	Cross-Reactive: Recombinant HER2 ECD at 100 ng/mL, polyclonal antibodies to the framework of trastuzumab Non-Cross-Reactive: Trastuzumab up to 200 µg/mL, anti-CDR monoclonal antibody to trastuzumab Data on file with Genentech (refer to BA.MET.2C4.012.AVR_1[3])
Interference	Interfering: Recombinant HER2 ECD at 4 µg/mL Non-Interfering: Hemoglobin, lipids, and trastuzumab (up to 200 µg/mL) Data on file with Genentech (refer to BA.MET.2C4.012.AVR_1[3])
Pertuzumab Tolerance	500 ng/mL of positive source antibody (lot 45176-80 and lot bab-07Oct13-2) detectable in the presence of up to 200 µg/mL of pertuzumab
Neat Analyte Stability	Up to 30 hours at room temperature 9 freeze/thaw cycles thawed at room temperature and frozen at -80 °C ± 10 °C

[a] Cut point factors and confirmatory cut points determined by Genentech using data provided by (b) (4) [redacted] (b) (4)

[b] Statistics obtained from runs 73RAAL2 to 75RAAL2, 77RAAL2 to 82RAAL2, 84RAAL2 to 92RAAL2, 94RAAL2, 95RAAL2, and 97RAAL2.

[c] Acceptance ranges for use in sample analysis determined using 21 acceptable validation runs (73RAAL2 to 75RAAL2, 77RAAL2 to 82RAAL2, 84RAAL2 to 92RAAL2, 94RAAL2, 95RAAL2, and 97RAAL2) and the (b) (4) [redacted]

[d] (b) (4) [redacted]

Note: *The table was provided for ease of reference. All parameters were re-validated except for Interference and cross reactivity which are not expected to change. Each parameter that was revalidated is discussed in greater depth below.*

Overview of the validation results:

Ninety-seven validation runs were performed (1RAAL2-97RAAL2). Of these, 90 met the acceptance criteria in the prospectively generated method validation plan. One supplemental run (0RDQR-ST1) was performed to evaluate analyte stability resulting from freeze-thaw and thawed matrix, and the results met acceptance criteria. Of the

rejected runs, #3RAAL2, 4RAAL2, 7RAAL2, 8RAAL2 and 93RAAL2 were rejected due to the positive screening control (PSC) being negative. Run 26RAAL2 was rejected due to technical error and run 96RAAL2 was rejected due to unacceptable OD response %CV for the positive screening control.

Assay runs 1RAAL2-66RAAL2 described above utilized a positive screen control (PSC) and a positive titer control (PTC) that exhibited highly variable performance. The PSC and PTC had been prepared by Genentech from a single lot of source material, affinity purified mAb to pertuzumab CDR hu2C4 lot 45176-80, which at the time of this validation had reached the end of its shelf life; it is stated that at the time of runs 63-66RAAL2, the positive control was past its expiration date. Data from these runs were provided for informational purposes in Appendix B. These runs were used for establishment of assay cut points, as the results for cut point establishment are independent of positive control performance. A new PSC and PTC were prepared by (b) (4) using a different lot of affinity purified mAb to pertuzumab CDR hu2C4, lot bab-07Oct113-2, supplied by Genentech. The new PSC and PTC controls were used for assay runs 67RAAL2-97RAAL2 to generate all the validation data other than the cut point analysis.

Reviewer comment: *. Use of positive control samples near the end of the acceptable shelf life could potentially explain the variability in PSC/PTC response observed with the earlier runs (1-66RAAL2) at (b) (4) It is also good justification for establishing new positive controls, as was done by (b) (4)*

Assay Validation:

Negative Control: Pooled normal human serum from pertuzumab naïve individuals. Aliquots are stored at -80+/-10C. It is used in all tiers of analysis at 8 wells/assay.

Reviewer comment: *It is not stated how many individuals were represented. The following IR was conveyed to the Sponsor on November 28, 2017.*

> *"From how many individuals was the pooled normal human serum negative control fo (b) (4) method ICDIM 193 derived?"*

In an e-mail response received on December 5, 2017, the Sponsor stated the pooled normal human serum control was prepared from 3 male and 3 female donors. The number is low, and ideally would be higher to capture normal variability; however for the disease state control, which is the most relevant control, they utilized 100 treatment naïve individuals (early and metastatic breast cancer) to establish the assay cut point. This is deemed acceptable.

Positive Controls

As was stated above, new positive control stocks were generated after the first 66 validation runs. The following table provides details on the derivation of the stocks.

Reagent	Source	Lot/ Notebook No.	Concentration	Expiration Date
Positive Screen Control	Genentech	69716-49[a]	24.0 ng/mL	01 Nov 2015
Positive Titer Control	Genentech	69716-48[a]	500 ng/mL	01 Nov 2015
Affinity Purified mAb to Pertuzumab (CDR hu2C4)[b]	Genentech	45176-80	0.790 mg/mL	16 Dec 2019
Positive Screen Control	(b) (4)	NB10858-80-01[c]	5.00 ng/mL	SPAR[d]
Positive Titer Control	(b) (4)	NB10858-75-01[c]	50.0 ng/mL	SPAR[d]
Affinity Purified mAb to Pertuzumab (CDR hu2C4)[e]	Genentech	bab-07Oct13-2	500 µg/mL	08 Oct 2018

[a] Positive controls used for runs 1RAAL2 to 66RAAL2.
[b] Positive control source material used to prepare Genentech-prepared positive controls.
[c] Positive controls used for runs 67RAAL2 to 97RAAL2 and 0RDQR-ST1.
[d] See Periodic Analysis Results (SPAR)
[e] Positive control source material used to prepare (b) (4) -prepared positive controls.

Reviewer comment: *Source material at different dilutions (bottom 3 rows above) was used for the new positive controls in the current submission by (b) (4) The reason for the different (lower) concentrations of the PSC and PTC was stated to be that the new antibody lot, bab-07Oct13-2, used for positive control preparation had high affinity. Due to this, the acceptance criteria for the assay controls needed to be reestablished. This is reviewed under a separate section below.*

Reviewer comment: *There is no defined expiry date for the new PSC or PTC. It is noted that at the end of the shelf life for the previous PSC and PTC, these positive controls exhibited variable performance. The following comment was conveyed to the Sponsor on November 28, 2017.*

> *"We note that no formal expiry date has been provided for the new PSC and PTC derived for lot bab-07Oct13-2. Provide an expiry date, or prospectively define criteria that will be used to determine when these critical reagents will be considered expired."*

In an e-mail response received on December 5, 2017, the Sponsor stated that (b) (4) utilizes prospective criteria to determine reagent expiry. The PSC and PTC controls are considered expired when >50% of assays fail over 2 consecutive days due to PSC or PTC performance.

Information on the generation, purification and characterization of the positive control antibodies was reviewed as part of the original BLA. In response to IR#1, Question 26b conveyed during review of the original BLA, Genentech stated that the purified positive controls were tested for specificity to pertuzumab relative to 5 other antibodies. The following question was conveyed to the Sponsor on November 28, 2017.

> *"We note that new positive controls were prepared from source material lot bab-07Oct13-2. Provide information on the generation, purification and*

characterization of the positive control antibody stock. If this is the same as in the original BLA, provide a reference to the communication in which this information was originally provided."

In an e-mail response received on December 5, 2017 the Sponsor explained that Balb/c mice were hyperimmunized with pertuzumab in Ribi adjuvant followed by boosting twice weekly for 6 weeks. B cells from lymph nodes were harvested and fused with mouse myeloma cells. Hybridoma clones demonstrating anti-pertuzumab activity by ELISA were subcloned by limiting dilution at 1 cell/well. Supernatants from the subclones were further characterized by ELISA for reactivity against pertuzumab, trastuzumab, human IgG1 and two other human IgG1 framework recombinant antibodies. The best performing clone was expanded in a 1000L bioreactor and antibody capture on a MabSelect Sure FF column and dialyzed against 1x PBS pH 7.4 for 24h followed by 0.2uM filtration. The antibody was minimally characterized by mass spectrometry and capillary electrophoresis. This is deemed acceptable.

Positive Screen Control (PSC):
As with the original PSC, a minimum dilution of 1:20 was used for analysis. This new control was prepared in normal human serum at a concentration of 5ng/mL. Aliquots are stored at -80+/-10C. It is used in all tiers of analysis at 2 wells/assay.
Reviewer comment: *From my review of the original assay in the BLA, it was stated that the concentration of 24ng/mL that was used for the PSC was 3 fold greater than the concentration established for relative sensitivity. Relative sensitivity is revalidated in the current submission. The new positive stock lot was reported to have high affinity so it was necessary for the Sponsor to increase the dilution. This is reasonable.*

Positive Titer control (PTC): This control was prepared in normal human serum at a concentration of 50ng/ml. The PTC was used at a minimum dilution of 1:20 and then serially diluted two-fold 7 times. Aliquots are stored at -80+/-10C. It is used in all 3 tiers of analysis at 1 well per dilution.

Minimum Required Dilution (MRD): The minimum dilution was set at 1:20 in assay diluent. Assay diluent is 1x DPBS/0.5% BSA/0.5% Tween-20 /0.5% ProClin 300 in PBS pH 7.4+/-0.1. The Sponsor previously provided data to support that the drug tolerance was higher at this dilution than at 1:100, which was the other dilution tested.
Reviewer comment: *It is not necessary to revalidate this. The assay buffer in which samples are diluted has not changed. It is expected that the minimum dilution ranges from 1:5- 1:100. Previously the Sponsor explored dilutions of 1:20 and 1:100 and found better drug tolerance at the lesser dilution of 1:20.*

Screening Assay Multiplication/Cutpoint Factor (sCPF):
The screening assay cut point was designed to have a targeted 5% untreated positive rate, and was evaluated for specific disease states (presented below).
Reviewer comment: *This approach is appropriate.*

- **Breast Cancer:**

For breast cancer, 50 early and 50 metastatic pertuzumab naïve patient serum samples were screened in triplicate in 12 runs (19RAAL2 – 25RAAL2, 27RAAL2-30RAAL2 and 54RAAL2). The runs were performed over 5 days by 2 analysts. For screening runs, the only acceptance criterion defined was that the mean PSC signal must be ≥ the previously validated assay sCPF of 1.23. All runs prior to 66RAAL2 utilized the old PSC control (24ng/ml) from the original Genentech validation. No acceptance criteria were applied to the NC or the PTC, nor were control outliers removed prior to calculating the disease specific cut point factor (sCPF). Raw data generated by (b) (4) were sent to Genentech for calculations. Sample scores were calculated as the log transformation of the ratio of the average sample signal to the average negative control signal. For each assay, the estimated 95% is computed using (average+ 1.645 x standard deviation), where 1.645 is the 95th percentile of the standard normal distribution. The sCPF is the average of the estimated 95 the percentile of the scores across the assays. Based on this, the specific cutpoint for the breast cancer samples was 0.617. Data to support this are provided in Appendix D. One biological outlier (b) (6) was identified and removed by the analyst from all 3 replicates, and 9-10 statistical outliers were identified and removed by the analysis software.

Reviewer comment: *Raw signal data and signal scores in the early and metastatic breast cancer serum samples were provided in Appendix D pages 161-165 and reviewed. The data points that were removed (as biological/statistical outliers) were visibly out of trend with the majority of the data and if included would have skewed the cut point to a higher value (presumably lowering the untreated positive rate). Thus, their removal is deemed appropriate. The reviewer was curious whether there should be a differential cut point for early vs. metastatic breast cancer serum samples. To address this the reviewer utilized the scores provided in Appendix D and compared the mean score standard deviation between the early and metastatic samples and found the scores to be similar with overlapping error bars. Therefore, the reviewer agrees that it is appropriate to combine these samples for the purposes of determining disease specific cut point.*

The cut point factor identified was based on the average of 3 replicates as summarized below.

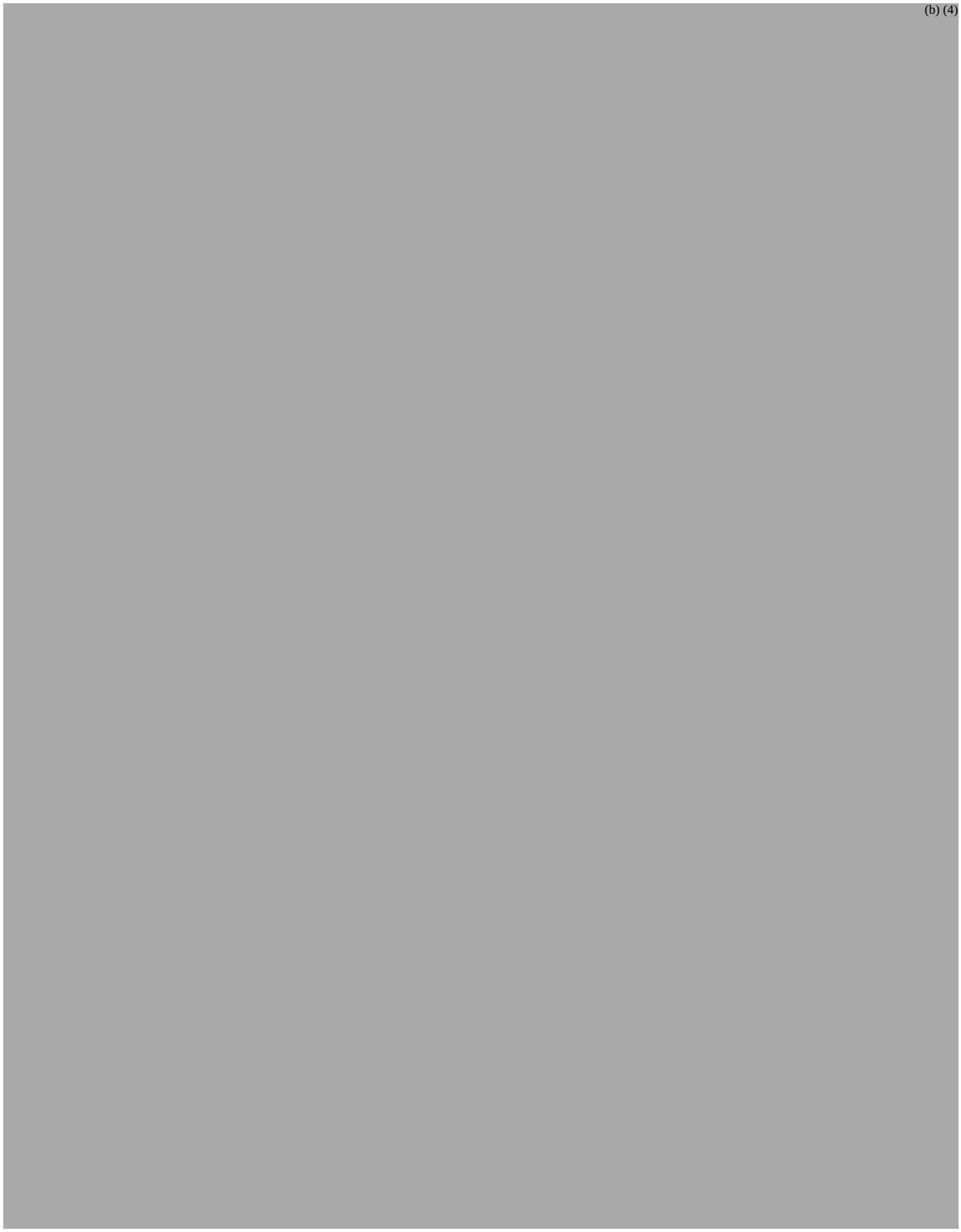
Table 5: Cutpoint Factors

	20%	10%	5%	3%	1%
Exp. 1	(b) (4)				
Exp. 2					
Exp. 3					
Average	0.48	0.533	0.617		

The breast cancer serum screened lower than the normal serum (data not reproduced here) necessitating a cut point of <1.0 to be able to identify ATA in breast cancer serum samples. Due to this a titer offset of 0.0842 was calculated from 4x the standard

deviation from all negative control wells. This offset was applied to the PTC titer curves for the breast cancer serum samples.

(b) (4)



(b) (4)

Confirmatory Assay

As was mentioned above, an immunodepletion study is performed on potential positives identified in the screening assay to determine the specificity of any positive signal observed. For this, sample is pre-incubated with pertuzumab (50ug/ml) for 1h prior to the addition of biotin and DIG conjugated-rhu-MAB 2C4. The remainder of the assay is as described under the screening assay above (refer to section "Description of the screen ELISA"). A significant decline in signal upon pre-incubation (relative to untreated control) indicates that immune complexes have formed and the response is specific to pertuzumab. For this assay, the aim was to have a 1% untreated positive rate.
Reviewer Comment: *The proposed 1% untreated positive rate is deemed appropriate.*

Confirmatory Assay Cut Point Determination

- **Breast Cancer**:

The same 50 EBC and 50 MBC samples naïve for pertuzumab were used to determine the confirmatory assay cut point in breast cancer. Samples were immunodepleted for 1h in the presence of 50.0 ug/ml pertuzumab, with controls held in the absence of

pertuzumab. This panel was stated to have been screened in duplicate in 6 runs (47RAAL2-51RAAL2 and 53RAAL2) performed over 4 days by 2 analysts. A minimum dilution of 1:20 was used. Percent inhibition was determined for treated and untreated samples run on the same plate. For confirmatory cut point screening runs, it is stated that the mean PSC must meet the validated assay cutpoint of >1.23 previously validated at Genentech (see original BLA review) with the old PSC that was used for this assay. No criteria were applied to NC or PTC and control outliers were not removed prior to cut point calculation. As with the screening assay, raw data generated by (b) (4) were sent to Genentech for analysis. For this assay the % inhibition is [signal- spiked signal/signal x 100%]. The confirmatory assay cut point for 1% untreated positive was calculated as: [mean inhibition score + 2.33 x standard derivation of inhibition scores]. Based on the data provided, there were a total of 3 statistical outliers and 1 biological outlier. The data presented in Appendix D pages 166-170 (not reproduced here) were reviewed.
Reviewer comment: *The degree of inhibition seen with the outliers was outside the ranges seen for the other samples. It is reasonable for these data points to have been excluded. Based on the data presented in Appendix D, a cut point of 21.5% inhibition was determined for the breast cancer serum samples for a 1% untreated positive rate. Excluding the biological and statistical outliers that were removed, in looking through the inhibition data for the samples that were all meant to be negative, two untreated positives were identified, one of which was 22%, the other was 24%.*

For this data set, (b) (4) *while the samples were stated to have been screened in duplicate on page 13 of the validation report, data provided in Appendix D list a single data point. Perhaps these are averages, but this isn't specifically stated. The following comment was conveyed to the Sponsor on November 28, 2017.*

> *"It is stated on page 13 of the validation report that the breast,* (b) (4) *serum samples were screened in duplicate in the confirmatory cut point determination, however the data provided in Appendix D only list a single data point for the unspiked and spiked signal respectively. Please clarify."*

In the response received on December 5, 2017, the Sponsor clarified that the data in Appendix D does represent the mean of duplicate wells for both the spiked and unspiked samples. This is deemed acceptable.

(b) (4)

(b) (4)

Precision:

PSC/NC Experimental Design: Precision (intra- and inter-assay) was evaluated for the new PSC (from lot bab-07Oct 13-2) and NC on 21 runs that included the new controls; 73RAAL2 – 75RAAL2, 77RAAL2-82RAAL2, 84RAAL2-92RAAL2, 94RAAL2, 95RAAL2 and 97RAAL2. The PSC was run in duplicate wells on each plate, while the NC was run in 8 wells of each plate for a total of 42 and 168 data points respectively. Data for the negative control were presented in Table 2A, while data for the PSC were presented in Table 2B. The 21 independent assays were performed on 5 of 36 days by 8 different analysts.

Reviewer comment: *Apart from runs 77RAAL2 and 78RAAL2, which are indicated to have been performed by analyst B/C, the analyst was consistent within an assay. The following comment regarding these runs was conveyed to the Sponsor on November 28, 2017.*

> *"In reference to Table 2A and 2B "NC Intra- and Inter-Assay Precision" and " PSC (5.0ng/mL) Intra- and Inter-Assay Precision), it is noted that runs 77RAAL2 and 78RAAL2, were indicated to have been performed by analyst B/C. Clarify the responsibilities of each operator for these runs."*

In an e-mail response received on December 5, 2017, the Sponsor clarified that analyst B set up the assay on day 1, while analyst 2 completed it on day 2.

The design for inter-assay precision is consistent with the FDA recommendation of evaluation on at least 3 different days (they had 5) with two analysts (they had 8 analysts) preparing at least 6 independent preparations (they had 21). For intra-assay precision, it is recommended that 6 independent preparations are tested per plate independently prepared by the same analyst. If this is not possible it is recommended that 3 samples are prepared per plate on 9 independent preparations. For the NC, 8 samples were tested per plate, while for the PSC only 2 samples were tested. However, the total number of data points for the PSC 42 (2 x 21), and independent preparations for the PSC (21) exceeds the 27 (3 x 9) in the recommendations.

Intra-assay Precision:

The overall OD response % CV for intra-assay precision ranged from (b) (4)% (2 data points per run) for the PSC and from (b) (4)% for the NC (8 data points per run).
Reviewer comment: *It is recommended in the FDA Guidance on Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (April 2016), that the precision coefficient of variance is <20%. Intra-assay precision results obtained are consistent with this recommendation, but higher than with the original version of the assay validated at Genentech, where the PSC and NC had %CV of 4 and 3% respectively.*

Inter-assay Precision:
The data described above were also used to calculate the inter-assay precision, which for the PSC was (b) (4)% (42 data points) and for the negative control was (b) (4)% (168 data points).
Reviewer comment: *The data for the PSC are consistent with recommendations of <20%. For the negative control, the value for %CV is high. There were 8 analysts (the recommendation is for at least 2) and this may have added to the variability. However, it is important to remember that this assay has a floating cut point, which is determined per plate. Thus, the analysis described above also reflects plate to plate variability and would be expected to result in a higher %CV. To address this the Sponsor performed the analysis below, which links the OD response to the plate specific cut point.*

In addition, to the PSC % OD response, the Sponsor analyzed the mean OD PSC response relative to the assay cut point (which varies per plate). The data were provided in Table 2E (below).

Table 2E. PSC to Cut Point Ratio

Run ID	PSC (Mean OD)	BC Assay CP (OD)	BC PSC/CP Ratio	(b) (4)
73RAAL2	0.209	0.0754	2.76	
74RAAL2	0.217	0.0747	2.90	
75RAAL2	0.236	0.0808	2.91	
77RAAL2	0.208	0.0797	2.61	
78RAAL2	0.202	0.0819	2.46	
79RAAL2	0.199	0.0691	2.87	
80RAAL2	0.207	0.0727	2.84	
81RAAL2	0.239	0.0909	2.63	
82RAAL2	0.225	0.0780	2.88	
84RAAL2	0.254	0.0974	2.60	
85RAAL2	0.275	0.103	2.67	
86RAAL2	0.271	0.103	2.63	
87RAAL2	0.280	0.106	2.65	
88RAAL2	0.282	0.110	2.56	
89RAAL2	0.181	0.0590	3.07	
90RAAL2	0.284	0.116	2.45	
91RAAL2	0.352	0.161	2.19	
92RAAL2	0.321	0.138	2.33	
94RAAL2	0.222	0.0699	3.17	
95RAAL2	0.219	0.0669	3.26	
97RAAL2	0.203	0.0804	2.52	
		N	21	
		Overall Mean	2.71	
		SD	0.269	
		%CV	0.0993	

Reviewer comment: *As can be seen from Table 2E presented above, the PSC OD response %CV, when normalized per plate, as a ratio of PSC OD/cut point is much tighter (0.0993%) than when only the OD response is considered. This is a more accurate method of calculating inter-assay precision and shows acceptable precision of the assay.*

PTC:

Inter-Assay Precision of the PTC was evaluated on 1 well (50ng/mL) dilution/plate over 21 runs. The data are presented in Table 2C below. (b) (4)

Table 2C. PTC (50.0 ng/mL) Inter-Assay Precision

(b) (4)

Reviewer comment: (b) (4) *The data are expressed as titer units. The assay cut point is used to calculate these titer values, thus explaining the increased precision based on OD response observed with the PTC relative to the PSC. This is acceptable.*

Acceptance Criteria for Assay Controls:

Data from the same 21 runs that were designed to evaluate precision (73RAAL2 – 75RAAL2, 77RAAL2-82RAAL2, 84RAAL2-92RAAL2, 94RAAL2, 95RAAL2 and 97RAAL2) (b) (4) were used to establish the acceptance criteria for the assay controls (PSC and PTC) to be applied post-validation. The acceptance range is based on mean responses = (Ratio mean PSC/CP +-2.33 x sd). The PSC range for breast cancer was determined to be 2.0-3.27; (b) (4) as a signal <1.0 is considered negative). The raw data used for the

calculations were presented in Table 2F (not reproduced here). For the PTC, the acceptable ranges were determined from the same runs as mean titer +/-0.3 titer units. (b) (4)

Relative Sensitivity:

The relative sensitivity was determined from the PTC data from the same 21 runs that were used to evaluate precision. For this assay, the PTC was run at 0.2391, 0.781, 1.56, 3.13, 6.25, 12.5, 25 and 50 ng/mL. The relative sensitivity is calculated as:

$$\text{Relative Sensitivity} = Ca + \frac{(Oa - \text{Screening Cut point OD}) * (Cb - Ca)}{Oa - Ob}$$

Ca: concentration above cutpoint
Cb: concentration below cutpoint
Oa: absorbance of the concentration at or above the cut point
Ob: absorbance of the concentration below the cut point.

Results for breast (b) (4) were presented in Table 3A (see below).

Table 3A. Relative Sensitivity in Breast Cancer (b) (4) Serum

(b) (4)

Table 3A. Relative Sensitivity in Breast Cancer (b) (4) Serum—*Continued*

(b) (4)

Reviewer comment: *Apart from runs 74 and 82RAAL2, the PTC was detectable between (b) (4) with results consistently closer to (b) (4) The calculated mean relative sensitivity from these 21 runs (b) (4) which is deemed acceptable and is more sensitive than the FDA recommendation of at least 100ng/ml.*

(b) (4) Over the 21 runs, the PTC was detectable between (b) (4) ng/ml, with the overall mean sensitivity falling at (b) (4)

Reviewer comment: *This exceeds the recommendation in the FDA 2016 "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products" guidance of at least 100 ng/ml. This is acceptable.*

Recovery:

Recovery was examined in 10 samples from each disease state using the new positive control material (lot bab-07Oct13-2) at 10ng/ml (breast (b) (4) Also included in each analysis were unspiked (referred to as unfortified) cancer serum control (SP) samples and both spiked (SPF) and unspiked (SP) negative controls. Data were provided in Tables 4A-7B. All tables were reviewed and are discussed, however, only the breast cancer results are shown below.

Table 4A. Recovery in Early Stage Breast Cancer Serum – Unfortified

	Individuals										NC Pool
Run ID 91RAAL2	SP 16 Dil 20 (OD)	SP 17 Dil 20 (OD)	SP 18 Dil 20 (OD)	SP 19 Dil 20 (OD)	SP 20 Dil 20 (OD)	SP 21 Dil 20 (OD)	SP 22 Dil 20 (OD)	SP 23 Dil 20 (OD)	SP 24 Dil 20 (OD)	SP 25 Dil 20 (OD)	SP 57 Dil 20 (OD)
Mean Response	0.106	0.131	0.120	0.119	0.136	0.131	0.116	0.117	0.139	0.140	0.237
%CV	7.37	1.63	4.71	1.79	2.61	2.16	3.06	2.42	3.05	1.01	0.597
Results	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive

Legend:
SP Blank (unfortified) recovery sample

Run 91RAAL2 assay cut point (OD): 0.161

Table 5A. Recovery in Metastatic Breast Cancer Serum – Unfortified

	Individuals										NC Pool
Run ID 92RAAL2	SP 31 Dil 20 (OD)	SP 32 Dil 20 (OD)	SP 33 Dil 20 (OD)	SP 35 Dil 20 (OD)	SP 36 Dil 20 (OD)	SP 37 Dil 20 (OD)	SP 38 Dil 20 (OD)	SP 39 Dil 20 (OD)	SP 40 Dil 20 (OD)	SP 41 Dil 20 (OD)	SP 57 Dil 20 (OD)
Mean Response	0.0810	0.0735	0.104	0.0880	0.0995	0.0775	0.0810	0.0980	0.122	0.101	0.206
%CV	1.75	6.73	10.9	11.2	3.55	0.912	3.49	5.77	12.2	4.20	2.06
Results	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive

Legend:
SP Blank (unfortified) recovery sample

Run 92RAAL2 assay cut point (OD): 0.138

Reviewer comment: *As can be observed by the tables scanned above, all non-fortified (SP) breast cancer serum samples screened below the assay cut point. As expected the unspiked negative control pool (SP) screened positive (as a cut point factor of 0.617 is used for breast cancer serum samples).*

The spiked (fortified) data are presented below.

Table 4B. Recovery in Early Stage Breast Cancer Serum – Fortified at 10.0 ng/mL

	Individuals										NC Pool
Run ID 91RAAL2	SPF 16 Dil 20 (OD)	SPF 17 Dil 20 (OD)	SPF 18 Dil 20 (OD)	SPF 19 Dil 20 (OD)	SPF 20 Dil 20 (OD)	SPF 21 Dil 20 (OD)	SPF 22 Dil 20 (OD)	SPF 23 Dil 20 (OD)	SPF 24 Dil 20 (OD)	SPF 25 Dil 20 (OD)	SPF 57 Dil 20 (OD)
Mean Response	0.438	0.454	0.437	0.426	0.420	0.451	0.456	0.431	0.432	0.493	0.661
%CV	0.808	1.56	1.13	3.16	1.18	0.627	1.55	0.656	1.96	1.43	0.535
Results	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive

Legend:
SPF Recovery sample fortified with 10.0 ng/mL positive control source material (lot bab-07Oct13-2)

Run 91RAAL2 assay cut point (OD): 0.161

Table 5B. Recovery in Metastatic Breast Cancer Serum – Fortified at 10.0 ng/mL

	Individuals										NC Pool
Run ID 92RAAL2	SPF 31 Dil 20 (OD)	SPF 32 Dil 20 (OD)	SPF 33 Dil 20 (OD)	SPF 35 Dil 20 (OD)	SPF 36 Dil 20 (OD)	SPF 37 Dil 20 (OD)	SPF 38 Dil 20 (OD)	SPF 39 Dil 20 (OD)	SPF 40 Dil 20 (OD)	SPF 41 Dil 20 (OD)	SPF 57 Dil 20 (OD)
Mean Response	0.409	0.458	0.421	0.369	0.453	0.380	0.487	0.421	0.420	0.408	0.607
%CV	1.38	12.8	1.34	1.53	1.25	0.372	0.290	0.336	0.506	0.693	1.28
Results	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive

Legend:
SPF Recovery sample fortified with 10.0 ng/mL positive control source material (lot bab-07Oct13-2)

Run 92RAAL2 assay cut point (OD): 0.138

Reviewer comment: *As can be observed from the tables provided above, all fortified samples screened positive in the presence of early or metastatic breast cancer serum. In the current version of the assay, a spike of 10ng/mL was detectable in the breast cancer serum. The spiked negative control pool, also screened positive as expected. The new assay appears to perform better with regard to recovery than the previous version. In the previous version of the assay, spikes as low as 16 ng/ml were detectable in the spiked negative control pool, however in the breast cancer serum in the previous version of the assay, the lowest value of spike that met the assay acceptance criterion of 90% positive, was a spike level of 100ng/ml.*

Reviewer comment: [redacted] (b) (4)

Pertuzumab Tolerance:

Tolerance was tested using high levels of PTC in the presence of pertuzumab levels up to 200 ug/ml. The results are presented in the table below.

Table 8. Pertuzumab Tolerance

Run ID: 89RAAL2

Pertuzumab Concentration (µg/mL)	500 ng/mL ATA			
	Mean (OD)	%CV	Result BC	Result (b) (4)
200*	0.574	0.246	Positive	
150	0.777	1.18	Positive	
100	1.17	1.27	Positive	
75.0	1.41	1.10	Positive	
60.0	1.71	1.74	Positive	
50.0	1.98	1.90	Positive	
0.00	3.92	0.0361	Positive	

Legend:
* 500 ng/mL of ATA (positive source control material, lot bab-07Oct13-2) detectable in the presence of up to 200 µg/mL of pertuzumab.

Run 89RAAL2 assay cut points (OD): 0.0590 (BC), [redacted] (b) (4)

Reviewer comment: *A deficiency with this analysis is that the Sponsor only used a high ATA control (500ng/ml). The Sponsor should have also used a lower level positive control in addition to be able to better distinguish the impact of pertuzumab interference at lower levels of therapeutic antibodies. This is an issue that was addressed during the previous validation exercise (see discussion for the original BLA review below). However, as can be discerned from the discussion below, the revalidated version of the*

immunogenicity assay appears to have better pertuzumab drug tolerance, at least at high levels of ATA.

The following discussion was taken from the original BLA review.

In IR #1, Question 26h, the Sponsor was requested to comment on how the validated pertuzumab drug tolerance level compared to actual pertuzumab serum levels at the time of sample collection for ATA testing. The Sponsor stated that based on observed PK concentrations from study W020698C/TOC4129g, the range of C_{min} PK levels was expected to be around 63-95 µg/ml. In addition the following data were provided:

Table Q26h-1 **Drug Tolerance in Pooled Breast Cancer Serum at 40, 45, 50, 55, and 60 µg/mL of Pertuzumab**

Monoclonal Antibody to Pertuzumab (ng/mL)	Pertuzumab Concentration											
	0 µg/mL (Mean OD)	Screen Result (+/-)	60 µg/mL (Mean OD)	Screen Result (+/-)	55 µg/mL (Mean OD)	Screen Result (+/-)	50 µg/mL (Mean OD)	Screen Result (+/-)	45 µg/mL (Mean OD)	Screen Result (+/-)	40 µg/mL (Mean OD)	Screen Result (+/-)
500	0.907	+	0.125	+	0.141	+	0.139	+	0.144	+	0.200	+

Note: Cutpoint = 0.103.
OD = optical density.

Table Q26h-2 **Drug Tolerance in Pooled Breast Cancer Serum at 40, 80, and 100 µg/mL of Pertuzumab**

Monoclonal Antibody to Pertuzumab (ng/mL)	Pertuzumab Concentration							
	0 µg/mL (Mean OD)	Screen Result (+/-)	100 µg/mL (Mean OD)	Screen Result (+/-)	80 µg/mL (Mean OD)	Screen Result (+/-)	40 µg/mL (Mean OD)	Screen Result (+/-)
500	1.082	+	0.078	-	0.107	-	0.175	+

Note: Cutpoint = 0.143.
OD = optical density.

As can be observed from the tables scanned above, at pertuzumab concentrations of 80 µg or greater, pertuzumab interferes with the ability of the assay to detect a high titer anti-pertzumab antibody. The assay is able to detect anti-pertuzumab antibodies in the presence of 60 µg/ml of pertuzumab. However, at which point between 60 and 80 µg/ml pertuzumab the assay is no longer able to detect anti-pertuzumab antibodies was not defined, thus the cut off for pertuzumab drug tolerance should be considered 60 µg/ml pertuzumab. Given that pertuzumab serum concentrations were anticipated to range between 63-95 µg/ml, we do not have assurance that this assay is able to detect anti-pertuzumab antibodies. In the response to the IR, the Sponsor argued that a surrogate antibody as used in the validation study would not represent every immune response, but that the assay did detect ATAs in the clinical trial. While this is true, it should be noted that the observed level of anti-pertuzumab antibodies was 2.8% (11/386) in patients in the pertuzumab arm of the trial, relative to 6.2% (23/372) patients in the placebo treated arm. This decrease in the pertuzumab arm may be due to interference

by serum levels of pertuzumab. However, pertuzumab is given in conjunction with trastuzumab, and the assay does not distinguish responses to the two antibodies. The package insert was therefore amended to reflect this knowledge and now reads "The presence of pertuzumab in patient serum at the levels expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-pertuzumab antibody development."

An amended package insert is associated with the current supplement, however the language below remains unchanged and continues to address this concern:

"The presence of pertuzumab in patient serum at the levels expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-pertuzumab antibody development.:

Reviewer comment: *Using the new reagents, the 500ng/ml high ATA control is detectable in up to 200 ug/ml pertuzumab, whereas in the previously the 500ng/ml high ATA control was detectable only up to 60 ug/ml pertuzumab, which was less than the expected serum concentration of 63-95 ug/ml. This suggests that currently the assay may have greater drug tolerance than previously observed, but does not negate the need for the language regarding this issue contained in the package insert.*

Interference/cross reactivity:
It was stated in the current submission that validation of interference/cross reactivity was not repeated.
Reviewer comment: *Interference and cross reactivity were evaluated as part of the original BLA review (see review). This is not expected to change and it is deemed acceptable that this was not revalidated.*

Robustness/Ruggedness:
It is stated in the Validation Plan that this will be addressed by the use of > 2 analysts, use of different instruments and use of different lots or vials of reagents.
Reviewer comment: *The is deemed sufficient.*

Neat Analyte Stability:
One run was performed for neat analyte stability. For this run the NC, PSC and PTC (from the new positive source control) were subjected to 9 freeze thaw cycles (-80C to room temperature) and remained at room temperature for up to 30 hours prior to analysis. The data for breast (b) (4) are provided in the table below.

Table 9A. Neat Analyte Stability in Breast Cancer (b) (4) Serum after 30 Hours at Room Temperature and 9 Freeze/Thaw Cycles

(b) (4)

Reviewer comment: *As can be observed from the table presented above, the PSC remained positive and the change to the PTC titer value is less than 0.3 titer units, meeting the assay acceptance criteri* (b) (4)

SOP Deviations during the Validation Exercise:
One major deviation occurred, which was the use of expired PTC and PSC for runs 63RAAL2 to 66RAAL2. These reagents just within expiry dating were used in runs 1RAAL2- 62RAAL2. It was stated that they exhibited high variability in the PTC and PSC response, but as results were independent of the controls the data were used for sCPF and CCP determination.
Reviewer comment: *It is reasonable to have used the data from these runs for the determination of cut point, as I concur with the Sponsor's statement that this is independent of the positive controls. This deviation was recognized and resulted in the generation of a new PSC and a new PTC.*

Environmental Analysis:
A request for categorical exclusion from an environmental assessment was not included in the submission. The following IR was conveyed to the Sponsor on December 8, 2017.

> Regarding STN 125409/113-S submitted on February 28, 2017: The submission does not address the requirements for environmental

assessment, as per 21 CFR 25.15. Submit this information to the supplemental BLA application by COB December 11, 2017. Please also submit this information by email to facilitate review.

Reviewer comment: *In the response received on December 11, 2017, the Sponsor submitted a claim for a categorical environmental exclusion under 21 CFR 25.31(c). This is acceptable.*

Reviewer conclusions: Sufficient data from an assay revalidation exercise was provided to support that their new controls (negative control, positive screening control and positive titer control), as well as their new reagents (biotin- and DIG-rhuMAB 2C4 conjugates and streptavidin coated plates) and the assay itself perform as intended.

Future Inspection Items: None

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/s/

KATHRYN E KING
12/14/2017

WENDY C WEINBERG
12/14/2017

SUSAN L KIRSHNER
12/14/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s113

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: November 17, 2017

To: Julia Beaver, M.D., Director
Division of Oncology Products 1(DOP1)

Kim Robertson, Regulatory Project Manager, DOP1

William Pierce, PharmD, Associate Director for Labeling, DOP1

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Brian Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Perjeta® (pertuzumab) injection, for intravenous use

BLA: 125409/s-113 and 118

In response to DOP1's consult request dated August 16, 2017, OPDP has reviewed the proposed product labeling (PI) for Perjeta® (pertuzumab) injection, for intravenous use (Perjeta).

Supplement 113 proposes to convert the subpart E indication to full approval.

Supplement 118 proposes a new indication: (b) (4)

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP1 (Kim Robertson) on November 3, 2017, and are provided below.

OPDP has reviewed the attached proposed container label and carton labeling submitted by the Sponsor to the electronic document room on November 14, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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

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/s/

KEVIN WRIGHT
11/17/2017

LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 22, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 125409/S-113 and S-118
Product Name and Strength:	Perjeta (pertuzumab) Injection, 420 mg/14 mL (30 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Genentech
Submission Date:	September 18, 2017
OSE RCM #:	2017-1702
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Genentech submitted an Efficacy Supplement with updated Perjeta Prescribing Information (PI) to revise the labeling for neoadjuvant treatment of patients with HER2-postive cancer and to include information to support the use of Perjeta for (b) (4)

Per the request of DOP1, DMEPA evaluates the proposed Perjeta Prescribing Information (PI) to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed revisions to Section 2 (Dosage and Administration) of the Perjeta PI and found the revisions acceptable from a medication error perspective. However, we noted that Table 1 in (b) (4) contains dose modification information, which may be more appropriate to be relocated to Section 2.(b) (4) Dose Modification.

4 CONCLUSION & RECOMMENDATIONS

The proposed revisions to the Perjeta could be improved to ensure safe product use. We provide one recommendation in Section 4.1 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Since Table 1 in [redacted] (b) (4) contains dose modification information, consider moving Table 1 to Section 2. (b) (4) Dose Modification.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Perjeta that Genentech submitted on September 18, 2017.

Table 2. Relevant Product Information for Perjeta	
Initial Approval Date	6/08/2012
Active Ingredient	pertuzumab
Indication	**Current:** Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. (1.1) Use in combination with trastuzumab and chemotherapy as • neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. **Proposed addition:** Use in combination with trastuzumab and chemotherapy as • (b) (4)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	420 mg/14 mL
Dose and Frequency	The initial PERJETA dose is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion. **MBC:** Administer PERJETA, trastuzumab, and docetaxel by intravenous infusion every 3 weeks. **Neoadjuvant:** Administer PERJETA, trastuzumab, and chemotherapy by intravenous infusion preoperatively every 3 weeks for 3 to 6 cycles. **Adjuvant:** Administer PERJETA, trastuzumab, and chemotherapy by intravenous infusion postoperatively every 3 weeks for a total of 1 year (up to 18 cycles).
How Supplied	Single-use vial

Table 2. Relevant Product Information for Perjeta	
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 Closure	20 mL colorless (b) (4) glass vial, sealed with a (b) (4) stopper, and crimped with a (b) (4) seal fitted with a (b) (4) plastic cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 13, 2017, we searched DMEPA's previous reviews using the terms, Perjeta. Our search identified 2 previous reviews[a,b], and we confirmed that our previous recommendations were implemented.

[a] Fedenko K and Ida-Lina Diak. FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary Analysis for Perjeta, BLA 125409. Silver Spring (MD): FDA, CDER, OND, OSE (US); 2017 MAR 23. Panorama Reference #1906.

[b] Abdus-Samad, J. Label and Labeling Review for Perjeta (BLA 125409). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 MAY 8. RCM No.: 2012-130.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 13, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care and Community
Search Strategy and Terms	Match Exact Word or Phrase: Perjeta

D.2 Results

The search retrieved no articles.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Perjeta labels and labeling submitted by Genentech on September 18, 2017.

- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

N/A

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

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/s/

TINGTING N GAO
09/22/2017

CHI-MING TU
09/24/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s113

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 009900

MEETING PRELIMINARY COMMENTS

Genentech Inc.
Attention: Ardelle Ying, MD, PhD
Associate Program Director, Global Regulatory Affairs (PDR-PM)
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Ying:

Please refer to your Supplemental Biologic License Application (sBLA) submitted under the Public Health Service Act for Perjeta® (pertuzumab).

We also refer to your November 10, 2016, correspondence, received November 10, 2016, requesting a meeting to discuss the upcoming sBLA submission in February 2017 to revise the label for neoadjuvant treatment of patients with HER-2 positive early breast cancer, as well as, your intent to fulfill PMR 2 and PMC 4 from the Accelerated Approval letter for Supplement 051 dated September 30, 2013.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact me at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-sBLA

Meeting Date and Time: January 26, 2017
Meeting Location: Teleconference

Application Number: IND 009900
Product Name: Perjeta® (pertuzumab).
Indication: Neoadjuvant treatment of patients with HER2-positive early breast cancer (EBC)
Sponsor/Applicant Name: Genentech, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for discussion at the teleconference scheduled for January 26, 2017, at 10:00 AM, between Genentech, Inc. and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the teleconference. The meeting minutes will reflect agreements, important issues, and any action items discussed during the teleconference and may not be identical to these preliminary comments following substantive discussion at the teleconference. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the teleconference, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the teleconference.

1.0 BACKGROUND

The purpose of this Type B meeting is to discuss the upcoming sBLA submission in February 2017 to revise the label for neoadjuvant treatment of patients with HER2-positive early breast cancer (EBC) and the intent to fulfill PMR 2 and PMC 4 from the September 30, 2013, Accelerated Approval letter for Supplement 051.

Pertuzumab (rhuMAb 2C4 [Perjeta]) is a recombinant, humanized immunoglobulin (Ig)G1k monoclonal antibody, which targets the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2). By binding to sub-domain II of the HER2 receptor extra-cellular domain (ECD), Perjeta inhibits ligand-dependent HER2 dimerization with other HER family members, as well as homodimerization with HER2. This results in inhibition of downstream signaling of

pathways important to cancer cell proliferation and survival such as PI3K and MAPK. Perjeta is also believed to mediate antibody-dependent cell-mediated cytotoxicity (ADCC).

On June 8, 2012, Perjeta was approved for use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. On September 30, 2013, Perjeta received accelerated approval for the following indication:

- Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.

Postmarketing Requirement (PMR) 2 stated:

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

Final Protocol Submission: 01/14
Trial Completion: 08/16
Final Report Submission: 02/17

Postmarketing Commitment (PMC) 4 stated:

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

Final Protocol Submission: 01/14
Study Completion: 08/16
Final Report Submission: 08/17

The NEOSPHERE and TRYPHAENA clinical trials established the use of Perjeta in neoadjuvant Herceptin/taxane-containing regimens for patients with HER2-positive EBC. The BERENICE trial (WO29217) was conducted in fulfillment of PMR 2, to assess the cardiac safety of two neoadjuvant anthracycline/taxane-based chemotherapy regimens in combination with neoadjuvant Perjeta and Herceptin. General safety and efficacy (pCR rate) were also assessed. BERENICE was a non-randomized, open-label, multicenter, multinational, phase 2 trial with 2 parallel groups of patients. Based on investigator preference at a given site, patients were allocated to one of the following regimens:

- Cohort A: Dose-dense doxorubicin and cyclophosphamide every 2 weeks for 4 cycles with G-CSF support, followed by weekly paclitaxel for 12 weeks, with Perjeta and

Herceptin every 3 weeks from the start of paclitaxel (4 cycles of Perjeta and Herceptin prior to surgery).

OR

- Cohort B: 5-fluorouracil, epirubicin and cyclophosphamide, given every 3 weeks x 4 cycles, followed by docetaxel every 3 weeks x 4 cycles. Perjeta and Herceptin were administered every 3 weeks from the start of docetaxel (4 cycles of Perjeta and Herceptin prior to surgery).

Postoperatively, patients in both treatment arms were given additional adjuvant Perjeta and Herceptin every 3 weeks to complete a total of 17 cycles of Perjeta and Herceptin therapy, for approximately 1 year of treatment.

Key inclusion criteria included centrally confirmed HER2-positive, locally advanced, inflammatory or early-stage breast cancer and scheduled for neoadjuvant therapy. The primary tumor was to be >2 cm in diameter or >5 mm in diameter and node positive. Baseline left ventricular ejection fraction (LVEF) was required to be ≥55%. The primary safety endpoints were investigator-assessed:

- Incidence of NYHA Class III and IV heart failure during the neoadjuvant period
- Incidence of LVEF declines (≥10%-points from baseline and to a value of <50%) during the neoadjuvant period.

The main efficacy endpoint was pCR, defined as eradication of invasive disease in the breast and axilla, assessed at the time of surgery.

An exploratory biomarker analysis was conducted to explore an analysis of the relationship of pCR with intrinsic breast cancer subtypes.

A total of 401 patients were enrolled at 75 centers, 199 to Cohort A and 202 to Cohort B. The data were analyzed without making comparisons between the cohorts. As of the time of the clinical cutoff date for the primary analysis, March 3, 2016, there were no unexpected safety signals. The cardiac safety profiles for both regimens during the neoadjuvant period were consistent with the known cardiac safety profiles of Perjeta and Herceptin. The pCR rates were similar in Cohort A (61.8%) and Cohort B (60.7%).

2.0 DISCUSSION

Question 1

Does the Agency agree that the results demonstrated in the primary analysis of Study WO29217/BERENICE provide an acceptable basis for the proposed application?

FDA Response: We agree with the plan to submit the data; the acceptability of the results will be a review issue.

Question 2

Does the Agency agree that the results of the WO29217/BERENICE study are adequate to support updates to the Perjeta label to revise the indication statement and other label sections, as appropriate?

FDA Response: Possibly, see Question 1.

Question 3

Does the Agency agree with the Applicant's proposal that the Integrated Summary of Safety (ISS) and Integrated summary of efficacy (ISE) in Module 5 will be based on data from Study WO29217/BERENICE and that the ISS and ISE will cross-refer to the summary of clinical safety (SCS) and summary of clinical efficacy (SCE) in Module 2, respectively?

FDA Response: Yes.

Question 4

Does the Agency agree that the proposed content and format of the sBLA are acceptable, specifically as outlined in Section 8?

FDA Response: Yes, however we request that you update the clinical pharmacology information of Perjeta with the newly acquired clinical data.

Question 5

Does the Agency agree with the proposal regarding the safety update report?

FDA Response: Yes.

Question 6

Does the Agency agree that submission of the WO29217/BERENICE primary CSR in the proposed sBLA will be acceptable to fulfill PMR #2 and PMC #4?

FDA Response: Please see response to Question 1.

Question 7

Does the Agency have any other comments on the proposed format and contents of the planned sBLA?

FDA Response: No.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 21, 2016, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at:
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format:* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site.

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

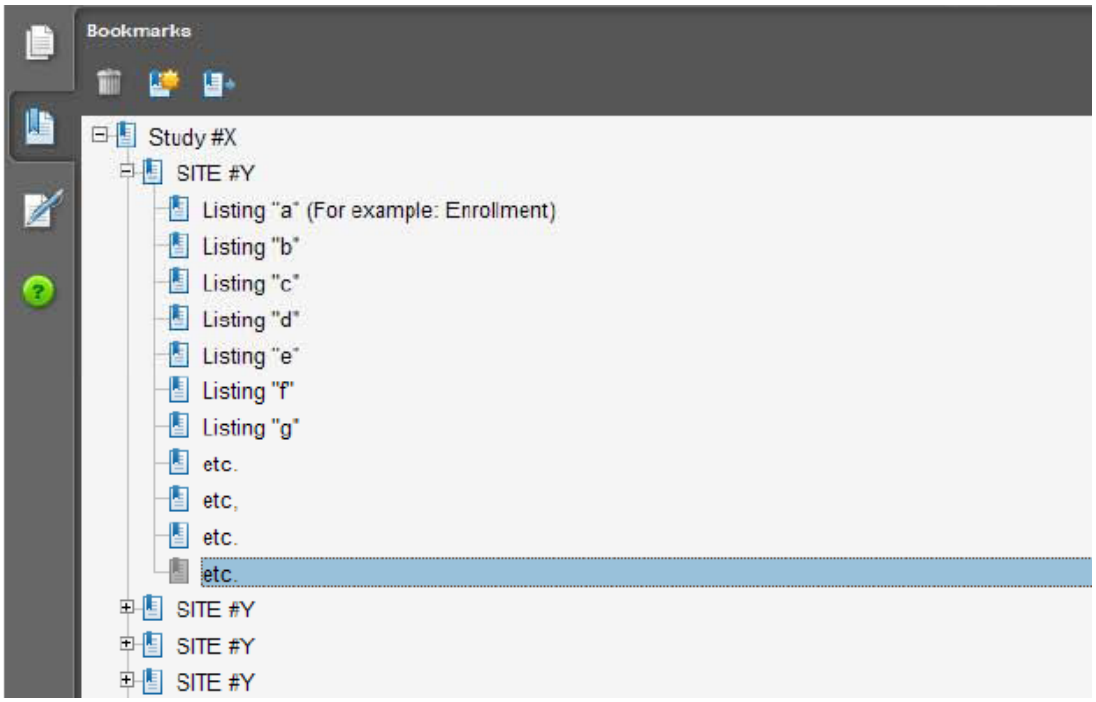
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring.

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

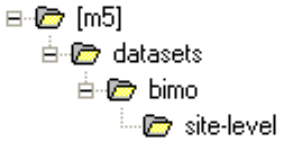
Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1:
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page:
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

AMY R TILLEY
01/18/2017