CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s0051

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125409\51
Priority or Standard	Priority
Submit Date(s)	April 30, 2013
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PDUFA Goal Date	October 31, 2013
Division / Office	DOP1 / OHOP
Reviewer Name(s)	Laleh Amiri-Kordestani, MD (efficacy) Suparna Wedam, MD (safety) Patricia Cortazar, MD (CDTL)
Review Completion Date	9/25/2013
Established Name	Pertuzumab
(Proposed) Trade Name	Perjeta®
Therapeutic Class	Monoclonal antibody
Applicant	Genentech, Inc
Formulation(s)	420 mg/14mL (30mg/mL) in a single use vial
Dosing Regimen	Initial dose of 840 mg IV infusion, followed by 420 mg IV infusion every 3 weeks thereafter
Proposed Indication(s)	“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 containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin”.
Intended Population(s)	Patients with early breast cancer

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on review of the clinical data, the clinical review team recommends accelerated approval of supplement biologics license application (sBLA) 125409/51 pertuzumab (Perjeta®) for the following indication:

> Perjeta is a HER2/neu antagonist indicated for use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin. 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 basis for this recommendation is a favorable benefit-risk profile for pertuzumab when added to trastuzumab and docetaxel as part of a neoadjuvant regimen in HER2-positive, locally advanced, inflammatory or early breast cancer. (see section 1.2, Risk Benefit Assessment). In the main neoadjuvant study, NEOSPHERE (WO20697), a statistically significant improvement in pCR rate was observed in patients receiving pertuzumab plus trastuzumab and docetaxel compared to those receiving trastuzumab plus docetaxel [difference of pCR rates: 17.8%, p-value 0.0063, Cochran-Mantel-Haenszel test]. Additionally, in the other neoadjuvant supportive study (TRYPHAENA, BO22280), high pCR rates were observed in all three pertuzumab containing treatment arms. The long term benefit, improvement in event-free survival or overall survival that may result from these improvements in pCR rates has not been established. The CLEOPATRA (WO20698) trial demonstrated a clinically meaningful and statistically significant improvement in Progression Free Survival (PFS) and Overall Survival (OS) favoring the pertuzumab containing treatment arm in the metastatic breast cancer setting.

The safety profile of pertuzumab was acceptable for this curable intent population. In NEOSPHERE (WO20697), the most common adverse reactions (> 30%) with pertuzumab in combination with trastuzumab and docetaxel in the neoadjuvant setting were alopecia, diarrhea, nausea and neutropenia. The most common (> 2%) NCI – CTCAE (version 3) Grade 3 – 4 adverse reactions were neutropenia, febrile neutropenia, diarrhea, leukopenia and menstrual irregularity. There was evidence of increased cardiac dysfunction with the addition of pertuzumab to trastuzumab and docetaxel. Other significant adverse reactions reported with pertuzumab include infusion-related reactions, hypersensitivity reactions, and anaphylaxis. Pertuzumab is being approved with a new BOXED WARNING regarding cardiomyopathy.

The FDA review team finds that the totality of data submitted, including the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) study results, the overall survival improvement seen in CLEOPATRA (WO20698/TOC4129g) and the tolerable safety profile, support an accelerated approval for pertuzumab in the neoadjuvant setting. The conversion to regular approval will be contingent upon the results of the fully accrued Phase 3 APHINITY (BO25126) trial.

1.2 Risk Benefit Assessment

Breast cancer is the second leading cause of cancer-related death among women. An estimated 232,340 women will be diagnosed with breast cancer, and 39,620 will die from the disease in 2013, according to the National Cancer Institute.[1] Almost 20 percent of breast cancers have increased amounts of the HER2 protein. Patients with HER2 positive are considered to be at high risk for relapse and have poor prognosis. Although with the approval of trastuzumab in early breast cancer, the prognosis of patients with HER2 positive breast cancer has significantly improved, still about one third of these patients relapse.[2] Currently, there are no FDA approved agents for the neoadjuvant therapy of patients with breast cancer.

Pertuzumab was approved in June 2012 and 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.[3]

The pertuzumab sBLA is primarily supported by the NEOSPHERE (WO20697) study, a multicenter, randomized trial designed to evaluate four neoadjuvant regimens in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d).[4] Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery: trastuzumab plus docetaxel, pertuzumab plus trastuzumab and docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel. The main comparison for this sBLA review is trastuzumab plus docetaxel (control) vs. pertuzumab plus trastuzumab and docetaxel (experimental). Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity. The primary endpoint of the study was pathological complete response (pCR) rate defined as absence of invasive cancer in the breast (ypT0/is). Statistically significant improvements in pCR rates were observed in patients receiving pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel. The pCR rates and magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors.

Two additional studies to support this sBLA application have been submitted. TRYPHAENA (BO22280) is a randomized Phase 2 study conducted in 225 patients with HER2-positive, locally advanced, operable, or inflammatory (T2-4d) breast cancer.[5] Patients were randomized 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

pertuzumab and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with pertuzumab, or 6 cycles of TCH in combination with pertuzumab. The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study. Secondary endpoints were pCR rate in the breast (ypT0/is), DFS, PFS, and OS. Higher pCR rates were observed in the 3 pertuzumab treatment arms compared to the NEOSPHERE (WO20697) study possibly due to the incorporation of the anthracycline regimen preoperatively. The results were consistent using the two pCR definitions (ypT0/is and ypT0/isypN0).

CLEOPATRA (WO20698/TOC4129g) is a randomized, double-blind, placebo-controlled, multicenter trial in patients with HER2-positive metastatic breast cancer. The trial enrolled 808 patients who were randomly allocated (1:1) to receive pertuzumab in combination with trastuzumab and docetaxel (n=402) or placebo in combination with trastuzumab and docetaxel (n=406).[6] This trial was the basis of the initial approval. A statistically and clinically significant 6.1 month improvement in progression-free survival (PFS) in patients receiving pertuzumab compared to those receiving placebo [HR 0.62 (95% CI: 0.51, 0.75; p< 0.0001, log-rank test)] was seen. The median PFS was 18.5 and 12.4 months for patients on the pertuzumab and placebo arms, respectively. At the time of PFS analysis, a planned interim analysis for overall survival (OS) was performed. The first interim OS analysis showed a trend towards improved survival with pertuzumab [HR 0.64 (95% CI: 0.47, 0.88), p=0.0053]. At the second interim analysis, the stopping boundary for statistical significance (p<0.0138) was crossed.[7] Thus, the pertuzumab treatment arm demonstrated superiority in overall survival [HR=0.66, 95% CI (0.52, 0.84) p=0.0008]

Common side effects with pertuzumab in the neoadjuvant setting include neutropenia, diarrhea, nausea, rash, mucosal inflammation, myalgia, fatigue, and stomatitis. In this curative intent setting, treatment was delivered as planned in the majority of patients. The addition of pertuzumab led to an increased incidence of all cardiac events including left ventricular dysfunction. Discontinuation due to cardiac toxicity was low and all cases of left ventricular dysfunction in NEOSPHERE (WO20697) eventually recovered to left ventricular ejection fraction (LVEF) >50%. All but one cases of left ventricular dysfunction in TRYPHAENA (BO22280) eventually recovered to LVEF >50%. Most cases of left ventricular dysfunction in the NEOSHERE (WO20697) and TRYPHAENA (BO22280) studies were asymptomatic with a LVEF decline of ≥10% with a decrease to less than 50%.

Within the current sBLA there is no data regarding long term efficacy or safety of pertuzumab given in the neoadjuvant setting. Genentech plans to submit the efficacy and safety data from the fully accrued Phase 3 APHINITY (BO25126) study in 2017.[8] This study is investigating pertuzumab in the adjuvant setting, with a primary endpoint of invasive disease-free survival (IDFS). The final analysis of IDFS from this study could permit confirmation of the clinical benefit observed for pertuzumab in the neoadjuvant setting and support conversion of accelerated approval to regular approval for the proposed indication.

In conclusion, the FDA review team finds that the totality of data submitted, including the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) study results, the overall survival improvement seen in CLEOPATRA (WO20698/TOC4129g) and the acceptable safety profile, support an accelerated approval for pertuzumab in the neoadjuvant breast cancer setting. This will be the first agent approved for the treatment of early breast cancer in the neoadjuvant setting after the release of FDA Draft Guidance for Industry - Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval.[9-10]

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS or Medication Guide is required for marketing of pertuzumab.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical team recommends the following Postmarketing Requirement (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).

Rationale: Genentech proposes to use the APHINITY trial as the confirmatory trial to support the conversion from accelerated approval to regular approval. This adjuvant trial is a randomized controlled trial in 4800 women with HER2-positive early breast cancer designed to demonstrate the superiority of adjuvant pertuzumab plus trastuzumab in combination with standard chemotherapy compared to placebo pertuzumab plus trastuzumab plus standard chemotherapy. The primary endpoint is invasive disease-free survival. This trial is also needed to better characterize the overall toxicity profile of pertuzumab in the early breast cancer population.

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.

Rationale: The NEOSPHERE and TRYPHAENA studies showed there was an increase rate of left ventricular dysfunction with the addition of pertuzumab treatment. Although most of the cases of cardiac dysfunction were asymptomatic and reversible, the cardiac safety needs to be further explored with chemotherapy

regimens that are commonly used in the USA. This PMR study will look at the cardiac and overall safety of two different neoadjuvant pertuzumab and anthracycline-containing regimens in two parallel cohorts.

The clinical team recommends the following Postmarketing Commitments (PMCs):

1) Submit the final event-free survival (EFS) analysis of trial WO20697 (NEOSPHERE).

Rationale: The final event-free survival (EFS) results of trial WO20697 (NEOSPHERE) would support the pathological complete response results favoring the pertuzumab treatment arm in the NEOSPHERE trial.

2) 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.

Rationale: HER2-positive breast cancer is very heterogeneous. It appears from prior studies that different HER2-positive subtypes could have different sensitivity to HER2 targeted agents, which probably impacts pathological complete response endpoint. It is important to address this issue with pretreatment molecular subtyping to help identify patients who are at higher risk of relapse and death despite the best available anti HER2 therapies.

2 Introduction and Regulatory Background

2.1 Product Information

Please refer to original review of pertuzumab BLA 125409.

2.2 Currently Available Treatments for Proposed Indications

There are currently no drugs approved in the U.S. for the neoadjuvant treatment of HER2+ breast cancer. However, regimens appropriate in the adjuvant setting are often used in the neoadjuvant setting. A few acceptable regimens are:

-Anthracyclines (Adriamycin and cyclophosphamide = AC or fluorouracil, epirubicin and cyclophosphamide = FEC) + Taxanes (Paclitaxel or Docetaxel) + trastuzumab

-Non-anthracycline regimen docetaxel + carboplatin+ trastuzumab (TCH)

Ado-trastuzumab emtansine and lapatinib are other anti-HER2 agents that are only approved for treatment of breast cancer in the metastatic setting. These agents are not recommended to be used in the adjuvant period by NCCN guidelines and may rarely be used for the proposed indication.

2.3 Availability of Proposed Active Ingredient in the United States

Pertuzumab was approved for use in June 2012 in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

2.4 Important Safety Issues with Consideration to Related Drugs

Trastuzumab:

Trastuzumab carries the following Boxed Warnings:

- Cardiomyopathy: Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy.
- Infusion reactions
- Pulmonary toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.
- Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.

In addition, trastuzumab has an associated 'Warnings and Precautions' for exacerbation of chemotherapy-induced neutropenia.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- **May 2001**: pre-IND Meeting
- **June 2001**: IND submission
- **May 2011**: Type C Meeting to reach agreement on original BLA 125409 submission in metastatic setting
    - FDA: Agency requested an additional PFS sensitivity analysis for patients discontinued due to toxicity. For time to cardiac event, Agency

recommended analyses based on cumulative incidence considering non-cardiac death as competing events.
  - FDA: Genentech will need to submit a PMA supplement if using an FDA approved HER2 test. If using a test kit that is not FDA approved, they will need to submit a PMA.

- **August 2011**: CMC pre-BLA 125409 meeting

  - Quality by design approach for Drug Product
  - Stability data
  - Statistical approach for qualification of the scale down models

- **September 2011**: Type B pre-BLA meeting. Summary of meeting minutes:

  - FDA: The efficacy and safety results from study TOC4129g, a single study intended to support marketing approval, are sufficient to characterize the benefits and risks of pertuzumab and to form the basis of a BLA for the proposed indication. However, whether or not the application will support full or accelerated approval will be based on FDA's review.
  - Genentech: Final OS analysis in late 2013 at 385 events. Will provide a proposal by November 2011 for the statistical analysis plan for conducting an additional OS analysis, should FDA request this.
  - Genentech: Will provide high level safety results and stand-alone datasets for study TRYPHAENA (BO22280).
  - FDA: determination of review designation will be made after a determination that the application can be filed and will be conveyed in the filing letter.
  - FDA: Based on the information in the meeting package, FDA is not requesting that a REMS be proposed, however a final determination on the need for REMS will be made during the review of the application.
  - FDA: Determination on the need for an ODAC review will be made after the BLA is submitted.

- **December 2011**: Initial BLA 125409 was submitted to agency for the first-line treatment of HER2+ MBC

- **June 2011**: FDA approval of pertuzumab in combination with trastuzumab and docetaxel for the first-line treatment of HER2+ MBC

- **December 2011**: Discussion of breast cancer portfolio, including potential filing based on pCR in the neoadjuvant setting

- **December 2012**: sBLA 125409/32 was submitted to FDA. Statistically significant results for overall survival from 2nd interim analysis in CLEOPATRA study for first-line treatment of HER2+ MBC. The priority review was granted.

- **January 2013:** Type-B pre- supplemental sBLA meeting. The purpose of the meeting was to discuss the proposed contents and format of a sBLA to support the proposed indication: "Perjeta in combination with trastuzumab and chemotherapy is indicated for the neoadjuvant treatment of HER2-positive breast cancer patients". Summary of meeting minutes:

    - FDA: Regulatory pathway of accelerated approval for neoadjuvant breast cancer based on pCR is novel; this efficacy supplement will likely require discussion at an Oncologic Drug Advisory Committee. Draft Guidance "Use of Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early Stage Breast Cancer as an Endpoint to Support Accelerated Approval" has not been finalized. Agency has not yet determined whether a single large neoadjuvant trial in which both pCR and EFS/OS can be assessed would be better than a smaller neoadjuvant trial using pCR for accelerated approval with a large adjuvant randomized trial used to confirm clinical benefit
    - FDA: Agency does not know what magnitude of improvement in pCR is likely to translate into an improvement in EFS or OS.
- FDA: NEOSPHERE (WO20697) is under-powered to detect differences in EFS/DFS or OS between treatment arms.
- FDA: NEOSPHERE (WO20697) was not designed with the degree of type 1 error control typical of registration studies.
- FDA: The NEOSPHERE (WO20697) primary endpoint, breast pCR, is not as strongly associated with EFS and OS as are the other pCR definitions.
- FDA considers ypT0/isypN0 or ypT0ypN0 as the acceptable pCR definition to support approval of neoadjuvant trials. You will need to provide adequate data on axillary status and management to assess axillary response.
- FDA: Assuming that the two trial strategy is acceptable, the adjuvant APHINITY trial may be overpowered to detect small incremental improvements in IDFS of questionable clinical meaningfulness and questionable benefit-risk given the additive toxicities of pertuzumab. Therefore, APHINITY may not provide confirmatory evidence of benefit. We are also concerned about a long potential lag between sBLA filing and submission of APHINITY (estimated to be Q1 2017).
- FDA: It is possible that some lower risk patients (i.e. hormone receptor +, small tumor burden, lymph node negative) may not benefit from the addition of pertuzumab and may be exposed to unnecessary risk. Therefore, your proposed indication may be too broad.

- **April 2013**: FDA approval of sBLA 125409/32 to include confirmatory OS data in the pertuzumab USPI

- **April 2013**: sBLA 125409/51 was submitted to FDA for the neoadjuvant treatment of breast cancer.

Reviewer Comment: *There are no USA FDA approved drugs in the neoadjuvant setting for the treatment of breast cancer. In May 2012, the Agency released a draft guidance titled "Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval".[9-10] In March 2013, the agency had a workshop related to drug approval in neoadjuvant treatment. However, in a pooled analysis, pCR has been proven to be informative at a patient level. [11]The analysis could not establish whether an increase in pCR rate between treatment groups predicts for the superiority of one regimen over another in terms of EFS or OS. As a consequence, it is uncertain whether the difference in pCR rates demonstrated in the NEOSPHERE study, will be associated with improved long-term outcome. Due to the uncertainty around pCR and its association with the long term outcome, the Agency can only consider giving an accelerated approval. The Accelerated Approval Regulations state that: FDA may approve a new product based on adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The Agency had a public breast cancer workshop in March 2013, to discuss this regulatory path and in the panel's opinion; pCR could be considered reasonably likely to predict clinical benefit. The Agency has previously used non-validated surrogate endpoints as basis of AA (e.g. ORR). AA requires subsequent confirmation of benefit, in this case, confirmation of the long-term outcome such as DFS or OS and includes a provision for withdrawal of indication if trials fail to confirm the clinical benefit*

2.6 Other Relevant Background Information

Breast cancer is the second leading cause of cancer-related death among women. An estimated 232,340 women will be diagnosed with breast cancer, and 39,620 will die from the disease in 2013, according to the National Cancer Institute. Almost 20 percent of breast cancers have increased amounts of the HER2 protein. Since the approval of trastuzumab for early stage Her2 positive breast cancer, there has been a significant improvement in the survival for these patients, but still greater than 20-30% of patients recur and die from their metastatic disease. Having new drugs available earlier for these high risk patients is crucial.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear to be acceptable.

3.2 Compliance with Good Clinical Practices

According to the Applicant, the study was conducted in full conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country where the research was conducted, whichever provided greater protection to the individual. The study adhered to the January 1997 ICH Guideline for Good Clinical Practice. Written informed consent was obtained from each participant in the study. The protocol and subsequent amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

Three audits at investigator sites were conducted by the Roche Clinical Quality Assurance group or designees.
Major finding(s) involving non-compliance with GCP were observed. However, appropriate corrective and preventive actions were undertaken.

The following centers were audited (Table 1).

Table 1: Applicant Audited Centers

Investigator	Location	Audit Date(s)
Prof. Younq-Hyuck lm	Seoul, Republic of Korea	06-07 AUG 2009
Dr. Nik Hauser	Baden, Switzerland	29-30 SEP 2009
Dr. Tadeusz Pienkowski	Warsaw, Poland	03-04 NOV 2009

(Source: CSR wo20697, page 12722)

Compliance and training visits were conducted at 11 investigator sites. The following compliance visits were conducted by members of the compliance and training network (Table 2):

Table 2: Applicant visited Centers for Compliance

Investigator	Location	Compliance Visit Date(s)
Dr. Ling-Ming Tseng	Taipei, Taiwan	08 & 14 MAY 2008
Dr. Paolo Morandi	Vicenza, Italy	09 JUN 2008
Dr. Vichien Srimuninnimit	Bangkok, Thailand	27 JUN 2008
Dr. Patrapim Sunpaweravonq	Sonqkhla, Thailand	18 AUG 2008
Dr. Luca Gianni	Milano, Italy	29 SEP 2008
Dr. Brigitte Poirier	Quebec City, Canada	04-05 NOV 2008
Dr. Anna Lowczak	Olsztyn, Poland	09 FEB 2009
Prof. Serqei Tjulandin	Moscow, Russian Federation	12 FEB 2009
Dr. Piotr Tomczak	Poznan, Poland	09 MAR 2009
Dr. Michael Thirlwell	Montreal, Canada	16 SEP 2009
Dr. Patrapim Sunpaweravonq	Songkhla, Thailand	03 FEB 2010

(Source: CSR wo20697, page 12722)

These compliance visits were part of the quality control process of the sponsor and were conducted to evaluate compliance of site and monitoring staff with Good Clinical Practice (GCP) guidelines, relevant local regulations and sponsor's Standard Operating Procedures.

FDA Clinical Inspection Summary:

A draft of the Clinical Inspection Summary was provided by Lauren Iacono-Connors, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, Office of Scientific Investigations (OSI). The OSI inspected three of the highest accruing sites in Italy, Poland and Spain. A summary of the site inspections is provided Table 3.

Based on the review of preliminary inspectional findings for clinical investigators Dr. Giulia V. Bianchi (Site 116798), Dr. Tadeusz Pienkowski (Site 116801), and Dr. Ana

Lluch Hernandez (Site 116814), StudyWO20697 data appear reliable based on available information.
One clinical site inspected, Dr. Giulia V. Bianchi (Site 116798) was issued a Form FDA 483 citing inspectional observations, and the preliminary classification for this inspection is Voluntary Action Indicated (VAI). The preliminary classifications for the remaining inspections of Dr. Tadeusz Pienkowski (Site 116801), and Dr. Ana Lluch Hernandez (Site 116814), are No Action Indicated (NAI).

The inspection of Dr. Bianchi's site (116798) found occasional use of pertuzumab and trastuzumab from inappropriate sources. Specifically, the firm had administered investigational drug, pertuzumab, provided to the site for another Roche-sponsored investigational study that also used pertuzumab, to two subjects enrolled in the Roche WO20697 clinical study over a two day period. In addition, on at least ten occasions commercial product trastuzumab was administered to study subjects when the site pharmacy apparently did not have enough investigational trastuzumab in stock for Study WO20697.

While these are valid inspectional observations, which must be addressed and corrected by this site, they should not impact data generated by this site.
Finally, regarding Dr. Hernandez' site (116814), there was one adverse event discrepancy between source documentation and data listings submitted to BLA 125409 s51. Specifically, Subject #3812 visited the Emergency Room on (b) (6) (in between study visits 2 and 3) due to fever and chills. Subject #3812 was diagnosed with pneumonia, confirmed by x-rays, and was prescribed antibiotics (Augmentin and Tavanic). This AE and the concomitant medications were not reported in the subject's eCRF by the site. Dr. Hernandez explained that in 2009 the subject's medical history/chart was still on hard copy and as such the information was not readily available to other medical departments in real-time. In practice, the study staff would learn of "out of visit AEs", such as this example, during a subject's interview at the subsequent study visit. In this case, apparently Subject #3812 did not inform the site staff of the ER visit, and subsequent diagnosis and treatment. Although regulatory violations were noted as described above, they are unlikely to impact primary safety and efficacy analyses. The overall data for Study WO20697
(NEOSPHERE) in support of this application may be considered reliable based on available information.

Table 3: Summary of OSI findings

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: **Giulia V. Bianchi, M.D. (Current CI)** **Luca Gianni, M.D. (Former** **CI)** Istituto Nazionale Per Lo Studio E La Cura Dei Tumori Milano, Italy	Protocol: WO20697 Site Number: 116798 Number of Subjects: 28	July 29, 2013 - August 2, 2013	Pending Interim classification: VAI
CI#2: Tadeusz Pienkowski, **M.D.** Centrum Onkologii-Inst. Im. MarII Sklodowskiej-Curie Warszawa, Poland	Protocol: WO20697 Site Number: 116801 Number of Subjects: 28	July 29, 2013 - August 2, 2013	Pending Interim classification: NAI
CI#3: Ana Lluch Hernandez, M.D. Hospital Clinico Universitario de Valencia Valencia, Spain	Protocol: WO20697 Site Number: 116814 Number of Subjects: 16	July 29, 2013 – August 3, 2013	Pending Interim classification: NAI

3.3 Financial Disclosures

Both NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies were sponsored by Roche and were not submitted to IND 9900. The CLEOPATRA (WO20698/TOC4129g) trial was jointly sponsored by Roche and Genentech and was submitted to IND 9900.

The sponsor received financial disclosure information from 100% of principal and sub-investigators on both NEOSPHERE (WO20697) and TRYPHAENA and from 99.8% of principal investigators and sub-investigators on CLEOPATRA (WO20698/TOC4129g). Disclosable financial interests were recorded by 1 out of 587 (<1%) in study NEOSPHERE (WO20697) as seen in Table 4.

Table 4: Summary of Financial Disclosures (Applicant Table)

Study Protocol Number	Clinical Site Number	Investigator Name	Patient Enrollment	Disclosure
WO20697	(b) (6)			Not able to obtain the $ specific amount

(Source: sBLA 125409 Section 1.3.4.1, financial disclosure)

Reviewer Comment: *The financial disclosures do not raise questions about data integrity in the NEOSPHERE (WO20697) study. The only Investigator with disclosable interest enrolled a small proportion of the total number of patient, such that introduction of bias is unlikely.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the CMC reviews of the original BLA 125409. The CMC review of the original BLA 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 the original BLA 125409 were Dr. Kathryn King (Traditional Elements) and Laurie Graham (Quality by Design). The BMAB reviewers were Drs. Bo Chi (Drug Substance) and Colleen Thomas (Drug Product).

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

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

4.4 Clinical Pharmacology

The updated population PK analysis results suggested that pertuzumab exposure in patients with early breast cancer in trial NEOSPHERE (WO20697) was similar to exposure in other historical patient types including first-line metastatic breast cancer. No significant exposure-response relationship was identified between predicted pertuzumab trough serum concentration and the probability of pCR response, the primary efficacy endpoint of the NEOSPHERE (WO20697) trial.

Please see the BLA 125409/51 clinical pharmacology review by Dr. Pengfei Song for additional details.

5 Sources of Clinical Data

Data from 3 clinical studies were submitted to the sBLA. Table 5 lists the clinical trials submitted in support of the sBLA application. Data from NEOSPHERE (WO20697) and TRYPHAENA (BO22280) are used for the primary basis of evaluation for efficacy and safety.

5.1 Tables of Studies/Clinical Trials

Table 5: Key Clinical Studies Submitted (Reviewer Table)

Protocol	Study Design	Disease	Doses	N	Primary EP	Status
NEOSPHERE WO20697	Phase 2b, randomized, open label, four-arm study, multi-center, international	Neoadj HER2+ early BC	Pertuzumab 420 mg q3w (840 mg load) x 4 cycles Trastuzumab 6 mg/kg q3w (8mg/kg load) x 4 cycles neoadj and up to 1 year post-op Docetaxel: 75 mg/m^2 q3w (option to increase to 100 mg/m^2) x 4 cycles	417	pCR	Ongoing Full report for primary analysis submitted
TRYPHAENA BO22280	Phase 2, randomized, open label, three-arm study, multi-center, international	Neoadj HER2+ early BC	Arm A: 5-Fluorouracil, epirubicin with cyclophosphamide (FEC), trastuzumab and pertuzumab every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles. Arm B: FEC every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles. Arm C: Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab every three weeks, for six cycles.	225	Safety	Ongoing Full report for primary analysis submitted
CLEOPATRA WO20698/ TOC4129g	Phase 3b, randomized, placebo controlled, double blind, multi-center, international	HER2+ MBC	Pertuzumab 420 mg q3w (840 mg load) Trastuzumab 6 mg/kg q3w (8mg/kg load) Docetaxel: 75 mg/m^2 q3w (option to increase to 100 mg/m^2)	808	PFS	Ongoing Full report for primary analysis submitted

BC=breast cancer; EP=endpoint

5.2 Review Strategy

The clinical review is based on the clinical study reports for the two phase2 trials in the neoadjuvant setting and the additional supportive trial in the metastatic setting outlined in 5.1. The efficacy review was conducted by Dr. Laleh Amiri-Kordestani and the safety review by Dr. Suparna Wedam. A statistical review was conducted by Dr. Lijun Zhang. Among the items reviewed were the case report forms, selected narratives, primary data sets for baseline characteristics, efficacy and toxicity submitted by the applicant, study reports for other pertuzumab clinical trials, research of the FDA data base for regulatory history of the pertuzumab IND/BLA, and a literature review for the role of neoadjuvant therapy in HER2+ breast cancer .

5.3 Discussion of Individual Studies/Clinical Trials

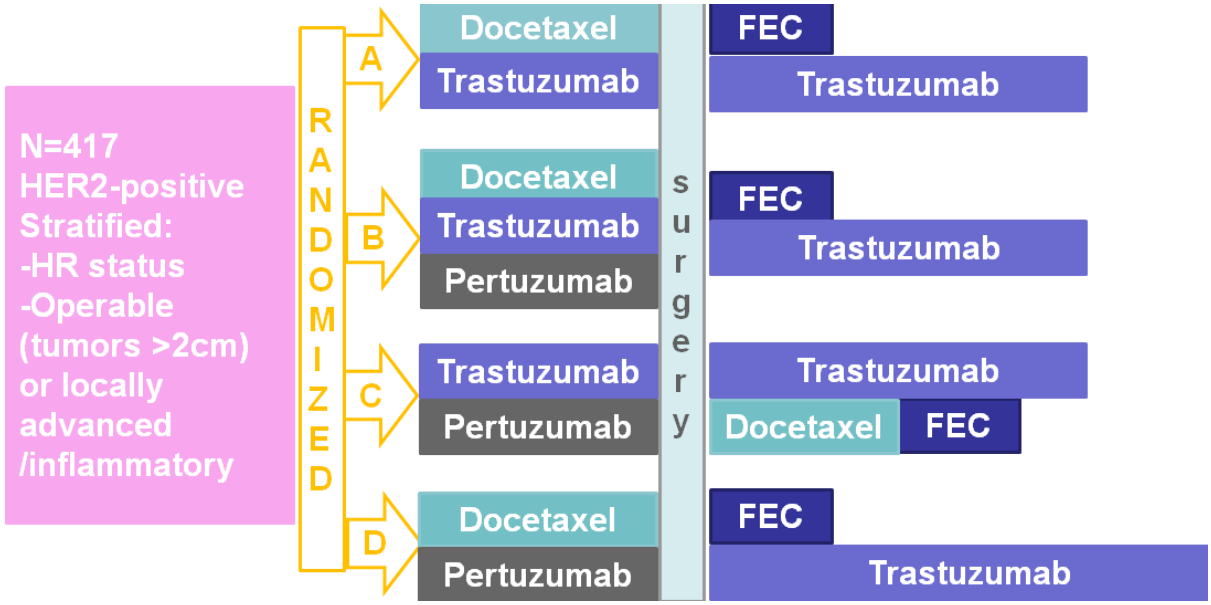
5.3.1 Phase 2 NEOSPHERE (WO20697)

This sBLA submission is primarily supported by results from a single industry-sponsored study, NEOSPHERE (WO20697), entitled:

> "A randomized, multicenter, multinational Phase II study on trastuzumab plus docetaxel versus trastuzumab plus docetaxel plus pertuzumab versus trastuzumab plus pertuzumab versus pertuzumab and docetaxel in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer"

NEOSPHERE study design is shown in Figure 1. In summary, it was a multicenter, randomized study to evaluate four neoadjuvant regimens in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d). Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery: trastuzumab plus docetaxel, pertuzumab plus trastuzumab and docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel. The main comparison for this sBLA review is trastuzumab plus docetaxel (Arm A=control) vs. pertuzumab plus trastuzumab and docetaxel (Arm B=experimental). Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity. The primary endpoint of the study was pathological complete response (pCR) rate defined as absence of invasive cancer in the breast (ypT0/is).

Figure 1 : NEOSPHERE (WO20697) Study Design



FEC=5-FU, epirubicin, and cyclophosphamide

NEOSPHERE (WO20697) Endpoints

Primary Endpoints: pCR (absence of invasive neoplastic cells at microscopic examination of tumor remnants after surgery following primary systemic therapy) in the breast.

Reviewer Comment: *FDA preferred definition of pCR is the absence of invasive breast cancer in breast and axilla. Based on the results of the FDA conducted Pooled analysis, this definition correlates better with long-term outcome. (Cortazar, et al SABCS 2012)*

Key Secondary Endpoints:

- Best tumor response/clinical response during neoadjuvant period
- Breast conserving surgery rate
- Progressive disease rate
- Progression-free survival (PFS)
- Disease-free survival (DFS)

-Clinical response rate: Clinical response rate is defined as the proportion of patients who achieve a clinical response during Cycles 1-4 (pre-surgery). Clinical response will be assessed at each cycle, between Days 15-21 or on study Day 1 of the next cycle.

Clinical response is defined as complete response (CR), partial response (PR) stable disease (SD) and progressive disease (PD) and is identified as per local practice based on RECIST criteria (ref: Journal of the National Cancer Institute. Page 205, Vol 92, No. 3, Feb 2000) however, clinical response will be defined by the clinical team using RECIST criteria as a guide. Time to clinical response rate is defined as the time from the date of first dose received to the date of assessment of clinical response.

-Breast conserving surgery rate: This is defined as the proportion of patients who achieved breast conserving surgery out of the intent-to-treat population without inflammatory breast cancer, as these patients will receive mastectomy irrespective of their response to neoadjuvant treatment.

-Disease-free survival (DFS): This was defined as the time from the first date of no disease (i.e. date of surgery) to the first documentation of progressive disease or death. Any evidence of contralateral disease in-situ will not be identified as progressive disease. DFS was described separately in patients who achieve a pCR from those who did not and overall for all patients that had surgery.

Patients who were withdrawn from the study without documented progression and for whom there exists eCRF evidence that evaluations have been made, were censored at the date of the last assessment when the patient was known to be disease-free.

-Progression-free survival (PFS): This was assessed from the day of the 1st dose of treatment.

Reviewer Comment: *Event free survival (EFS) is the preferred long-term endpoint for neoadjuvant trials as per the Draft Neoadjuvant Guidance. However, both NEOSPHERE (WO2097) and TRYPHAENA (BO22280) were written and conducted prior to the Draft Neoadjuvant Guidance. EFS should be used in future trials.*

Guidelines for Assessment of Pathological Response

Pathologic assessment of pCR, following breast surgery was performed by local pathologists and not centrally reviewed. This assessment was conducted based on St Gallen's guidelines briefly discussed in the protocol. *(Source: Appendix 3 of NEOSPHERE protocol)* This was reported in the appropriate CRF section. The size of the tumor or the size of the gross area presumed to be tumor were measured and all gross alterations within the size of the primary tumor were described. The status of margins was recommended to be assessed. Also non-invasive components were

reported and specified separately. For each individual patient the pattern(s) of residual tumor needed to be described.

Reviewer Comment: *This protocol was not meant to be a registration protocol and did not pre-specify details regarding pathology specimen handling and assessment. As described in the Draft Neoadjuvant Guidance, more detailed guidelines for tissue handling and pathology assessment are recommended and pathologists should be blinded to the study treatment arm.*

NEOSPHERE (WO20697) Eligibility Criteria

INCLUSION CRITERIA

Disease Specific Inclusion Criteria:

1. Female patients with locally advanced, inflammatory or early stage, unilateral and histologically confirmed invasive breast cancer.
2. Primary tumor > 2cm in diameter.
3. HER2 positive breast cancer confirmed by a central laboratory. Tumors must be HER2+++ by IHC or FISH/CISH + (FISH/CISH mandatory for HER2 ++ tumors).
4. Availability of FFPE tissue for central confirmation of HER2 eligibility (FFPE tumor tissue will subsequently be used for assessing status of biomarkers).

General Inclusion Criteria:

5. Age ≥ 18 years.
6. Baseline LVEF ≥ 55% (measured by echocardiography or MUGA).
7. Performance status ECOG ≤ 1.
8. At least 4 weeks since major unrelated surgery, with full recovery.
9. A negative pregnancy test must be available for pre-menopausal women and for women less than 2 years after the onset of menopause.
10. Signed informed consent.

EXCLUSION CRITERIA

Cancer related Exclusion Criteria:

1. Metastatic disease (Stage IV) or bilateral breast cancer.
2. Previous anticancer therapy or radiotherapy for any malignancy. Other malignancy, except for carcinoma in situ of the cervix or basal cell carcinoma.
3. Hematological, biochemical and organ function:
    a. Inadequate bone marrow function (e.g. Absolute Neutrophil Count (ANC) < 1.5 x 109/L, Platelet count < 100 x 109/L and Hb < 9 g/dL).

   b. Impaired liver function: (e.g. serum [total] bilirubin > 1.25 x ULN (with the exception of Gilbert's syndrome), AST, ALT > 1.25 x ULN, albumin < 25 g/L
   c. Inadequate renal function, serum creatinine > 1.5 x ULN.
4. Uncontrolled hypertension (systolic > 150 and/or diastolic > 100), unstable angina,
5. CHF of any NYHA classification, serious cardiac arrhythmia requiring treatment (exception, atrial fibrillation, paroxysmal supraventricular tachycardia), history of myocardial infarction within 6 months of enrollment, or LVEF < 55%.
6. Dyspnea at rest or other diseases which require continuous oxygen therapy.

Other Study Drug Related Exclusion Criteria:

7. Severe uncontrolled systemic disease (e.g. hypertension, clinically significant cardiovascular, pulmonary, metabolic, wound-healing, ulcer, or bone fracture).
8. Subjects with insulin-dependent diabetes.
9. Pregnant and/or lactating women.
10. Subjects with reproductive potential not willing to use highly effective non-hormonal method of contraception or two effective forms of non-hormonal contraception. Contraception use must continue for the duration of study treatment and for at least 6 months post discontinuation of study treatment. For details please see Section 7.2.4.
11. Received any investigational treatment within 4 weeks of study start.
12. Subjects with known infection with HIV, HBV, HCV.
13. Known hypersensitivity to any of the study drugs or excipients.
14. Subjects assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.

Reviewer Comment: *The eligibility criteria appear reasonable. However it is not clear why males were excluded.*

NEOSPHERE (WO20697) Trial Design and treatment plan:

Design: Patients were randomized to receive neoadjuvant therapy:

- Arm A: trastuzumab plus docetaxel
- Arm B: trastuzumab plus docetaxel plus pertuzumab
- Arm C: trastuzumab plus pertuzumab
- Arm D: pertuzumab plus docetaxel

Reviewer Comment: (b) (4)

Pertuzumab dose: 840 mg load IV; then 420 mg IV every 3 weeks x 4 cycles

Trastuzumab dose: 8 mg/kg load IV then 6 mg/kg every 3 weeks x 4 cycles neoadjuvant and up to 1 year total post-surgery

Docetaxel dose: 75 mg/m^2, with dose escalation to 100 mg/m^2, if tolerated, IV every 3 weeks for 4 cycles

Post-Surgery standard of care: 5-FU 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV every 3 weeks for 3 cycles. Hormonal therapy in HR+ patients and/or radiotherapy as per local practice after post-operative chemotherapy.

Safety: Adverse Events, Laboratory Parameters, LVEF by Echo or MUGA, Vital signs

NEOSPHERE (WO20697) Statistical Methods:

Pathological complete responses were established after 4 cycles of therapy and surgery, approximately 4 months from randomization. Pathological complete response rate was calculated for each arm by dividing the number of patients achieving pCR by the intent-to-treat (ITT) population.

A pCR rate of 25% was expected in Arm A and Arm D. A pCR rate of 40% in Arm B or Arm C would be of clinical interest. The following three individual hypotheses were tested using a one-sided Cochrane Mantel-Hansel test at an alpha level of 0.1.

Arm A versus Arm B
- Null hypotheses: pCR A rate = pCR B rate
- Alternative hypothesis: pCR A rate ≠ pCR B rate

Arm A versus Arm C
- Null hypotheses: pCR A rate = pCR C rate
- Alternative hypothesis: pCR A rate ≠ pCR C rate

Arm D versus Arm B
- Null hypotheses: pCR D rate = pCR B rate
- Alternative hypothesis: pCR D rate ≠ pCR B rate

As there were three individual comparisons, a Simes multiplicity adjustment was applied to the individual p-values obtained at the end of the study to maintain the overall false positive risk of 0.2. With a sample size of 400 (100 per arm) the study would have 80% power to detect an absolute percentage difference of 15% between arms for each of the three primary comparisons.

The comparisons were stratified by:
- Operable (T2-3, N0-1, M0), locally advanced (T2-3, N2 or N3, M0; T4a-c, and N, M0) and inflammatory (T4d, any N, M0)
- ER and/or PgR status (positive vs. both negative)

PFS: time from date of randomization to progressive disease or death

DFS: DFS was assessed only in patients who underwent surgery. DFS was defined as time from date of primary surgery to the first documentation of progressive (recurrent) disease or death.

PFS and DFS results are to be submitted in a follow-up report.

Reviewer Comment: *Alpha level of 0.1 is usually not acceptable for a study that will support marketing aproval, however, this study was not originally meant to be a registration study.*

Definition of Analysis Populations

ITT population: All randomized patients, regardless of whether they received any study medication. (This is a modification to the protocol definition of "all patients receiving any amount of study medication.") In analyses using the ITT population, patients are grouped according to their randomized treatment arm. All efficacy outputs were produced for the ITT population. The ITT population is the same as the All Patients population used for data listings, where data are reported by randomized treatment.

Per Protocol Population: A subset of the ITT population. It excludes patients who were deemed to have any major protocol violations prior to the adjuvant phase of the study. In analyses using the PP population, patients are grouped according to their randomized treatment arm. Selected efficacy outputs are produced for this population. The PP population includes patients who received ≥ 3 cycles (and not > 4 cycles) of their randomized study medication in the neoadjuvant setting.

Safety population: Patients who received at least one dose of study medication and at least one safety assessment performed at baseline. Patients were assigned to treatment groups according to treatment actually received.

Arm A (T+D)
-Trastuzumab: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV thereafter q3w
-Docetaxel: 75 mg/m^2 IV for Cycle 1 then 100 mg/m^2 IV for Cycles 2-4 q3w, if no dose limiting toxicity occurs.

Arm B (T+P+D)
-Trastuzumab: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV thereafter q3w
-Pertuzumab: loading dose 840 mg/kg IV, followed by 420mg IV q3w

-Docetaxel: 75 mg/m^2 IV for Cycle 1 then 100 mg/m^2 IV for Cycles 2-4 q3w, if no dose limiting toxicity occurs.

Arm C (T+P)
-Trastuzumab: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV thereafter q3w
-Pertuzumab: loading dose 840 mg/kg IV, followed by 420mg IV q3w

Arm D (P+D)
-Pertuzumab: loading dose 840 mg/kg IV, followed by 420mg IV q3w
-Docetaxel: 75 mg/m^2 IV for Cycle 1 then 100 mg/m^2 IV for Cycles 2-4 q3w, if no dose limiting toxicity occurs.

Drugs were administered in the order listed on the same day. Treatment cycles were 21 days in duration for four cycles and then the patient underwent breast surgery. Pertuzumab was administered only in the neoadjuvant treatment period.

Adjuvant Treatment:

Arm A, B and D
-Trastuzumab: 6mg/kg IV q3w for 3 cycles (Cycle 5-7). Thereafter, trastuzumab 6 mg/kg IV. every three weeks from Cycle 8 continuing until Cycle 17 for patients in Arm A and B and until Cycle 21 for Arm D patients.
-5-fluorouracil: 600mg/m^2 IV q3w for 3 cycles (Cycles 5-7)
-Epirubicin: 90 mg/m2 IV q3w for 3 cycles (Cycles 5-7)
-Cyclophosphamide: 600mg/m^2 IV q3w for 3 cycles (Cycles 5-7)

Arm C
-Trastuzumab: 6mg/kg IV q3w for 3 cycles (prior to docetaxel in cycles 5-8 and prior to FEC in cycles 9-11) Cycle 5-7). Continue 6mg/kg q3w from cycle 12 until cycle 17.
-Docetaxel: 75 mg/m2 IV for Cycle 5 then 100 mg/m2 IV for Cycles 6-8 q3w, if no dose limiting toxicity occurs.
-5-fluorouracil: 600mg/m^2 IV q3w for 3 cycles (Cycles 9-11)
-Epirubicin: 90 mg/m^2 IV q3w for 3 cycles (Cycles 9-11)
-Cyclophosphamide: 600mg/m^2 IV q3w for 3 cycles (Cycles 9-11)

After completion of post-operative chemotherapy, patients received radiotherapy as per local clinical standard. For patients whose tumors were estrogen-receptor positive, hormone manipulation administered as per local clinical standard. Drugs were administered in the order listed on the same day. Treatment cycles were 21 days in duration

Rationale for Dose Selection:

Trastuzumab: Standard every 3 week dose (rather than weekly regimen) for its greater convenience with 8 mg/kg IV loading dose followed by 6mg/kg IV every three weeks.

Pertuzumab: Loading dose of 840mg pertuzumab IV followed by 420mg IV every three weeks. This is the FDA approved dose of pertuzumab in combination with trastuzumab and docetaxel in the metastatic breast cancer setting.

Docetaxel: Starting dose of 75 mg/m^2, with escalation to 100mg/m^2 based on individual tolerability. A lower starting dose was used as 100mg/m^2 of docetaxel is not tolerated by all patients.

5-Fluorouracil/Epirubicin/Cyclophosphamide: 5-Fluorouracil 600mg/m^2 IV +epirubicin 90 mg/m^2 IV +cyclophosphamide 600 mg/m^2 IV given in combination every three weeks. These are the standard doses used in the adjuvant chemotherapy combination.

NEOSPHERE (WO20697) Drug Administration:

Trastuzumab was administered as an 8mg/kg IV loading dose and 6mg/kg in subsequent cycles. Pertuzumab was administered as an 840mg IV loading dose and 420mg IV in subsequent cycles. Docetaxel was administered 75mg/m^2 IV every 3 weeks. For patients who tolerated the first cycle without and dose limiting toxicities, docetaxel was increased to 100mg/m^2 for the remaining cycles. 5-fluorouracil was administered 600 mg/m^2 every three weeks. Epirubicin was administered 90 mg/m^2 every three weeks. Cyclophosphamide was administered 600mg/m^2 every 3 weeks. The dose of trastuzumab, docetaxel, 5-fluorouracil, epirubicin, and cyclophosphamide was recalculated if the patient's body weight had changed by >10% from baseline.

Treatment cycles were 21 days in duration.

The first infusion of trastuzumab was administered over 90 minutes and patients were observed for at least 30 minutes for infusion related symptoms. The first infusion of pertuzumab was administered over 60 minutes and patients were observed for 60 minutes for infusion related symptoms. Subsequent infusions of trastuzumab and pertuzumab could be delivered over 30 minutes if the first infusion was tolerated without infusion related adverse events.

Dose Delay and Modification:

Dose reductions due to toxicity were not allowed for trastuzumab and pertuzumab. Dose delay was allowed to asses or treat adverse events as shown in Error! Reference source not found.**.**

Dose reductions for docetaxel, 5-fluorouracil, epirubicin, and cyclophosphamide are allowed as indicated in the relevant SPC and managed as per local practice. Prophylactic GCSF administration to maintain the dosing schedule was allowed.

In the neoadjuvant setting, up to two dose delays (each up to two weeks) were allowed before the patient was discontinued from the study.

Table 6 : NEOSPHERE (WO20697): Dose Modifications for Pertuzumab and Trastuzumab Toxicity (Applicant Table)

Toxicity related to study treatment	Action
1. Non-hematological, Grade 1 or 2 (NCI-CTCAE; excluding cardiac*) toxicity	Continue with study treatment
2. Non-hematological, Grade 3 or 4 (NCI-CTCAE; excluding cardiac*) toxicity	Hold study treatment (all medication in the cycle) until recovery to Grade ≤ 2. Toxicity resolved to Grade ≤ 1 within a maximum of 2 weeks calculated from last administration: Resume study treatment. Toxicity did NOT resolve to Grade ≤ 2 within a maximum of 2 weeks calculated from last administration: Discontinue the related study medication (pertuzumab or trastuzumab) permanently. Continue treatment as deemed suitable by local investigator.
3. Recurrence of non-hematological, Grade 3 or 4 (NCI-CTCAE; excluding cardiac*) toxicity upon re-challenge	Discontinue the related study medication (pertuzumab or trastuzumab) permanently. Continue treatment as deemed suitable by local investigator.
4. Cardiac toxicity (asymptomatic drop in LVEF or symptomatic congestive heart failure)	Study treatment (all medication in the cycle) to be held, continued or resumed according to the algorithm depicted in Appendix 5. Related study medication (pertuzumab or trastuzumab) to be discontinued permanently in case of symptomatic CHF
5. Cardiac toxicity (NCI-CTCAE; other cardiac toxicities not covered by treatment algorithm in Appendix 5)	Actions must follow rules 1. to 3. for non-hematological toxicities
6. Hematological toxicity – Neutropenia	Hold study treatment (all medication in the cycle) until neutrophils ≥ 1.5 x 10^9/L.

* Severity corresponding to NYHA criteria (see Appendix 4)

(Source: NEOSPHERE (WO20697) protocol, page 54)

The schedule of assessments is provided below in Table 7 *(source NEOSPHERE (WO20697) protocol, Table 2).*

Table 7: NEOSPHERE (WO20697): Schedule of Assessments (Applicant Table)

Table 2 Schedule of Assessments (Treatment Period)

Cycle	Screening / Baseline		Pre-Surgery Treatment Period				Surgery	Post-Surgery Treatment Period									Final Visit/ Withdrawal from Treatment[a]
			1	2	3	4	4	5	6	7	8	9	10	11	12 - 17	18- 21	
Day	-28	-14	1	1	1	1	22 -35	1	1	1	1	1	1	1	1	1	
Informed Consent[b]	X																
Medical History, including demographics	X																
Complete physical examination	X							X									X
Limited physical examination			X	X	X	X			X	X	X	X	X	X	X	X	
Vital Signs[c]			X	X	X	X		X	X	X	X	X	X	X	X	X	X
Weight[d]			X	X	X	X		X[t]	X	X	X	X	X	X	X	X	X
Height		X						X[t]									
Bone scan[6]	X																
Mammogram (and ultrasound as per local practice)		X				X											X
CBC with platelet & differential counts		X	X[1]	X	X	X		X[t,2]	X[2]	X[2]	X	X[2]	X[2]	X[2]	X[y]	X[y]	X
INR and aPTT		X						X[t]									
Serum chemistries & electrolytes[e]		X	X[1]	X	X	X		X[t,v]									X
Limited serum chemistries & electrolytes[f]									X[2]	X[2]	X	X	X[2]	X[2]			
Urinalysis (dipstick)		X						X									
Pregnancy Test[g]		X			X				**X**			**X**			**X[5]**	**X[5]**	**X**
Hormone receptor status[h]	X																
Clinical tumor assessment/breast examination[i]	X		X	X	X	X			X	X	X	X	X	X	X	X	X
Chest X-ray	X																
12-Lead ECG[j]	X							X[j]			X[j]				X[j]		X
ECHO or MUGA[k]	X			X		X		X			X			X	X[k]		X
ECOG Performance Status		X	X[1]	X	X	X		X[t]	X	X	X	X	X	X	X	X	X

Cycle	Screening / Baseline		Pre-Surgery Treatment Period				Surgery	Post-Surgery Treatment Period									Final Visit/ Withdrawal from Treatment[a]
			1	2	3	4	4	5	6	7	8	9	10	11	12 - 17	18 -21	
Day	-28	-14	1	1	1	1	22 -35	1	1	1	1	1	1	1	1	1	
Serum sample for ECD/HER2 and HER ligands		X					X[3]										
Optional BSR serum and plasma collection [m]		X		X		X	X	X			X			X	X[m]		X
Clinical genotyping full blood sample for assessment of Fcγ polymorphism		X															
FFPE tumor tissue sample for confirmation of HER2 status[n]	X		X[o]				X										
Surgery including Pathological Response Assessment[p]							X[p]										
Docetaxel[q]			X[1]	X	X	X		X[4]	X	X	X						
Trastuzumab[r]		X[1]	X[1]	X	X	X		X	X	X	X	X	X	X	X	X[z]	
Pertuzumab[s]		X[1]	X[1]	X	X	X											
5-Fluorouracil[v]								X[2]	X[2]	X[2]		X[2]	X[2]	X[2]			
Epirubicin[v]								X	X	X		X	X	X			
Cyclophosphamide[v]								X	X	X		X	X	X			
Adverse Events[w]			Continuously														
Concomitant medication[x]			Continuously														

Notes:

a) Final visit or early termination visits will optimally be scheduled for 28 days following the last dose of study medication and will include all evaluations scheduled for the final visit

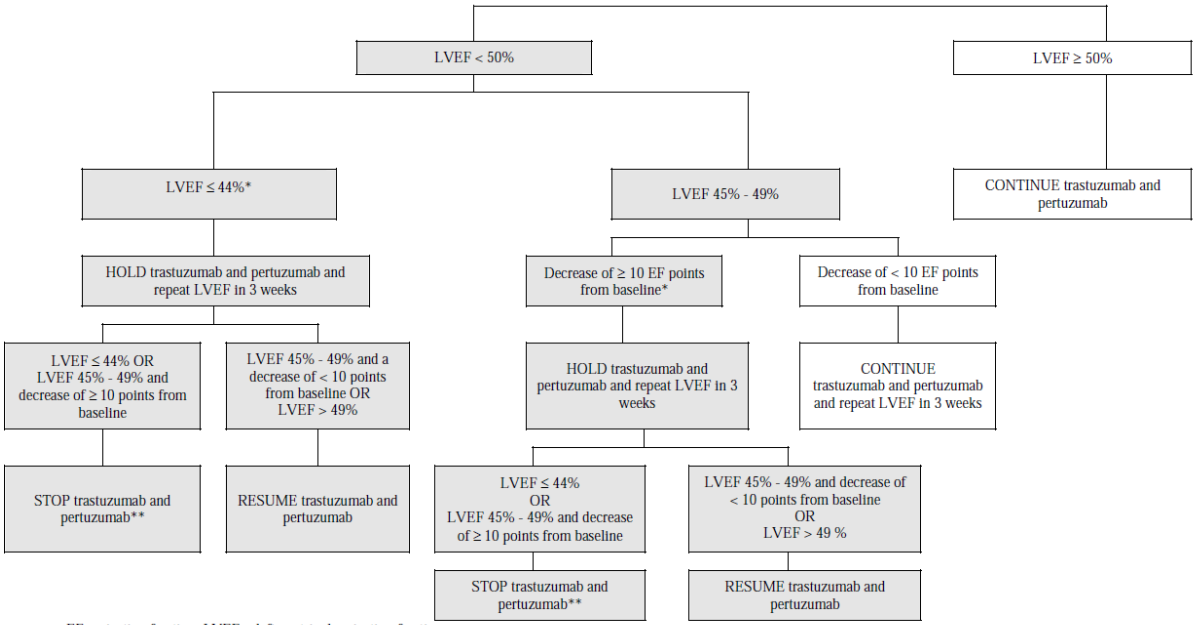
b) Written informed consent must be obtained before any study specific screening assessments are performed.

c) On days of chemotherapy alone, vital signs will be taken pre-dose. During trastuzumab infusion, vital signs will be taken pre and post infusion. During the Pertuzumab infusion, vital signs will be taken pre, post infusion and at the end of the observation period.
d) Weight to be measured on Day 1 of each cycle and compared to baseline. If ± 10% variation occurs the trastuzumab and chemotherapeutic doses will be recalculated.
e) Glucose, urea/BUN, creatinine, uric acid, total protein, albumin, total, direct and indirect bilirubin, alkaline phosphatase, AST, ALT, LDH. Serum electrolytes (P-, Ca2+, Na+, K+, Cl-).
f) Alkaline phosphatase, AST, ALT, LDH, total, direct and indirect bilirubin and creatinine.
g) For all women of childbearing potential, and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization, pregnancy tests must be performed via serum β-HCG at baseline to be performed within 7 days prior to first administration of study medication (study Day 1 or -7 for the sub study). A urine pregnancy test should be administered during the treatment period within 3 days prior to every third treatment cycle starting at Cycle 3 (and as clinically indicated) and at the treatment discontinuation visit and then every 3 months thereafter until six months post discontinuation of study treatment. Any positive urine pregnancy test must be confirmed via serum β-HCG. Treatment period pregnancy test results must be available prior to the drug infusion.
h) Oestrogen-receptor positive patients to be prescribed anti-estrogen therapy as per local guidelines after completion of post-operative chemotherapy or discontinuation of the study.
i) Clinical tumor assessment will be performed as per local medical practice.
j) A baseline ECG to be performed for all patients. ECGs are required to allow assessment prior to and after the completion of FEC chemotherapy. For all patients, ECG to be performed within ≤ 7 days prior 8. For Arm A, B and D patients ECG to be performed within ≤ 7 days prior to Cycle 5. For Arm C only, ECG to be performed ≤ 7 days prior to Cycle 12. Additional ECG to be performed as clinically indicated.
k) For patients whose LVEF cannot be assessed by ECHO, LVEF can be assessed by MUGA. The same method should be used throughout the study for each patient and preferably performed and assessed by the same assessor. All assessments will be performed between Days 15-21 of the cycle to allow evaluation of the results before the next treatment cycle, with the exception of Cycle 5 which will be performed within ≤ 7 days prior to Cycle 5 dosing. Between Cycles 12-16, only ONE LVEF assessment is required at Cycle 15 between Days 15-21. Cycle 17 will be performed ≥ 28 days after dosing. Patients in Arm D only, require an additional assessment ≥ 28 days after the last dosing (Cycle 21).
l) Screening measurements can be used as Day 1 assessments.
m) Samples to be taken at baseline, on treatment and during surgery. Sample collection on treatment would ideally take place according to schedule of LVEF evaluation, but if it is not possible to take the samples on the same day as the LVEF, the samples can be taken shortly before the next dose of study medication is given. Between Cycles 12-17, only ONE sample is required at Cycle 15.
n) FFPE tumor tissue sample will also be used for biomarker analysis.
o) For centers participating in the sub study where dosing of trastuzumab and pertuzumab commences on Day -7 a second core biopsy is required on Cycle 1 Day 1 prior to administration of study treatment.
p) Pathological response assessment to be performed using the resected tumor according to Appendix 3/guidelines provided.
q) Arm A, B & D patients to receive Docetaxel 75 mg/m2 at Cycle 1 then 100 mg/m2 every 3 weeks (Cycles 2-4). Arm C patients to receive Docetaxel 75 mg/m2 at Cycle 5 then 100 mg/m2 every 3 weeks (Cycle 6-8). CBC to be performed on Day 8 of Cycles 1-4 and Cycles 5-8 to assess hematological toxicity prior to dose escalation or if needed dose reduction for docetaxel in Arm A, B, D and C, respectively.
r) All patients to receive trastuzumab loading dose 8 mg/kg on Cycle 1 Day 1. Cycle 2 -4 all patients to receive trastuzumab 6 mg/kg.

NEOSPHRE (WO20697) Cardiac Monitoring Algorithm:

Echocardiography or MUGA was used to assess LVEF. LVEF had to be done ≤ 4 weeks prior to the first administration of trastuzumab and/or pertuzumab and must be ≥ 55% before the subject could be enrolled in the study. The same method of assessment was to be used throughout the study for each patient. LVEF was performed between Days 15 and 21 of Cycles 2, 4, 8, 11 and 15, after surgery and with ≤ 7 days prior to Cycle 5. LVEF assessment was to be performed ≥ 28 days after Cycle 17 and patients in Arm 1, B and C proceeded into the treatment free follow up period. Patients in Arm D had an LVEF assessment ≥ 28 days after Cycle 17 or prior to Cycle 18 dosing. The algorithm for continuation and discontinuation of pertuzumab and/or trastuzumab is based on LVEF assessments presented in Error! Reference source not found..

Figure 2 : NEOSPHERE (WO20697): Cardiac Monitoring Algorithm (Applicant Figure)



EF = ejection fraction; LVEF = left ventricular ejection fraction.

* Report as AE – Reporting term 'Left ventricular systolic dysfunction'

** Report as AE (eCRF AE eform) and Non-Serious Event of Special Interest (SAE form) Reporting term 'Left ventricular systolic dysfunction'

Note: LVEF assessment results must be available before/or on the day of the next scheduled trastuzumab and pertuzumab/placebo equivalent administration.

(Source: WO20697 protocol Appendix 5)

NEOSPHERE (WO20697): Protocol Amendments:

Protocol Version B (dated 4th December, 2007)

The following key changes were made:

- Addition of a fourth treatment arm (arm D), in order to evaluate the efficacy of pertuzumab, in the absence of trastuzumab, in the neoadjuvant setting, with corresponding update of schedule of assessment and dosing information. There were a total of 29 patients who had been recruited on the original protocol prior to introduction of this arm.
- Increase in the number of patients participating in the study from 180 to 400, and corresponding increase in the number of centers, from 45-55 to 100.
- Amendment of efficacy endpoints, hypothesis testing and analyses to reflect addition of arm D and increased patient numbers.
- Addition of an exclusion criterion, to exclude patients with insulin-dependent diabetes from the study.
- Clarification of the offset dosing schedule.

Protocol Version C (11th December 2008)

- Correction of the tumor-node-metastasis (TNM) classes used to classify patients' disease for the stratification groups operable, locally advanced, or inflammatory cancer for this study.

Protocol Version D (27th June 2009)

- Updates to: the definition of post-menopausal women, the contraceptive requirements for women of child bearing potential as recommended by the MHRA in accordance with the ICH M3 guideline, and the pregnancy testing scheduling.
- Clarification of clinical response definition.

5.3.2 Phase 2 TRYPHAENA (BO22280)

Title:

"A randomized, multicenter, multinational Phase II study to evaluate pertuzumab in combination with trastuzumab, given either concomitantly or sequentially with standard anthracycline-based chemotherapy or concomitantly with a non-anthracycline-based chemotherapy regimen, as neoadjuvant therapy for patients with locally advanced, inflammatory or early stage HER2-positive breast cancer"

Objectives:

Primary objective: A preliminary assessment of the tolerability of neoadjuvant treatment with one of the following treatment regimens:

Arm A: 5-Fluorouracil, epirubicin with cyclophosphamide (FEC), trastuzumab and pertuzumab every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles.

Arm B: FEC every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles.

Arm C: Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab every three weeks, for six cycles.

Secondary objectives:

1. To make a preliminary assessment of the activity associated with each regimen as indicated by the rate of pathological complete response (pCR; defined as the absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery, following primary systemic therapy) in the breast.
2. To evaluate the safety profiles of each treatment regimen, including pre-operative (neoadjuvant) and post-operative (adjuvant) treatment (ie, trastuzumab).
3. To investigate the overall survival (OS), the time to clinical response (CR), time-to-response, disease-free survival (DFS) and progression-free survival (PFS) for each treatment arm.
4. To investigate the biomarkers that may be associated with primary and secondary efficacy endpoints in accordance with each treatment arm.
5. To investigate the rate of breast conserving surgery for all patients with T2-3 tumors for whom mastectomy was planned at diagnosis.

Safety endpoints:

• Incidence of symptomatic cardiac events as assessed by the Investigator (Grade 3, 4 or 5 symptomatic LVSD)
• Clinically significant LVEF declines over the course of the neoadjuvant period (LVEF decline of ≥10% from baseline and to a value of <50%).
• Incidence of symptomatic cardiac events and asymptomatic LVEF events
• LVEF measures over the course of the study
• Incidence and severity of AEs and SAEs
• Laboratory test abnormalities

Main Efficacy endpoint: pCR rate in the breast, evaluated after six cycles of treatment and surgery or following withdrawal from the study, whichever occurred sooner. pCR was defined at the time of surgery and the rate is the proportion of the ITT population that achieved a pCR. A 95% confidence interval (CI) was calculated around the observed pCR rate for each treatment arm in order to show the variability associated with the point estimate.

Other efficacy endpoints: Clinical response (CR) rate, time to clinical response, the proportion of patients achieving breast conserving surgery, overall survival (OS), disease free survival (DFS), progression-free survival (PFS) and an evaluation of biomarkers associated with response.

INCLUSION CRITERIA

1. Female patients with locally advanced, inflammatory or early stage, unilateral and histologically confirmed invasive breast cancer. The initial breast cancer assessment had to be performed by a physician with experience in surgery for breast cancer. Patients with inflammatory breast cancer must have had a core needle biopsy.
2. Primary tumor > 2cm in diameter.
3. HER2-positive breast cancer confirmed by a central laboratory. Tumors must be HER2 3+ by immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH)/ chromogenic in situ hybridization (CISH positive). FISH/CISH positivity mandatory for HER2 2+ tumors.
4. Availability of FFPE tissue (buffered formalin method of fixation was accepted) for central confirmation of HER2 eligibility (FFPE tumor tissue was subsequently used for assessing status of biomarkers).
5. Female patients, age ≥ 18 years.
6. Baseline LVEF ≥ 55% (measured by echocardiography or MUGA).
7. ECOG Performance Status ≤ 1
8. At least four weeks since major unrelated surgery, with full recovery.
9. A negative pregnancy test must have been available for premenopausal women and for women less than 12 months after the onset of menopause.

10. For women of childbearing potential, agreement 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 had to be continued for the duration of study treatment and for at least six months after the last dose of study treatment.
11. Signed informed consent.

EXCLUSION CRITERIA

1. Metastatic disease (Stage IV) or bilateral breast cancer.
2. Previous anticancer therapy or radiotherapy for any malignancy.
3. Other malignancy, except for carcinoma in situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin.
4. Inadequate bone marrow function (eg, absolute neutrophil count (ANC) < 1.5 x 109/L, platelet count < 100 x 109/L and Hb < 9 g/dL).
5. Impaired liver function: (eg, serum [total] bilirubin > 1.25 x upper limit of normal (ULN) (with the exception of Gilbert’s syndrome), AST, ALT > 1.25 x ULN, albumin < 25 g/L.
6. Inadequate renal function, serum creatinine > 1.5 x ULN.
7. Uncontrolled hypertension (systolic > 150 and/or diastolic > 100), unstable angina, congestive heart failure (CHF) of any New York Heart Association (NYHA) classification, serious cardiac arrhythmia requiring treatment (exceptions: atrial fibrillation, paroxysmal supraventricular tachycardia), history of myocardial infarction within six months of enrollment, or LVEF < 55%.
8. Dyspnea at rest or other diseases which require continuous oxygen therapy.
9. Severe uncontrolled systemic disease (eg, hypertension, clinically significant cardiovascular, pulmonary, metabolic, wound-healing, ulcer, or bone fracture).
10. Patients with insulin-dependent diabetes.
11. Pregnant and/or lactating women.
12. Patients with reproductive potential not willing to use a ‘highly effective’ method of contraception or two ‘effective’ methods of contraception.
13. Received any investigational treatment within four weeks of study start.
14. Patients with known infection with HIV, HBV, HCV.
15. Current chronic daily treatment with corticosteroids (dose of >10 mg methylprednisolone, or equivalent [excluding inhaled steroids])
16. Known hypersensitivity to any of the study drugs or excipients.
17. Patients assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

Reviewer Comment: *The eligibility criteria appear reasonable.*

TRYPHAENA (BO22280) Statistics:

The sample size was based on the primary (safety) endpoint. Approximately 75 patients per arm were planned to be recruited into the study (225 total).

Formal hypothesis testing was not planned. However, for pCR (the main efficacy endpoint) the approximate expected pCR rates were: Arm A: 50%, Arm B: 45% and Arm C: 40%. With this planned sample size, if these response rates were observed, the minimum true efficacy (lower bound of exact 95% confidence interval) of the estimates would be approximately A: 38.9% B: 33.8% C: 28.9%

For the assessment of incidence of symptomatic left ventricular systolic dysfunction (LVSD), if the true underlying incidence was 3%, the probability of observing more than five such events in a treatment arm was 0.025.

The Kaplan-Meier approach was used to estimate median PFS, DFS and time to clinical response for each treatment arm. The Cox proportional hazard model, stratified by operable, locally advanced, inflammatory breast cancer and estrogen and or progesterone receptor positivity were used to estimate the HR (i.e. the magnitude of treatment effect) and its 95% confidence interval (CI), for description purposes only.

To evaluate the effect of molecular markers on efficacy outcome, efficacy outcomes were summarized for all patients, and by treatment arm, within each subgroup determined by exploratory markers (exploratory biomarker analyses). Markers to be considered include the status of HER receptors, HER ligands, shed antigens (e.g. ECD/HER2), and other markers relevant for the HER family pathway. Efficacy outcomes considered for this analysis may include primary and secondary efficacy endpoints such as: pathological complete response rate, PFS, DFS and time to clinical response.

Design:

Phase 2, open-label, randomized, multinational, multi-center trial to evaluate the tolerability and activity associated with trastuzumab and pertuzumab when used in addition to anthracycline-based or carboplatin based chemotherapy regimens as neoadjuvant therapy in patients with HER2-positive breast cancer which is early stage and >2cm in diameter or locally advanced or inflammatory. Figure 3

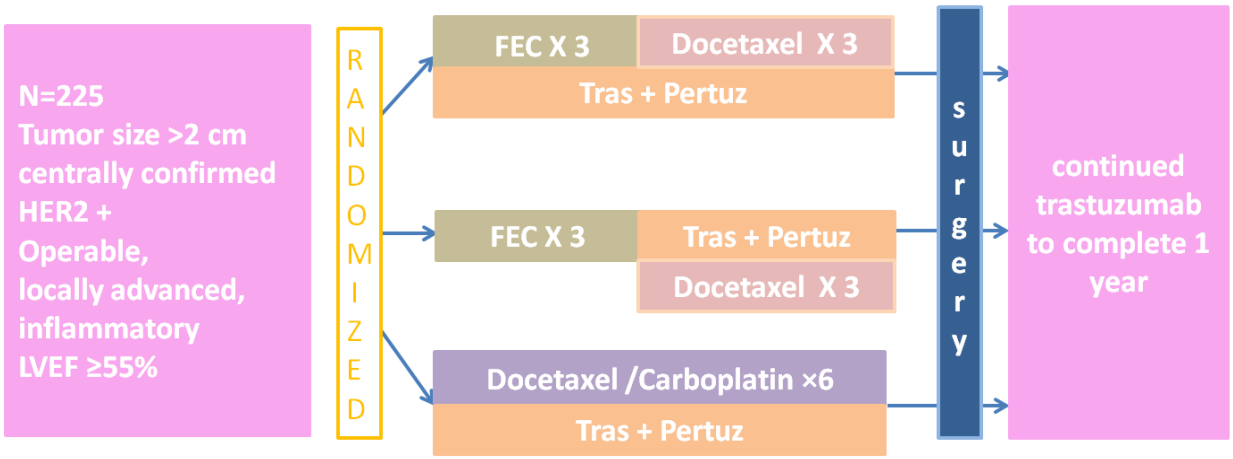
All patients were scheduled to receive trastuzumab, every three weeks up to one year from the start of trastuzumab treatment, regardless of any additional chemotherapy. For any patients who were also considered to require further post-surgery chemotherapy in addition to the standard six cycle neoadjuvant regimen, the recommendation was that the patients who received anthracycline-based neoadjuvant therapy (FEC) were given cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and the patients who received carboplatin-based neoadjuvant therapy (TCH), were given FEC. After the completion of surgery (and post-operative chemotherapy if required), patients received radiotherapy as per standard local clinical practice. Patients with tumors that were

estrogen-receptor positive received adjuvant hormonal therapy as per standard local clinical practice.

Patients whose neoadjuvant study treatment was discontinued prior to surgery were managed as per standard local clinical practice. Approximately 28 days after the last dose of study medication, patients underwent a final safety assessment (called Final Visit). After completion of the study treatment, patients were to be followed until disease progression or until five years after randomization of the last patient, whichever was earlier. After a patient had progressed they were to be followed for survival until the end of study. In case of withdrawal from the trial due to cardiac toxicity the patient was followed up for cardiac outcome, whenever possible.

Any patients whose disease progressed before the end of neoadjuvant therapy were withdrawn from study and treated as clinically indicated.
Patients who completed chemotherapy and surgery, but then relapsed (either during or at any time after completion of the follow-up treatment) were to be treated as clinically indicated and follow-up information about subsequent therapies and outcomes collected.

Figure 3: TRYPHAENA Study (BO22280) Design



FEC=5-FU, epirubicin, and cyclophosphamide; tras=trastuzumab; Pertuz=Pertuzumab

Reviewer Comment: *This is a well-designed study to assess the cardiac safety. However, the back-bone chemotherapy (FEC) is not the commonly used chemotherapy in the United States. Many also prefer paclitaxel vs. docetaxel in the adjuvant setting. However, there is no data comparing these Taxanes in the adjuvant setting*

Arm A
• 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2) followed by cyclophosphamide (600 mg/m2) for three cycles, followed by docetaxel for three cycles with trastuzumab (8 mg/kg on day 1 of the first treatment with epirubicin and 6 mg/kg every 3 weeks thereafter) and pertuzumab (840 mg on day 1 of the treatment with FEC with 420 mg every 3 weeks thereafter). The starting dose for docetaxel was 75 mg/m2 for Cycle 4

(first docetaxel cycle) then 100 mg/m^2 for Cycles 5-6, if no dose limiting toxicity occurred.

Arm B
• 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2) followed by cyclophosphamide (600 mg/m^2) for three cycles, followed by docetaxel for three cycles with trastuzumab (8 mg/kg on day 1 of the first treatment with docetaxel and 6 mg/kg every 3 weeks thereafter) and pertuzumab (840 mg on day 1 on the first day of docetaxel with 420 mg every 3 weeks thereafter). The starting dose for docetaxel was 75 mg/m2 for Cycle 4 (first docetaxel cycle) then 100 mg/m2 for Cycles 5-6, if no dose limiting toxicity occurred.

Arm C
Carboplatin (AUC6 followed by docetaxel on day 1 with trastuzumab (8 mg/kg on day 1 of the first treatment with carboplatin and docetaxel and 6 mg/kg every 3 weeks thereafter) and pertuzumab (840 mg on day 1 with 420 mg every 3 weeks thereafter) for six cycles. The dose for docetaxel is 75 mg/m^2 for all cycles.

Reviewer Comment: *The intravenous chemotherapy regimens used in this protocol were based on published data but not commonly used in the United States. Per the 2013 v3 NCCN guidelines preferred trastuzumab containing regimens are doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab (AC-TH), dose dense AC-TH and docetaxel, carboplatin and trastuzumab (TCH). Additionally, paclitaxel-Fluorouracil (5FU), epirubicin and cyclophosphamide (FEC) with trastuzumab is an acceptable neoadjuvant regimen per 2013 v3 NCCN guidelines.*

The schedule of assessments during treatment period and after that are provided below in Table 8 and Table 9. Additionally there *was an a*lgorithm for continuation and discontinuation of study medication based on LVEF Assessment (Figure 4)

Table 8: TRYPHAENA (BO22280): Schedule of Assessments (Treatment Period)

	Screening / Baseline		Pre-Surgery Treatment Period						Surgery	Post-Surgery Treatment Period												Final Visit/ Withdrawal from Treatment[b]
										Arms A. B and C											Arm B			
Cycle			1	2	3	4	5	6		7	8	9	10	11	12	13	14	15	16	17	18[r]	19	20	
Day	-28	-14	1	1	1	1	1	1	22 -35*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Clinical tumor assessment/breast examination[i]	X		X	X	X	X	X	X[2]		X	X	X	X	X	X	X	X	X	X	X	X[v]	X	X	X
Planned surgery assessment		X																						
Chest X-ray	X																							
12-Lead ECG[j]	X					X				X			X			X			X			X		X
ECHO or MUGA[k, x]	X			X		X		X		X			X		X			X			X[v]			X
ECOG Performance Status		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X[v]	X	X	X
Mandatory Serum sample for ECD/HER2 and HER ligands[w]		X							X[u]															
Optional RCR serum and plasma collection [m]		X		X		X		X	X	X			X		X			X			X[v]			X
Optional RCR Whole blood for DNA		X																						
Mandatory RCR clinical genotyping full blood sample for assessment of Fcγ polymorphism		X																						
Mandatory FFPE tumor tissue sample for confirmation of HER2 status[n]	X								X															
Surgery including Pathological Response Assessment[o]									X[o]															

	Screening / Baseline		Pre-Surgery Treatment Period						Surgery	Post-Surgery Treatment Period												Final Visit/ Withdrawal from Treatment[b]
										Arms A. B and C											Arm B			
Cycle			1	2	3	4	5	6		7	8	9	10	11	12	13	14	15	16	17	18[r]	19	20	
Day	-28	-14	1	1	1	1	1	1	22 -35*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Informed Consent[a]	X																							
Medical History, including demographics	X																							
Complete physical examination	X									X														X
Limited physical examination			X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X[v]	X	X	
Vital Signs[c]			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X[v]	X	X	X
Complete cardiac questionnaire			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X[v]	X	X	X
Weight[d]		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X[v]	X	X	X
Height		X								X														
Bone scan[y]	X																							
Mammogram[1] (and ultrasound as per local practice)		X						X[2]																X
CBC with platelet & differential counts[p]		X	X[Lp]	X[p]	X[p]	X[p]	X[p]	X[p]		X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p,v]	X[p]	X[p]	X
INR and aPTT or PTT		X								X														
Serum chemistries & electrolytes[e]		X	X[l]	X	X	X	X	X		X														X
Limited serum chemistries & electrolytes[f]											X	X	X	X	X	X	X	X	X	X	X[v]	X	X	
Urinalysis (dipstick)		X								X														
Pregnancy test[g]		X			X			X		X			X			X			X			X[v]		X
Hormone receptor status[h]	X																							

	Screening / Baseline		Pre-Surgery Treatment Period						Surgery	Post-Surgery Treatment Period												Final Visit/ Withdrawal from Treatment[b]
										Arms A, B and C											Arm B			
Cycle			1	2	3	4	5	6		7	8	9	10	11	12	13	14	15	16	17	18[v]	19	20	
Day	-28	-14	1	1	1	1	1	1	22 -35*	1	1	1	1	1	1	1	1	1	1	1	1	1	
ARM A: Trastuzumab[q]			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X				
Pertuzumab[r]			X	X	X	X	X	X																
FEC			X	X	X																			
Docetaxel						X	X	X																
Arm B: Trastuzumab[q]						X	X	X		X	X	X	X	X	X	X	X	X	X	X	X[v]	X	X	
Pertuzumab[r]						X	X	X																
FEC			X	X	X																			
Docetaxel						X	X	X																
ARM C: Trastuzumab[q]			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X				
Pertuzumab[r]			X	X	X	X	X	X																
Docetaxel/carboplatin			X	X	X	X	X	X																
Adverse events[s]	Continuously																							
Concomitant medication [t]	Continuously																							

NOTES:

a) Written informed consent must be obtained before any study specific screening assessments are performed.

b) Final visit or early termination visits will optimally be scheduled for 28 days following the last dose of study medication and will include all evaluations scheduled for the final visit
c) On days of chemotherapy, vital signs will be taken pre and post-dose in line with local prescribing information. During trastuzumab infusion, vital signs will be taken pre and post infusion. During the pertuzumab infusion, vital signs will be taken pre, post infusion and at the end of the observation period.
d) Weight to be measured on Day 1 of each cycle and compared to cycle 1 day 1 baseline weight. If ± 10% variation occurs the trastuzumab and chemotherapeutic doses will be recalculated.
e) Glucose, urea/BUN, creatinine, uric acid, total protein, albumin, total, direct and indirect bilirubin, alkaline phosphatase, AST, ALT, LDH. Serum electrolytes (P-, Ca2+, Na+, K+, Cl-).
f) Alkaline phosphatase, AST, ALT, LDH, total, direct and indirect bilirubin and creatinine.
g) For women of childbearing potential, a serum β-HCG test to be performed within 7 days prior to first administration of study medication (study Day 1). A urine pregnancy test should be performed every 3rd cycles during neoadjuvant and adjuvant chemotherapy; a positive test must be confirmed by a serum β-HCG test.
h) Patients with estrogen-receptor positive disease should receive anti-estrogen therapy as per local guidelines after completion of post-operative chemotherapy or discontinuation of the study.
i) Clinical tumor assessment will be performed as per local medical practice but should be performed by a physician with experience in surgery for breast cancer.
j) A baseline ECG to be performed for all patients, between Days -28 and Day -1 . ECGs are required to allow assessment prior to and after the completion of FEC neo-adjuvant chemotherapy (Arms A and B only) and every 3 cycles in the adjuvant setting (all patients). ECG should also be performed for any patients in Arm C who are deemed to require FEC post-surgery (prior to and after completion of FEC). Additional ECG to be performed as clinically indicated. For all patients on treatment, ECG to be performed within ≤ 7 days prior to dosing date.
k) For patients whose LVEF cannot be assessed by ECHO, LVEF can be assessed by MUGA. The same method should be used throughout the study for each patient and preferably performed and assessed by the same assessor. LVEF will be performed between Days 15 and 21 of Cycles 2, 4, and 6 for patients in all treatment arms to allow assessment prior to the next dosing cycle and surgery. After surgery and within ≤ 7 days prior to Cycle 7 dosing an LVEF assessment will be performed. LVEF assessments will then be performed between Days 15 and 21 of Cycles 10, 12 and 15 for patients in all treatment arms, to allow assessment prior to the next dosing cycle. For patients in arms A and C an LVEF assessment will also be carried out at the withdrawal visit. Patients in arm B will have an additional LVEF assessment performed between Days 15 and 21 of cycle 18 and then another assessment carried out at the withdrawal visit.
l) Screening measurements can be used as Day 1 assessments.
m) In those patients who consent to the optional serum sampling and sign the consent, samples to be taken at baseline, surgery and while on treatment. Sample collection on treatment would ideally take

place according to schedule of LVEF evaluation, but if it is not possible to take the samples on the same day as the LVEF, the samples can be taken shortly before the next dose of study medication is given.
n) FFPE tumor tissue sample will also be used for additional biomarker analysis if sufficient specimen and if patient agrees and signs optional informed consent.
o) Pathological response assessment to be performed using the resected tumor according to Appendix 3/guidelines provided.
p) CBC to be performed prior to study medication administration at each cycle (baseline sample is suitable for Cycle 1). CBC to be performed at Day 8 of cycles 1-6 and at Day 8 of any post-surgery cycles if chemotherapy is given (e.g. for those patients for whom additional therapy is deemed necessary by the Investigator).
q) All patients to receive trastuzumab loading dose 8 mg/kg on Cycle 1 Day 1 (except Arm B patients who start trastuzumab at Cycle 4), thereafter all patients to receive trastuzumab 6 mg/kg.
r) All patients to receive pertuzumab loading dose 840 mg from cycle 1 AFTER completion of the trastuzumab infusion plus a one hour observation period for cycle one only (except Arm B patients who start pertuzumab at Cycle 4). Subsequent cycles: pertuzumab maintenance dose of 420 mg to be administered after trastuzumab.
s) Adverse events will be collected during the full course of the study until 28 days after the last dose of study medication, and related SAEs and SUSARs will be collected long term. From the informed consent signature date until Study Day 1 (or date of first dosing of study medication) SAEs will be collected and recorded on the SAE form. No eCRF page should be completed. From Study Day 1 (or date of first dosing) onwards SAEs will be recorded in the eCRF and in the SAE form.
t) Concomitant medication will be recorded until the end of the treatment period.
u) Samples to be taken at surgery or 24 hours prior to surgery.
v) Cycles 18-20 assessments required for patients in arm B only.
w) sample to be taken within 7 days prior to the first administration of study medication (or on study day 1 provided that the sample is taken prior to the first study drug dose), only if the patient is eligible for, and will be enrolled into, the study
x) ECHOs and MUGAs will be recorded and sent to a central lab for confirmation of results.
y) In the absence of radioactive isotopes, MRI scan (with gadolinium enhancement if required) or F18 PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.
* Days from start of C6

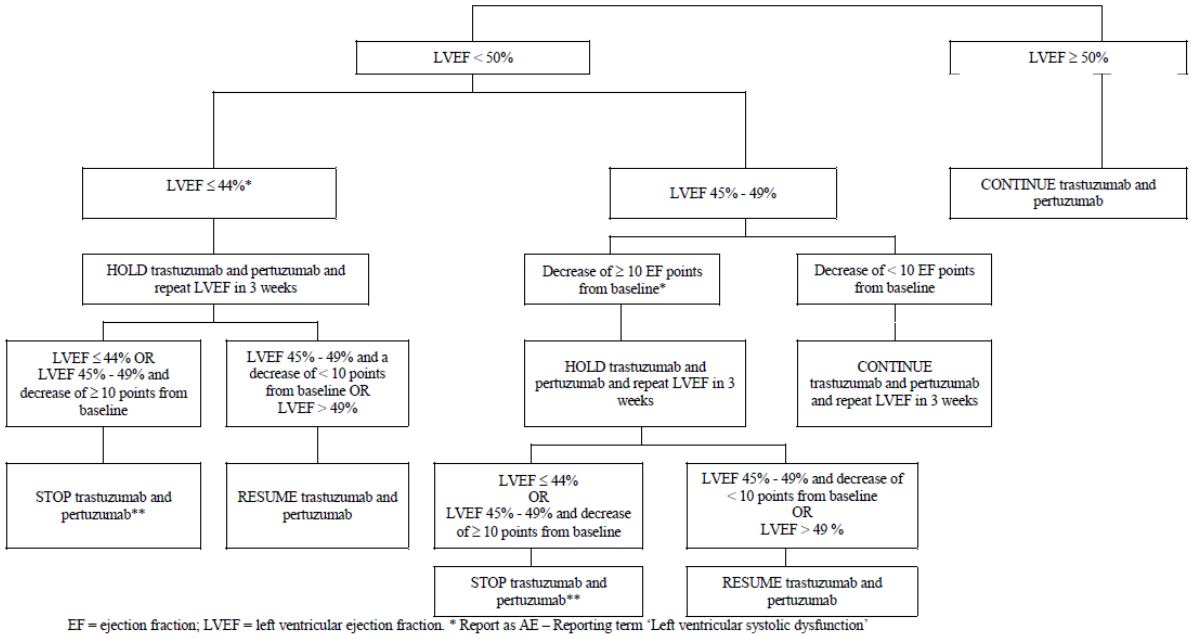
(Source TRYPHAENA (BO22280) protocol, Table 3, page 41)

Table 9: TRYPHAENA (BO22280): Schedule of Assessments (Treatment-free Follow-up)

	Follow-up After Treatment Period[a]	
Day/Week/Month	**Every 3 months[a]**	**As needed**
Limited Physical Examination	X	
Vital Signs	X	
ECOG PS	X	
CBC with platelet & differential counts		X
Serum chemistries & electrolytes		X
Pregnancy test	X[b]	
ECHO or MUGA	X[d]	
Chest X-ray		X
Ultrasound liver/skeletal survey and/or bone scan[c]		X
Complete survival follow-up	X	

(Source TRYPHAENA (BO22280) protocol, Table 4, page 45)

Figure 4: TRYPHAENA (BO22280): Algorithm for Continuation and Discontinuation of Study Medication Based on LVEF Assessment



EF = ejection fraction; LVEF = left ventricular ejection fraction. * Report as AE – Reporting term 'Left ventricular systolic dysfunction'

** Report as AE (eCRF AE eform) and Non-Serious Event of Special Interest (SAE form) Reporting term 'Left ventricular systolic dysfunction'

Note: LVEF assessment results must be available before/or on the day of the next scheduled trastuzumab and pertuzumab/placebo equivalent administration.

(Source: Protocol section Appendix 5)

TRYPHAENA (BO22280) Protocol Amendments

It appears that the protocol was amended once as the final version is called BO22280B. A summary of amendments are following (Source CSR):

- Screening mammogram extended to be performed up to 42 days prior to the start of treatment. The mammogram at screening, pre-surgery and final visit/withdrawal can be replaced by MRI at investigator discretion

5.3.3 Phase 3 CLEOPATRA (WO20698/TOC4129g)

Please refer to original BLA 125409 review by Dr. Gideon Blumenthal for details of CLEOPATRA protocol.

6 Review of Efficacy

6.1 Indication

Genentech proposed the following indication in their BLA submission:

> "Neoadjuvant treatment of breast cancer, in combination with trastuzumab and docetaxel for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin."

The TRYPHAENA (BO22280) study that is the basis of adding carboplatin in the indication was a small study and does not isolate the efficacy or safety of pertuzumab. Additionally, based on the internal discussions and concerns that were raised from Oncologic Drug Advisory Committee (ODAC), a language referring to the accelerated approval status was added to the indication. For these reasons a modified indication was proposed by our office:

> Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin. 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.

6.2 Methods

This review will focus primarily on the efficacy results of the single randomized controlled trial, NEOSPHERE (WO20697). In addition to the main study NEOSPHERE (WO20697), a review of efficacy data from the randomized phase 2 study TRYPHAENA (BO22280), and from a phase 3 study CLEOPATRA (WO20698/ TOC4129g) will be included. For a summary of the study designs of NEOSPHERE, TRYPHAENA and CLEOPATRA, see sections 5.3.
For the statistical review, please see Dr. Lijun Zhang's review.

6.2 NEOSPHERE (WO20697) Study

6.2.1 NEOSPHERE Subject Disposition

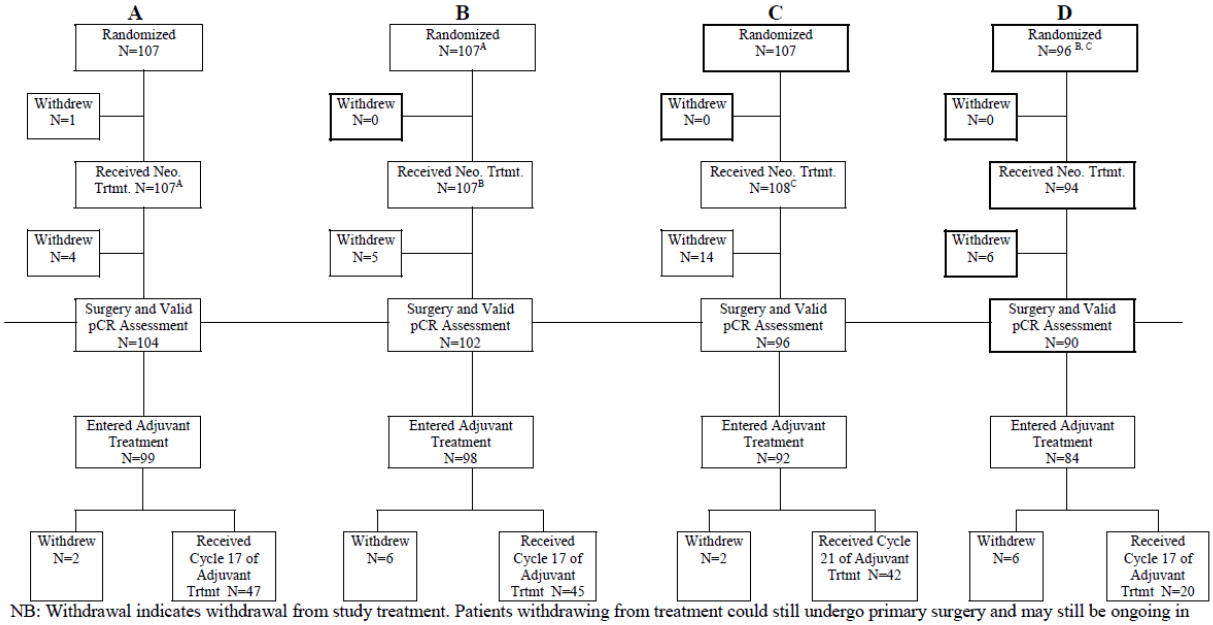
From the first patient visit on December 17, 2007 to the data cut-off of December 22, 2009, a total of 603 patients with early stage HER2-positive breast cancer were screened, and 417 patients were enrolled from 59 centers in 16 countries (Australia, Austria, Brazil, Canada, Italy, Mexico, Peru, Poland, Republic of Korea, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Thailand, United Kingdom). A total of 417 patients were randomized, 107 to Arm A, 107 to Arm B, 107 to Arm C, and 96 to Arm D, comprising the ITT population (Table 10 and Figure 5). The region with highest enrollment was Europe. **Error! Reference source not found.** summarized the analysis population in the NEOSPHERE (WO20697) study.

Table 10: NEOSPHERE (WO20697): Patient Disposition (As of March 9, 2012)

	Arm A H+T	Arm B P+H+T	Arm C P+H	Arm D P+T
Patients randomized	107	107	107	96
Received neoadjuvant treatment	107	107	108	94
Withdrew from neoadjuvant treatment	4	5	14	6
Withdrew from study during neoadjuv period	2	4	10	3
Entered adjuvant treatment phase	103	102	94	88
Withdrew from adjuvant treatment phase	5	8	4	14
Completed adjuvant treatment	98	94	90	74
Withdrew from study during adjuvant tx phase	8	4	2	5
Total study withdrawals during treatment phase	10	8	12	8
Entered post-treatment FU period	97	99	96	86
Withdrew from post-treatment FU period	11	7	10	12
Continued on study FU as of 9 March 2012	86	92	86	74

H=Herceptin; P=Pertuzumab; T=Docetaxel
(Source Sponsor CSR page 42)

Figure 5: NEOSPHERE (WO20697): Patient Disposition



NB: Withdrawal indicates withdrawal from study treatment. Patients withdrawing from treatment could still undergo primary surgery and may still be ongoing in the follow up phase). Withdrawal at any time up to the first adjuvant trial treatment cycle was counted as withdrawal from the neoadjuvant phase.

A One patient randomized to arm B (patient 152114/2141) actually received arm A treatment, and is therefore included in arm A safety population.

B Patient 116812/2523 was randomized to arm D but received treatment according to arm B.

C Patient 116836/3652 was randomized to arm D but received treatment according to arm C.

(Source CSR figure 2, page 75)

Table 11: NEOSPHERE (WO20697): Analysis Populations by Trial Treatment

Number of patients	Arm A H+T	Arm B P+H+T	Arm C P+H	Arm D P+T
ITT population	107	107	107	96
Received Randomized Treatment	106	106	107	94
Received a Non-Randomized Treatment	0	1	0	2
Received no Treatment	1	0	0	0
Safety Analysis Population	107	107	108	94

H=Herceptin; P=Pertuzumab; T=Docetaxel

(Source CSR Table 7, page 78)

6.2.2 NEOSPHERE (WO20697) Protocol Violations

The majority of protocol deviations were inclusion or exclusion criteria violations (Table 12). Across the treatment arms, between 8 and 11 patients per arm reported at least one inclusion criteria violation, of which the majority were due to a positive or missing baseline pregnancy test result. Between 7 and 14 patients reported at least one exclusion criteria violation, the most common of which was missing data for, or impaired liver function.

Table 12: NEOSPHERE (WO20697): Summary of Protocol Deviations by Trial Treatment (22DEC2009)

Number of patients	Arm A H+T	Arm B P+H+T	Arm C P+H	Arm D P+T
Inclusion criteria violations: • Positive pregnancy test or missing result • Baseline ECOG performance status > 1 or missing 1 • Baseline LVEF < 55% or missing 0 • Breast cancer not histologically confirmed • FFPE tissue for central confirmation of HER2 eligibility • not available • Not confirmed HER 2 positive by central lab on or prior to study day 1 • Primary tumor <= 2cm in diameter	11	11	8	8
Exclusion criteria violations • Impaired liver function or information missing • Other malignancy, except for carcinoma in situ of the cervix or basal cell carcinoma • Inadequate bone marrow function or information missing • Metastatic disease (Stage IV) or bilateral breast cancer • Insulin-dependent diabetes • Severe uncontrolled systemic disease	14	7	11	7
On Study violations • No. with at least one On Study Violation • No assessment for pCR and did not progress or die after at least 1 dose of each randomized study medication • Patient safety compromised in the adjuvant period • Patient safety compromised in the neo-adjuvant period • Received < 3 cycles of neo-adjuvant study medications and did not progress or die after at least 1 dose of each randomized study medication • Did not receive any study medication • Subject received treatment that was not randomized to	5	11	7	6

(Source CSR Table 8 Page 79), H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comment: *The protocol deviations appear to be random and distributed relatively equally across all arms.*

6.2.3 NEOSPHERE (WO20697) Demographics

The breakdown of enrollment by country is presented below in Table 13. Enrollment by region is shown in Table 14. Europe had the highest accrual (245).

Table 13 : NEOSPHERE (WO20697): Enrollment by country (Reviewer Table)

Country	Arm A H+T	Arm B P+H+T	Arm C P+H	Arm D P+T
Australia	1	0	0	96
Austria	0	1	0	94
Brazil	10	5	12	6
Canada	5	5	7	3
Great Britain	1	0	0	88
Italy	15	19	11	14
Mexico	0	0	1	74
Peru	2	3	2	5
Poland	14	12	12	8
Korea	7	8	11	86
Russia	20	13	10	12
Spain	8	21	9	74
Sweden	4	4	2	2
Switzerland	1	1	4	1
Taiwan	11	9	11	8
Thailand	8	6	2	3
Total	107	107	94	108

H=Herceptin; P=Pertuzumab; T=Docetaxel

Table 14: NEOSPHERE (WO20697): Enrollment by Region (Reviewer Table)

Region	Arm A H+T	Arm B P+H+T	Arm C P+H	Arm D P+T
Asia	26	22	22	25
Europe	63	71	62	49
North America	5	5	10	8
South America	12	9	13	14
Other	1	0	0	0

H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comment: *There is a diverse international representation. However, there was no enrollment from the United States.*

Patient's baseline characteristics are represented in Table 15. The two arms of interest are highlighted in gray.

Table 15: NEOSPHERE (WO20697): Baseline Characteristics (Reviewer Table)

Characteristics	Arm A H+T N=107	Arm B P+H+T N=107	Arm C P+H N=107	Arm D P+T N=96
Age (median)	51	50	50	49
Race **Caucasian** **Black** **Asian** **Other**	75% 0 23% 2%	72% 2% 21% 5%	74% 1% 21% 5%	64% 3% 26% 7%
HR+	47%	47%	48%	48%
Inflammatory	6%	9%	6%	5%
Locally Advanced	34%	30%	33%	32%
Operable	60%	61%	61%	63%
LN status **N0** **N1** **N2** **N3**	30% 45% 21% 5%	29% 50% 21% 0	30% 43% 22% 5%	29% 43% 23% 5%

H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comment: *Patients are well matched in terms of age, race and tumor characteristics. Approximately half of the patients were Hormone-receptor positive, 40% had inflammatory or locally advanced breast cancer and 70% were clinically node positive.*

6.2.4 NEOSPHERE (WO20697) Analysis of Primary Endpoint

The protocol specified pCR definition was absence of invasive breast cancer in the breast only (ypT0/is). Based on the protocol pCR definition, the addition of pertuzumab to trastuzumab and docetaxel led to a 16.8% improvement in pCR rate, which was statistically significant. (Table 16)

Table 16: NEOSPHERE (WO20697): pCR (ypT0/is), ITT Population (FDA Table)

	Arm A H+T (n=107)	Arm B P+H+T (n=107)	Arm C P+H (n=107)	Arm D P+T (n=96)
# of Responders (%)	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)
95% CI	20.6%,38.5%	36.1%, 55.7%	10.3%, 25.3%	15.8%, 33.7%
Comparison		B vs. A	C vs. A	B vs. D
Difference of Response (95% CI)		16.8% (4.1%, 29.6%)	-12.2% (-23.3%, -1%)	21.8% (9.0%, 34.6%)
Ratio of Response Rate		1.58 (1.10, 2.27)	0.58 (0.35, 0.97)	0.52 (0.35, 0.79)
Odds Ratio		2.16 (1.20, 3.88)	0.44 (0.22, 0.89)	2.84 (1.52, 5.32)
CMH p-value		0.0094	0.0198	0.0010
Adjusted CMH p-value		0.0141	0.0198	0.0030
Adjusted unstratified Fisher's exact p-value		0.024	0.05	0.0039
Adjusted rerandomization test p-value		0.0117	0.0202	0.0042

H=Herceptin; P=Pertuzumab; T=Docetaxel

The FDA preferred definition of pCR is the absence of invasive breast cancer in breast and axilla (ypT0/is ypN0).

A statistically significant 17.8% improvement in pCR rate is seen with the addition of pertuzumab to trastuzumab and docetaxel. (Table 17)

Table 17 : NEOSPHERE (WO20697): pCR (ypT0/is ypN0), ITT Population (FDA Table)

	Arm A H+T (n=107)	**Arm B P+H+T (n=107)**	**Arm C P+H (n=107)**	**Arm D P+T (n=96)**
# of Responders (%)	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)
95% CI	14.1, 30.5%	30.0, 49.2%	5.9, 18.8%	10.7, 26.8%
Comparison		B vs. A	C vs. A	B vs. D
Difference of Response (95% CI)		17.8% (5.7, 29.9%)	-10.3% (- 20.1, -0.47%)	21.5% (9.6, 33.5%)
Ratio of Response Rate		1.83 (1.19, 2.81)	0.52 (0.27, 0.99)	0.45 (0.28, 0.74)
Odds Ratio		2.46 (1.30, 4.66)	0.40 (0.18, 0.89)	3.28 (1.65, 6.53)
CMH p-value		0.0042	0.0223	0.0006
Adjusted CMH p-value		0.0063	0.0223	0.0018
Adjusted unstratified Fisher's exact p-value		0.011	0.0635	0.0033
Adjusted rerandomization test p-value		0.0036	0.0218	0.0006

H=Herceptin; P=Pertuzumab; T=Docetaxel

In Table 18, pCR results based on protocol specified and FDA preferred definitions are shown.

Table 18: NEOSPHERE (WO20697): Efficacy Results Using Two Pathological Complete Response Definitions (FDA Table)

	pCR (ypT0/isypN0)		**pCR (ypT0/is)**	
	Arm A H+T	**Arm B P+H+T**	**Arm A H+T**	**Arm B P+H+T**
	N=107	**N=107**	**N=107**	**N=107**
pCR, n (%)	23 (21.5%)	42 (39.3%)	31 (29.0%)	49 (45.8%)
95% CI	14.1, 30.5	30.0, 49.2	20.6, 38.5	36.1, 55.7
Difference of pCR Rates	17.8% (5.7%, 29.9%)		16.8% (4.1%, 29.6%)	
p-value*	0.0063		0.0141	

T=docetaxel, P=pertuzumab, H=trastuzumab
* with Simes corr. for CMH test
ypT0/isypN0 = Absence of invasive cancer in the breast and axillary nodes; DCIS allowed,
ypT0/is = Absence of invasive cancer in the breast and DCIS allowed; regardless of nodal involvement

Reviewer comment: *The results are consistent using both definitions.*

6.2.5 NEOSPHERE Analysis of Secondary Endpoints

Secondary endpoints of the study were:

- Best tumor response/clinical response during neoadjuvant period
- Time to first clinical response during neoadjuvant period
- Clinical response at the last assessment in neoadjuvant period
- Breast conserving surgery rate
- Progressive disease rate
- Progression-free survival (PFS)
- Disease-free survival (DFS)

Some of the secondary endpoint results are summarized in Table 19,Table 20, Table 21, and Table 22.

Table 19: NEOSPHERE (WO20697): Breast Conserving Surgery Patients with T2-3 Stage Tumor

	Arm A H+T N=107	**Arm B P+H+T N=107**	**Arm C P+H N=107**	**Arm D P+T N=96**
Planned Mastectomy, N	62	56	62	60
BCS achieved, N	14	13	12	19
% (95% CI)	22.6% (12.9%, 35.0%)	23.2% (13.0%, 36.4%)	19.4% (10.4%, 31.4%)	31.7% (20.3%, 45.0%)

H=Herceptin; P=Pertuzumab; T=Docetaxel; *(Source CSR Table 25 Page 103)*

Table 20: NEOSPHERE (WO20697) Surgical Procedures (FDA Table)

	Arm A H+T (N=103)	Arm B P+H+T (N=101)
Breast Surgery		
Lumpectomy	**10**	**8**
Mastectomy	**76**	**74**
Quadrantectomy	**15**	**19**
None	**2**	**0**
Axilla		
SLN only	**7**	**6**
ALND +/-SLN	**95**	**95**
Unknown	**1**	**0**

H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comment: *The addition of neoadjuvant pertuzumab to the treatment regimen did not decrease the rate of breast conserving surgery. This may be due to many factors. Patients and doctors may have already decided about the type of surgery desired, regardless of the amount of response to the neoadjuvant regimen. Additionally, pCR is an endpoint for which results are not known prior to performing the surgery and there is no reliable imaging method to assess and predict a pCR avoid surgery. At this time, surgery is the standard of care, even when there is felt that there is a full clinical response to chemotherapy.*

Table 21: NEOSPHERE (WO20697): Overall Response per Clinical Breast Exam (unconfirmed CR and PR)

	Arm A H+T N=107	Arm B P+H+T N=107	Arm C P+H N=107	Arm D P+T N=96
N	97	100	98	88
Responders, N	79	88	65	65
% (95% CI)	81.4% (72.3%, 88.6%)	88.0% (80.0%, 93.6%)	66.3% (56.1%, 75.6%)	73.9% (63.4%, 82.7%)

H=Herceptin; P=Pertuzumab; T=Docetaxel; *(Source CSR Table 21 Page 97)*

Reviewer Comment: *As expected, the ORR per clinical exam results are consistent with the pCR results.*

Table 22: NEOSPHERE (WO20697): Disease Progression and Death (FDA Table)

Cutoff date: March 9, 2012	Arm A H+T N=107	Arm B P+H+T N=107	Arm C P+H N=107	Arm D P+T N=96
All events (Death + Disease Progression)	12 (11.2%)	11 (10.3%)	19 (17.8%)	16 (16.7%)
Disease Progression During Neoadjuvant Period	0	1	8	2
Disease Recurrence Post Surgery	12 (11.2%)	9 (8.4%)	11 (10.3%)	14 (14.9%)
Deaths	2 (1.9%)	1 (0.9%)	1 (0.9%)	5 (5.2%)

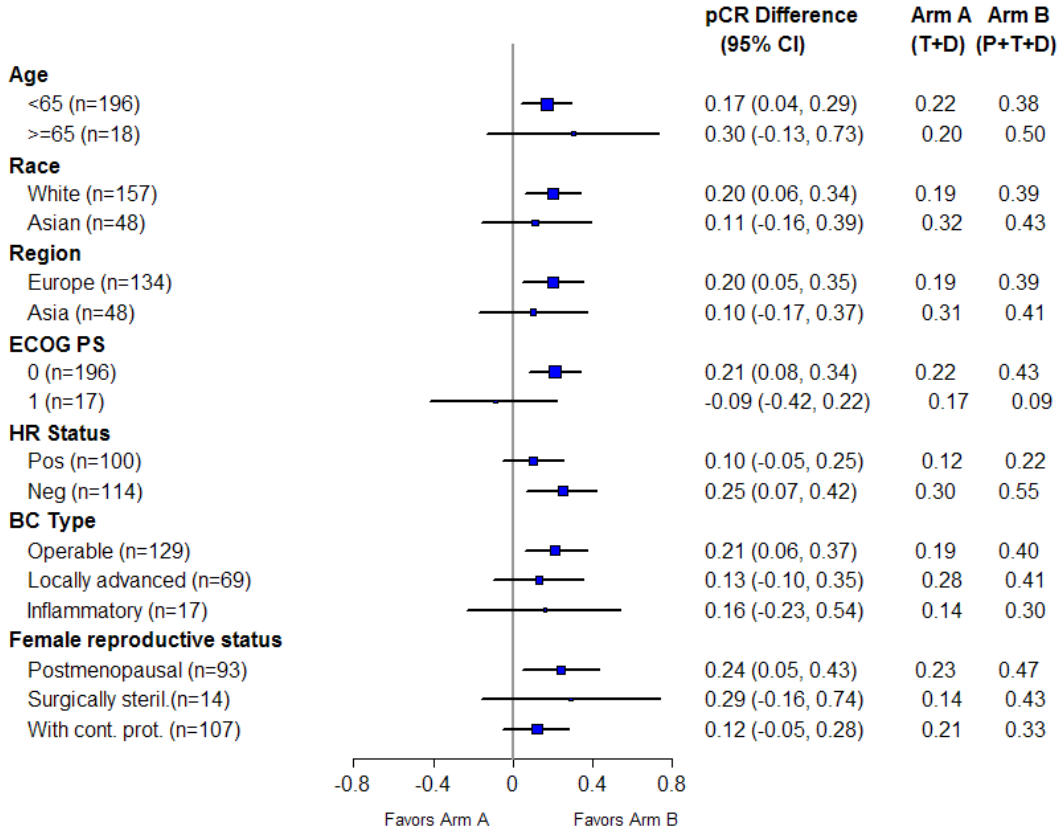
H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comment: *As of the most recent cutoff date of March 2012, only around 60 disease progression or death events have occurred overall cross the 4 arms. This study was small and not powered for survival or EFS. DFS and, PFS are secondary endpoints that will be analyzed 5-yrs after the last patient randomization per protocol.*

6.2.6 NEOSPHERE (WO20697) Subpopulations

The pCR results were consistent in all pre-defined subgroups favoring the pertuzumab treatment arm.(Figure 6) However, the improvement in pCR rates with the addition of pertuzumab in the hormone receptor negative subgroup was 24% compared to 10% in the hormone receptor positive subgroup. (Table 23)

Figure 6: NEOSPHERE Forest plot pCR (ypT0/is ypN0) (FDA Forest Plot)



Reviewer Comment: *The treatment effect is consistent in the different subgroups.*

Table 23: Subgroups Results Based on Hormone Receptor Status (FDA Table)

	NEOSPHERE		TRYPHAENA		
	H + T	**P + H + T**	**P+H+FEC/ P+H+T**	**FEC/ P+H+T**	**P+TCH**
Hormonal receptor-negative	N=57	N=57	N=34	N=40	N=37
pCR % [95% CI]	30 [18.4, 43.4]	54 [40.7, 67.6]	79 [62, 91]	65 [48, 80]	84 [68, 94]
Hormonal receptor-positive	N=50	N=50	N=39	N=35	N=40
pCR % [95% CI]	12 [4.5, 24.3]	22 [11.5, 36.0]	46 [30, 63]	49 [31, 66]	50 [34, 66]

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comment: *Although, the treatment effect is consistent in the different subgroups, the improvement in pCR rate in the hormone receptor (HR) positive patients is less and the CI crosses zero. However, we know from pooled FDA analysis that patients with HER2 / HR negative tumors had a less pCR rate and the addition of trastuzumab led to less improvement in pCR.[11] This signal was also observed in the NeoALLTO, CLEOPATRA, and EMILIA trials.[6-12-13] This may be due to the heterogeneity of HR positive patients and different biology of their tumor. There are some groups that benefit and some that do not benefit from the addition of pertuzumab. Genentech is currently conducting the PERTAIN study, which will evaluate the benefit of concurrent hormonal therapy and dual anti-Her2 therapy in the metastatic setting.[14]*

6.3 Supportive Neoadjuvant Study (TRYPHAENA/BO22280) Results

6.3.1 TRYPHAENA (BO22280) Subject Disposition

A total of 300 patients were screened, and 225 were randomized. Please see Figure 7

Figure 7: TRYPHAENA (BO22280) Patient Disposition (Applicant Figure)

(Source: CSR figure 2)

At the time of the clinical cut-off date, June 21, 2011, for the primary analysis, 51 patients in Arm A, 57 patients in Arm B and 53 patients in Arm C were alive and still on treatment.

6.3.2 TRYPHAENA (BO22280) Protocol Violations

Details of protocol violations are shown in Table 24.

Table 24: TRYPHAENA (BO22280) Protocol Violations (Applicant Table Modified by FDA)

Number of patients	P+H+FEC/ P+H+T	FEC/ P+H+T	P+TCH
Inclusion criteria violations: • Baseline LVEF < 55% • Baseline performance status ECOG > 1 or missing • HER2-negative breast cancer or HER2-positive breast cancer not confirmed by central laboratory • Positive pregnancy test or missing result • Primary tumor < 2cm in diameter tissue for central • confirmation of HER2 eligibility • Women of childbearing potential failed to use a 'highly-effective', non-hormonal form of contraception or two 'effective' forms of non-hormonal contraception by the patient and/or partner	10	4	5
Exclusion criteria violations • Impaired liver function or information missing • Inadequate bone marrow function or information missing • Metastatic disease (Stage IV) or bilateral breast cancer	9	4	6
On Study violations • Initiation of herbal remedies • Patient did not receive any study medication • Patient received > 6 cycles of Neoadjuvant treatment • Patient safety compromised in Neoadjuvant phase* • Received < 50% of pertuzumab & trastuzumab Neoadjuvant treatment (< 2 cycles) • Received < 50% of pertuzumab & trastuzumab Neoadjuvant treatment (< 3 cycles)	17	20	18

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel; (Source: CSR Table 9, Page 81-82)

Reviewer Comment: *The majority of violations were relatively minor and do not appear to compromise the integrity of the trial.*

6.3.3 TRYPHAENA (BO22280) Demographics

The study population was primarily Caucasian, with a median age of 49-50. (Table 25) Forty eight to 58% of patients were HR negative. The majority of patients had either operable (64-73%) or locally advanced breast cancer (20-31%) at baseline.

Table 25: TRYPHAENA (BO22280) Demographics (Applicant Table Modified by FDA)

Characteristics	P+H+FEC/ P+H+T N=72	FEC/ P+H+T N=75	P+TCH N=76
Female	100%	100%	100%
Age (median)	49	49	50
Race			
Black	4 (5.6%)	3 (4.0%)	2 (2.6%)
Caucasian	55 (76.4%)	52 (69.3%)	64 (84.2%)
Oriental	12 (16.7%)	18 (24.0%)	10 (13.2%)
Other	1 (1.4%)	2 (2.7%)	-

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel; (Source: CSR Table 10)

Reviewer Comment: *Patient baseline characteristics are balanced. Black patients were under-represented in the study.*

Table 26: TRYPHAENA (BO22280) Baseline Tumor Characteristics (Applicant Table Modified by FDA)

	P+H+FEC/ P+H+T	FEC/ P+H+T	P+TCH
Breast Cancer Subtype			
Ductal	69	70	72
Lobular	0	2	2
Medullary	0	0	1
Tubular	2	0	0
Mucinous	0	1	0
Comedo	0	0	1
Inflammatory	5	4	4
Other	3	1	3
Not Known	3	1	0
Estrogen receptor (ER) status			
Negative	37	44	37
Positive	36	31	39
Unknown	-	-	1
Progesterone receptor (PgR) status			
Negative	44	52	47
Positive	29	23	30
Breast cancer type			
Inflammatory Breast Cancer	5	4	4
Locally Advanced	15	17	24
Operable	53	54	49

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel; (Source: CSR Table 11, 12, and 13)

Reviewer Comment: *There was a slight imbalance in TNM classifications, with less operable breast cancer patients on TCH arm. Since the primary endpoint of study is cardiac safety, this imbalance will not bias the study results.*

6.3.4 TRYPHAENA (BO22280) Analysis of Primary Endpoints

Cardiac safety was the primary endpoint of this study. Please see Safety section 7 for the cardiac safety details (Reviewed by Dr. Wedam).

6.3.5 TRYPHAENA (BO22280) Analysis of Secondary Endpoints

Secondary endpoints were pCR rate in the breast (ypT0/is), DFS, PFS, and OS. Higher pCR rates were observed in the 3 pertuzumab treatment arms compared to the NEOSPHERE (WO20697) study possibly due to the incorporation of the anthracycline regimen preoperatively. The results were consistent using the two pCR definitions (ypT0/is and ypT0/isypN0), see Table 27. Similar to the NEOSPHERE (WO20697) study results, the pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors (46.2% to 50.0% and 65.0% to 83.8% respectively).

Table 27: TRYPHAENA (BO22280) pCR Results (FDA Table)

	P+H+FEC/P+H+T N= 73	**FEC/P+H+T N= 75**	**P+TCH N= 77**
pCR[1], n (%) 95% CI	45 (61.6%) [49.5, 72.8]	43 (57.3%) [45.4, 68.7]	51 (66.2%) [54.6, 76.6]
pCR[2] , n (%) 95% CI	41 (56.2%) [44.1, 67.8]	41 (54.7%) [42.7, 66.2]	49 (63.6%) [51.9, 74.3]

FEC=5-fluorouracil, epirubicin, cyclophosphamide, T= docetaxel, P= Pertuzumab, H= trastuzumab, TCH=docetaxel, carboplatin, trastuzumab, CI=Confidence Interval

[1] ypT0/is, [2] ypT0/isypN0, 95% CI for one sample binomial using Pearson-Clopper method.

6.4 Supportive Metastatic Study (CLEOPATRA) Results

Please see Dr. Gideon Blumenthal's review of the Original BLA 125409.

6.5 Efficacy Discussions

6.5.1 Foreign Data

The NEOSPHERE (WO20697) study was conducted entirely outside of the United States. During the review of this application, we questioned whether the results of this study were applicable to the patients of United States. There are only 28 patients in the NEOSPHERE (WO20697) study from North America and none were from US, but there were no apparent differences in the efficacy results for pertuzumab in different regions or races. (Table 28, Figure 8)

Figure 8: NEOSPHERE (WO20697) Enrollment by Region

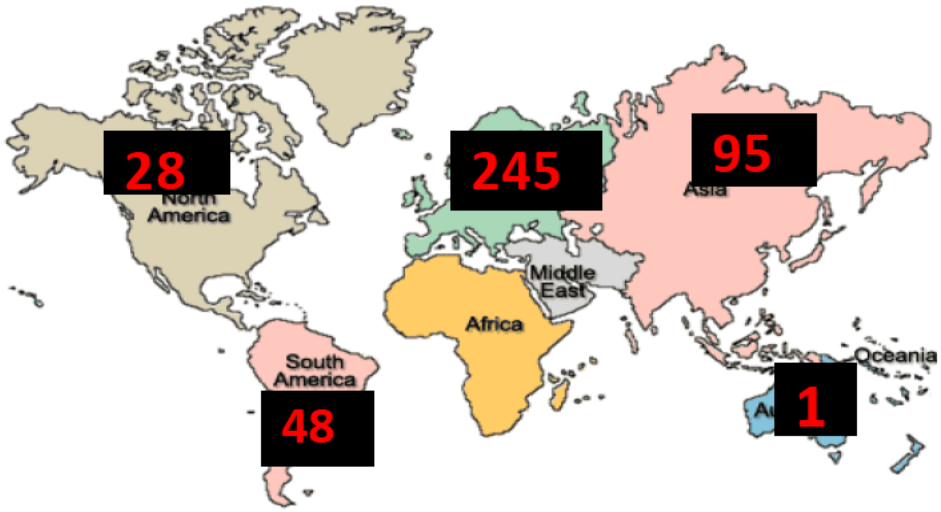


Table 28: NEOSPHERE (WO20697): pCR Results by Region & Race

	Arm A H+T N=107	Arm B P+H+T N=107
Region		
Asia	8/26 (30.8%)	9/22 (40.9%)
Europe	12/63 (19.1%)	28/71 (39.4%)
North America	0/5 (0%)	2/5 (40%)
South America	2/12 (16.7%)	3/9 (33.3%)
Australia	1/1 (100%)	0
Race		
White	15/80 (18.8%)	30/77 (39.0%)
Black	0	1/ 2 (50%)
Asian	8/25 (32%)	10/23 (43.5%)
Other	0/2 (0%)	1/5 (20%)

H=Herceptin; P=Pertuzumab; T=Docetaxel

6.5.2 Anthracycline-Containing Regimen

The anthracycline regimen and sequence that was used in the NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies is not widely used in the US. Both studies used epirubicin as part of FEC chemotherapy as opposed to doxorubicin which is more commonly used in the United States. We do not have any data regarding use of a doxorubicin based regimen pre-operatively with dual anti-HER2 therapy at this time. Additionally, the chemotherapy in NEOSPHERE (WO20697) was split before and after surgery as opposed to giving it all prior to surgery as typically done in a neoadjuvant therapy. In TRYPHAENA (BO22280), all the chemotherapy was given prior to surgery which led to higher pCR rates as discussed previously. Since the TRYPHAENA (BO22280) study was small, and does not isolate the effect of pertuzumab, we do not have sufficient safety information to recommend the pre-operative regimens that were used.

6.5.3 Optimal Duration of Pertuzumab Therapy

Pertuzumab was only given during the neoadjuvant period, for 4 cycles in the NEOSPHERE (WO20697) study and for 3-6 cycles in the TRYPHAENA (BO22280) study. In the confirmatory APHINITY trial that is conducted in the adjuvant setting, pertuzumab is given for 1 year, similar to trastuzumab. At this time, there is not enough information to use dual anti HER2 therapy for 1 year.

Reviewer comment: *Duration of therapy with trastuzumab has been studied in many trials and based on the most recent results of the PHARE and HERA trials, 1 year of adjuvant therapy is now recommended.* [15-16] *The optimal duration of pertuzumab therapy needs to be further studied in future trials.*

6.5.4 Pathology Assessments

The NEOSPHERE (WO20697) and TRYPHAENA (BO22280) studies were designed and conducted, before the release of FDA's draft guidance for industry, regarding the use of pCR as an endpoint, to support accelerated approval of drugs in the neoadjuvant setting.

Since these studies were conducted prior to this guidance, there are some limitations. The pathologists were not blinded and the standard operating procedures were not pre-specified. Future studies should follow the current recommendations from the Neoadjuvant Guidance, which include a plan to have pathologists blinded to study therapy, to reduce potential bias and also should have standard operating procedures for the collection, handling and interpretation of pathology specimens.

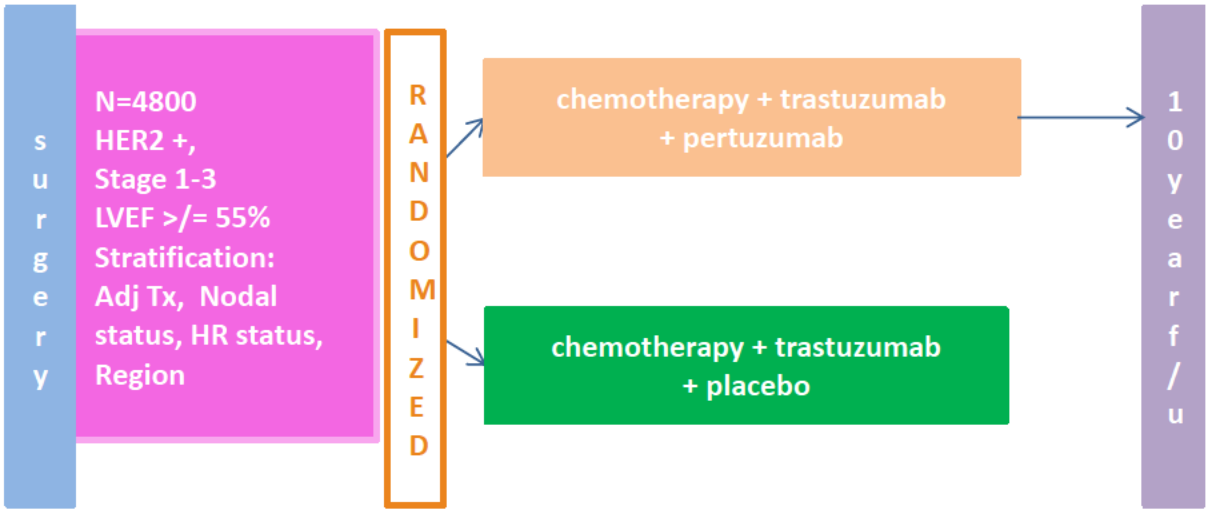
6.5.4 Association of pCR with Long Term Outcome

It is uncertain whether the difference in pCR rates demonstrated in the NEOSPHERE (WO20697) study, will be associated with improved long-term outcome. pCR has been proven to be informative at a patient level, but the pooled analysis could not establish whether an increase in pCR rate between treatment groups predicts for the superiority of one regimen over another in terms of EFS or OS. As a consequence, the Agency can only consider giving an accelerated approval. The Accelerated Approval Regulations state that:

FDA may approve a new product based on adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. There was a recent public breast cancer workshop, to discuss this regulatory path and in the panel's opinion, pCR could be considered reasonably likely to predict clinical benefit. AA requires subsequent confirmation of benefit, in this case, confirmation of the long-term outcome such as DFS or OS and includes a provision for withdrawal of indication if trials fail to confirm the clinical benefit.

Applicant is seeking accelerated approval and has proposed the fully accrued APHINITY trial (BO25126) to serve as the confirmatory trial. (Figure 9)

Figure 9: Confirmatory Trial APHINITY (BO25126)



Primary endpoint: Invasive disease-free survival (IDFS)
Key secondary endpoints: OS, DFS, cardiac safety, overall safety, QOL
Anti-HER2 therapy: 1 year

7 Review of Safety

Safety Summary

In this sBLA, the Applicant submitted safety data for two phase 2 neoadjuvant studies, NEOSPHERE (WO20697), and TRYPHAENA (BO22280) with the original submission. Safety databases were not submitted with the updated 90 day submission. In addition to NEOSPHERE (WO20697), and TRYPHAENA (BO22280), safety data from the metastatic breast cancer study CLEOPATRA (WO20698) and an additional 12 protocols was submitted in the integrated safety database (ISS) for a total of over 2100 patients.

The focus of this safety review will be based on data from the neoadjuvant period of NEOSPHERE (WO20697) since it was able to isolate both the efficacy and toxicity of pertuzumab. Data from TRYPHAENA (BO22280) and the ISS will be presented as supportive evidence in key areas.

In NEOSPHERE (WO20697), the control arm is considered as trastuzumab and docetaxel (H+T) in the neoadjuvant setting and the experimental arm is considered trastuzumab and docetaxel in addition to pertuzumab (P+H+T) in the neoadjuvant setting. In TRYPHAENA (BO22280) pertuzumab was administered in the neoadjuvant period of all three treatment arms.

Key safety findings from NEOSPHERE (WO20697) and TRYPHAENA (BO22280) are summarized below:

- Deaths: As of the last data cut off on February 28, 2013 there were 14 deaths on NEOSPHERE (WO20697), and 10 deaths on TRYPHAENA (BO22280). There was one death due to fulminant hepatitis during the neoadjuvant treatment period on NEOSPHERE (WO20697), which was attributed as due to docetaxel.

- Serious Adverse Events (SAE) and Dose Modifications: In the neoadjuvant setting of NEOSPHERE (WO20697), there were less SAEs on the experimental arm as compared to the control arm (11% vs. 17%). In addition, in the neoadjuvant setting, there were few treatment discontinuations due to safety and he rates of dose modifications or interruptions were similar in the two treatment arms of interest (35% in control arm vs. 33% in experimental arm).

  In TRYPHAENA, the rate of SAEs for the neoadjuvant period was highest in the TCH+P treatment arm. Grade 3-4 adverse events in the neoadjuvant period were lowest in the FEC/P+H+T treatment arm.

- Grade 3 and 4 Adverse Reactions: In NEOSPHERE (WO20697), there were fewer grade 3-4 adverse reactions on the experimental arm with pertuzumab as compared to the control arm (61% vs 75%) in the neoadjuvant setting. Grade 3-4 adverse events more common on the experimental arm (P+H+T) with the

addition of pertuzumab included: diarrhea, asthenia, and mucosal inflammation Grade 3-4 adverse events more common on the control arm (H+T) included: neutropenia and leukopenia.

- Common Adverse Reactions: In NEOSPHERE (WO20697), adverse events of all grades in the neoadjuvant period of NEOSPHERE (WO20697), that had a greater than 5% incidence and were more common in the experimental arm included diarrhea, nausea, mucosal inflammation, rash, stomatitis, vomiting, febrile neutropenia, and infusion related reactions.

- Hepatic Toxicity: There was one death due to fulminant hepatitis in the neoadjuvant treatment period on NEOSPHERE. A search of the ISS revealed no other cases of Hy's Law and thus there is no suggestion that pertuzumab is hepatotoxic.

- Cardiac Toxicity: In NEOSPHERE (WO20697), there was a higher rate of LVEF decline in the experimental arm as compared to the control arm. In TRYPHAENA (BO22280) rates of LVEF decline were highest in the treatment arm with sequential anthracycline therapy followed by pertuzumab, trastuzumab and docetaxel (FEC/P+H+T). Most cases were asymptomatic and this cardiac toxicity did appear reversible. A boxed warning is recommended concerning cardiac toxicity.

- Pulmonary Toxicity: There were two cases of interstitial lung disease (ILD) in NEOSPHERE (WO20697) and one case of ILD in TRYPHAENA (BO22280). None of the cases appeared to be due to pertuzumab.

- Diarrhea: In NEOSPHERE (WO20697) in the neoadjuvant period, the incidence of diarrhea was higher in the experimental arm of interest (P+H+T). In TRYPHAENA (BO22280), the highest rate of diarrhea was in the TCH+P treatment arm.

- Rash: In NEOSPHERE (WO20697) in the neoadjuvant period, the incidence of rash was higher in the experimental arm of interest (P+H+T). In TRYPHAENA (BO22280), the highest rate of rash was in the TCH+P treatment arm.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The claim for efficacy and safety for the application is based on two phase 2 studies in the neoadjuvant setting (NEOSPHERE/WO20697, TRYPHAENA/BO22280) with supportive data from a randomized phase 3 trial (CLEOPATRA, WO20698) in patients with HER2+ MBC. A brief summary of results are provided (ISS section 5.10) from study BO17931, a randomized phase 2 study in platinum sensitive recurrent ovarian cancer

with pertuzumab in combination with carboplatin based chemotherapy versus carboplatin based chemotherapy alone.

Key features of studies NEOSPHERE (WO20697), TRYPHAENA (BO22280), and CLEOPATRA (WO20698) are summarized in Table 5. Details of the trial design for the 3 trials are discussed in Section 5 and efficacy results are presented in Section 6. Reference will be made to CLEOPATRA (WO20698) and to any signals from the ISS, as appropriate.

7.1.2 Categorization of Adverse Events

Safety coding appears generally appropriate. Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) v.15 thesaurus terms. AEs were summarized by MedDRA primary system organ class (SOC), high level group term (HLGT), high level term (HLT) and Preferred Term (PT). The NCI CTCAE version 3.0 was used to grade toxicities. The Roche Drug Thesaurus was used to code and classify medications.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The ISS includes data from more than 2100 patients exposed to pertuzumab in 15 clinical trials. This includes:

- 641 patients treated from clinical studies using neoadjuvant pertuzumab (NEOSPHERE/WO20697 and TRYPHAENA/BO22280) in early stage breast cancer
- 804 patients from the phase 3 trial using pertuzumab in Her2+ metastatic breast cancer (CLEOPATRA/WO20698)
- 152 patients with ovarian cancer treated with pertuzumab+carboplatin (BO17931)
- The other patients are from phase 1 and 2 clinical studies

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the NEOSPHERE study (WO20697), 416 patients received at least one cycle of treatment on one of four different treatment arms. Pertuzumab was administered only in the neoadjuvant period. The first two treatment arms are the treatments arms of interest. Treatment in Arm A consisted of trastuzumab and docetaxel for four cycles in the neoadjuvant period and was considered the control arm. Treatment in Arm B consisted of trastuzumab and docetaxel in addition to pertuzumab for four cycles in the neoadjuvant period and was considered the experimental arm. Docetaxel was initiated at 75mg/m^2 and could be escalated to 100mg/m^2 for subsequent cycles if well tolerated. Patients in all treatment arms received three cycles of FEC chemotherapy after surgery

and continued trastuzumab to complete one year of therapy. Patients in Treatment Arm C (P+H) also received four cycles of docetaxel after surgery prior to FEC chemotherapy.

Table 29, Table 30, and Table 31 summarize patient exposure to neoadjuvant study treatment in all four treatment arms. The two arms of interest are highlighted in blue. In addition, Table 32 summarizes the percentage of patients in the two treatment arms of interest that were able to complete the full planned treatment regimen consisting of neoadjuvant therapy, surgery and adjuvant therapy.

Table 29: NEOSPHERE (WO20697): Exposure to Pertuzumab (Reviewer Table)

	H+T N=107	P+H+T N=107	P+H N=108	P+T N=94
Mean number of Cycles	**N/A**	**3.9**	**3.9**	**3.9**
Mean Dose Received (mg)	**N/A**	**2059.6**	**2047.7**	**2051**
Median Dose Received (mg)	**N/A**	**2100**	**2100**	**2100**
Range (mg)	**N/A**	**300-2940**	**1260-2100**	**840-2100**

H=Herceptin; P=Pertuzumab; T=Docetaxel; N/A=not applicable

Table 30: NEOSPHERE (WO20697): Exposure to Neoadjuvant Trastuzumab (Reviewer Table)

	H+T N=107	P+H+T N=107	P+H N=108	P+T N=94
Mean number of Cycles	**4.0**	**3.9**	**3.9**	**N/A**
Range	**2-4**	**1-4**	**2-4**	**N/A**
Mean Dose Received (mg)	**1784.6**	**1710.1**	**1740.1**	**N/A**
Median Dose Received (mg)	**1742.0**	**1664.0**	**1726.0**	**N/A**
Range (mg)	**924-3111**	**420-4192**	**746-2756**	**N/A**

H=Herceptin; P=Pertuzumab; T=Docetaxel; N/A=not applicable

Table 31: NEOSPHERE (WO20697): Exposure to Docetaxel (Reviewer Table)

Dose Intensity (mg/m2/week)	H+T N=107	P+H+T N=107	P+H N=108	P+T N=94
Mean	**29.1**	**28.5**	**28.6**	**28.9**
Median	**30.3**	**30.3**	**29.6**	**29.6**
Range	**(22,33)**	**(16,32)**	**(19,33)**	**(20,33)**

H=Herceptin; P=Pertuzumab; T=Docetaxel

Table 32: NEOSPHERE (WO20697): Completion of Treatment (Reviewer Table)

	H+T N=107	P+H+T N=107
Neoadjuvant Period	**N=107**	**N=107**
Pertuzumab	**--**	**95%**
Trastuzumab	**98%**	**94%**
Docetaxel	**99%**	**95%**
Adjuvant Period	**N=103**	**N=102**
FEC	**100%**	**94%**
Trastuzumab	**96%**	**89%**
1 yr of trastuzumab therapy*	**92%**	**83%**

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel; *17 cycles

Reviewer Comments: *Patients in the control arm did receive a slightly higher mean dose intensity of docetaxel as compared to the experimental arm. This may be the cause of the higher rate of neutropenia in the control arm as will be discussed in Section 7.2. The majority of patients in the two treatment arms of interest were able to complete the planned treatment course of neoadjuvant chemotherapy, surgery and adjuvant FEC chemotherapy. There were a lower percentage of patients in the experimental arm that were able to complete the full one year of trastuzumab therapy. Several of the patients that were not able to complete the full one year of trastuzumab had missed one cycle of therapy.*

In TRYPHAENA (BO22280), a total of 223 patients received at least one cycle of treatment on one of the three treatment arms. Pertuzumab was administered in the neoadjuvant period of all three treatment arms for either 3 or 6 cycles. Treatment in Arm A consisted of 3 cycles of FEC with pertuzumab and trastuzumab followed by 3 cycles of pertuzumab, trastuzumab and docetaxel. Treatment Arm B consisted of 3 cycles of FEC followed by 3 cycles of pertuzumab, trastuzumab and docetaxel. Treatment Arm C consisted of 6 cycles of TCH (docetaxel, carboplatin, trastuzumab) along with pertuzumab. All patients continued trastuzumab to receive one full year. Table 33 summarizes the percentage of patients able to complete the planned therapy in TRYPHAENA (BO22280).

Table 33: TRYPHAENA (BO22280): Completion of Treatment (Reviewer Table)

	P+H+FEC/P+H+T	FEC/P+H+T	TCH+P
Neoadjuvant Period	**N=72**	**N=75**	**N=76**
Pertuzumab	**92%**	**88%**	**92%**
Trastuzumab	**93%**	**88%**	**92%**
Docetaxel	**94%**	**88%**	**91%**
FEC	**96%**	**92%**	**--**
Carboplatin	**--**	**--**	**91%**
Adjuvant Period	**N=68**	**N=65**	**N=67**
Trastuzumab	**91%**	**92%**	**96%**
1 yr of trastuzumab therapy*	**86%**	**80%**	**84%**

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel; *17 cycles

Reviewer Comments: *The lowest rate of treatment completion was in the sequential anthracycline, pertuzumab, trastuzumab treatment arm (FEC/P+H+T). Overall, a slightly lower percentage of patients were able to complete neoadjuvant therapy on TRYPHAENA as compared to NEOSPHERE and comparatively, fewer patients entered the adjuvant period to complete one year of trastuzumab therapy.*

Demographic information is provided in Section 6 of this review for patients in NEOSPHERE (WO20697) and TRYPHAENA (BO22280).

7.2.2 Explorations for Dose Response

Explorations for dose response were not conducted.

7.2.3 Special Animal and/or In Vitro Testing

See Pharmacology/Toxicology review from the BLA 125, 409 Clinical Review (Section 7.2.3) for more information.

7.2.4 Routine Clinical Testing

In the NEOSPHERE study (WO20697), patients were required to have baseline evaluations, including a complete medical history and physical examination, ECOG performance status, chest x-ray, 12 lead ECG, bone scan and LVEF assessment by echocardiogram or MUGA within 28 days of starting treatment. Baseline laboratory analyses (including CBC with differential, serum chemistry and liver tests, INR/PTT and urinalysis were required within 7 days of starting treatment. Physical exam (including clinical tumor assessment), vital signs, and ECOG performance status were required prior to each cycle, at study drug completion and every three months in the post treatment follow up period. Laboratory analyses were performed prior every cycle of treatment and at the final visit. Pregnancy test was performed with 7 days of starting treatment at baseline and within 3 days prior to every third cycle of treatment, at treatment discontinuation and then every 3 months thereafter until six months post discontinuation of study treatment.

LVEF assessments by echocardiogram or MUGA were performed at baseline, during Days 15-21 of cycles 2, 4, 5, 8, 11, 15, 17 (final visit done $\geq$ 28 days after dosing; one additional assessment $\geq$ 28 days after last dosing in cycle 21 required for Arm D only) and then at the final visit and every 6 months in the post treatment follow up period for two years.

Reviewer Comments: *Testing appears adequate.*

7.2.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology review from BLA 125, 409 for more information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The current pertuzumab label carries a boxed warning for embryo-fetal toxicity. Other drugs currently approved in the US that block HER2 include trastuzumab, lapatinib and ado-trastuzumab emtansine. All of these drugs are associated with a risk of decreased in LVEF. Both the trastuzumab and ado-trastuzumab emtansine labels contain a boxed warning for a risk of cardiomyopathy and embryo-fetal toxicity. In addition, the trastuzumab label also carries a boxed warning for infusion reactions, pulmonary reactions, and the ado-trastuzumab emtansine also carries a boxed warning for hepatotoxicity. The lapatinib label contains a boxed warning for hepatoxicity.

Reviewer Comments: *The sponsor has appropriately identified adverse events of interest to further investigate in this submission.*

7.3 Major Safety Results

Table 34 provides a safety overview for NEOSPHERE (WO20697). Results are shown for all four treatment arms in the neoadjuvant and overall periods. The two arms of interest are highlighted in blue.

Table 34: NEOSPHERE (WO20697): Safety Overview (Reviewer Table)

	H+T n=107		P+H+T n=107		P+H n=108		P+T n=94	
	Neoadj	Overall	Neoadj	Overall	Neoadj	Overall	Neoadj	Overall
AE Grade ≥ 3	75%	82%	61%	73%	11%	60%	71%	80%
SAE	17%	21%	11%	21%	4%	18%	17%	23%
Deaths (# of patients)	0	3	1	2	0	2	0	7

H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comments: *There was a higher rate of Grade 3 and 4 adverse events and SAEs in the neoadjuvant period in the control arm (H+T) which lacked pertuzumab as compared to the experimental arm (P+H+T). The higher rate of Grade 3 and 4 adverse events was mainly due to a higher rate of neutropenia in the control arm. As discussed above, this may have been due to a slightly higher mean dose intensity of docetaxel received by patients in the control arm.*

Table 35 provides a safety overview for TRYPHAENA (BO22280). Results are shown for all three treatment arms in the neoadjuvant and overall periods.

Table 35: TRYPHAENA (BO22280): Overview of Safety (Reviewer Table)

	P+H+FEC/P+H+T n=72		FEC/P+H+T n=75		TCH+P n=76	
	Neoadj	**Overall**	**Neoadj**	**Overall**	**Neoadj**	**Overall**
AE Grade ≥ 3	**70%**	**74%**	**60%**	**61%**	**73%**	**73%**
SAE	**28%**	**32%**	**20%**	**24%**	**36%**	**41%**
Deaths (#of patients)	**0**	**3**	**0**	**4**	**0**	**3**

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comments: *Grade 3-4 adverse events and SAE's were highest in the TCH+P treatment arm for the neoadjuvant period.*

7.3.1 Deaths

Deaths in NEOSPHERE (WO20697):

As summarized in Table 36, there were a total of 14 deaths on NEOSPHERE at the time of the final data cutoff on February 28, 2013 (WO20697). There was one death in the neoadjuvant period on the pertuzumab+trastuzumab+docetaxel treatment arm. There were no deaths in the adjuvant period on any treatment arm and the remaining 13 deaths occurred in the post treatment follow up period either due to disease progression or metastasis.

Table 36: NEOSPHERE (WO20697): Deaths (Reviewer Table)

	Treatment Period		
Treatment Arm	**Neoadj**	**Adj**	**Post-Trt**
H+T	**0**	**0**	**3**
P+H+T	**1**	**0**	**1**
P+H	**0**	**0**	**2**
P+T	**0**	**0**	**7**
Total (February 28, 2013)	**14**		

H=Herceptin; P=Pertuzumab; T=Docetaxel

Following is a brief synopsis for the one patient that died in the neoadjuvant period:

Neoadjuvant Period:

- Patient 116863/1747 (Arm B: P+H+T): The patient died due to fulminant hepatitis. This patient had a history of obesity, diabetes and poorly controlled hypertension receiving multiple medications. The patient had normal liver function tests prior to administration of all 4 cycles of neoadjuvant chemotherapy. However, two days after administration of cycle 4, the patient had a greater than 100 fold increase in her transaminase levels from baseline and an increased serum bilirubin level. The patient was treated at a local hospital away from the study center and complete information regarding the treatment course was never obtained. A hepatitis panel, liver biopsy and an autopsy were not performed. The patient died just 6 days after cycle 4 administration. The Investigator and Study Steering Committee attributed this death to docetaxel, which is a known hepatotoxic agent with a boxed label warning.

Reviewer Comments: *The death rate was low in both neoadjuvant studies as would be expected in a curative intent setting. The one case of fulminant hepatitis in the experimental arm of interest did raise a concern for hepatotoxicity with pertuzumab. We asked the Applicant to carefully review this across the pertuzumab experience. At this time, over 10,000 patients have been exposed to pertuzumab, including approximately 1600 patients from completed clinical studies. A review of this data has yielded no other cases of potential drug induced liver injury and currently there appears to be no suggestion that pertuzumab is hepatotoxic.*

The remaining 13 deaths were due to either disease progression or metastases. These deaths all occurred more than 30 days after the last dose of pertuzumab and were not considered to be related to pertuzumab.

Deaths in TRYPHAENA (BO22280):

As of the February 28, 2013 data cutoff date, a total of ten deaths were reported on TRYPHAENA (BO22280). No deaths occurred in the neoadjuvant period. One patient died in the adjuvant period as a result of an adverse event reported as 'metastatic neoplasm'. Disease recurrence in the lung and bone were confirmed before the patient died. The other 9 deaths occurred in the post-treatment follow-up period and were due to disease recurrence.

Reviewer Comments: *All 10 deaths were due to disease recurrence or metastases and were not considered to be related to pertuzumab.*

7.3.2 Nonfatal Serious Adverse Events

In the NEOSPHERE study (WO20697), as of the March 9, 2013 data cut-off date, 60 patients experienced Serious Adverse Events (SAEs) in the neoadjuvant treatment period. Table 37 highlights the most common (>1%) SAEs by preferred term. The two treatment arms of interest are highlighted in blue. There were few SAEs in the neoadjuvant period in Treatment Arm C which lacked cytotoxic chemotherapy in this period. There were numerically more SAEs in the control arm (H+T) compared to the experimental arm (P+H+T). There was a higher percentage of neutropenia SAEs with the experimental arm, although there was a higher rate of neutropenia overall in the neoadjuvant period for the control arm as discussed later.

Table 37: NEOSPHERE (WO20697): SAE preferred terms >1% in either Treatment Arm in the Neoadjuvant Setting (Reviewer Table)

	H+T % N=107	P+H+T % N=107	P+H % N=108	P+T % N=94
Febrile Neutropenia	**6.5**	**5.6**	**0**	**6.4**
Neutropenia	**0.9**	**3.7**	**0**	**6.4**
Cellulitis	**0**	**0**	**0**	**1.1**
Diarrhea	**1.9**	**0**	**0**	**1.1**
Staphylococcal Sepsis	**0**	**0**	**0**	**1.1**
Uterine Hemorrhage	**0**	**0**	**0**	**1.1**
Total SAE	**22**	**15**	**4**	**18**

H=Herceptin; P=Pertuzumab; T=Docetaxel

7.3.3 Dropouts and/or Discontinuations

As seen in Table 38, as of the March 9, 2012 data cut-off date, 20 patients discontinued study treatment due to an adverse event in the NEOSPHERE study (WO20697). A total of 7 patients discontinued therapy due to left ventricular dysfunction or congestive heart failure (CHF).

Table 38: NEOSPHERE (WO20697): Treatment Discontinuations (Reviewer Table)

	H+T N=107		P+H+T N=107		P+H N=108		P+T n=94	
	Neo	Adj	Neo	Adj	Neo	Adj	Neo	Adj
Pregnancy					1			
CHF					1			
Septic Shock						1		
LV Dysfunction				4				2
Chest pain						1		
Primary Biliary Cirrhosis								1
Neutropenia							1	
Strangulated abd hernia				1				
Fulminant Hepatitis			1					
Hypersensitivity			1		1	2		
Ulcerative colitis							1	
Asthenia						1		
Total	0		7		8		5	

H=Herceptin; P=Pertuzumab; T=Docetaxel

Treatment discontinuations in TRYPHAENA (BO22280) are shown in Table 39.

Table 39: TRYPHAENA (BO22280): Treatment Discontinuations (Reviewer Table)

AE (preferred term)	P+H+FEC/P+H+T		FEC/P+H+T		TCH+P	
	Neo	Adj	Neo	Adj	Neo	Adj
CVA					1	
Lung Abscess	1					
Dehydration			1			
Erythema		1				
Left Ventricular Dysfunction	1*	2	2	2	1	
Rash	1					
Pneumonitis			1			
Hepatotoxicity			1			
Hypersensitivity	1				2	
Elevated Creatinine					1	
Neutropenia					1	
Chest Discomfort	1*					
Total	7		7		6	

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel; *Same Patient

7.3.4 Significant Adverse Events

This section will summarize the data from both the NEOSPHERE study (WO20697) and the TRYPHAENA study (BO22280) regarding two significant adverse events known to occur with pertuzumab and pre-specified by the applicant: cardiac events and neutropenia AE grouped terms (AEGT) to include neutropenia, neutropenia infection and febrile neutropenia.

Cardiac events and cardiac SAEs:

Cardiac toxicity is a well-known adverse event with Her2 targeted agents and was of particular interest in both submitted neoadjuvant studies. Cardiac monitoring was

similar in both neoadjuvant studies. Patients had LVEF assessment by echocardiogram or MUGA and the same modality was used throughout the study. Patients had assessment at baselines, every six weeks in the neoadjuvant period, after surgery within one week of starting adjuvant therapy and then every 3-4 cycles in the adjuvant period as stipulated by the protocol. LVEF assessment was again made at the end of treatment and every 6 months for a total of two years.

There were no deaths due to cardiac toxicity on either neoadjuvant study.

In both NEOSPHERE and TRYPHAENA, asymptomatic left ventricular dysfunction was defined as a LVEF decline of ≥10% from baseline and a drop to less than 50% or an asymptomatic decline requiring treatment or leading to discontinuation of study treatment.

In both neoadjuvant studies, pertuzumab was administered only in the neoadjuvant period; therefore, the focus was on this treatment period. Cardiac toxicity in the other treatment periods was also reviewed to look for a "carry over" effect.

Show in Table 40 are the rates of asymptomatic left ventricular dysfunction for the two treatment arms of interest in NEOSPHERE (WO20697). The rate of asymptomatic left ventricular dysfunction was higher in the experimental arm (P+H+T) overall and in each of the three treatment phases.

Table 40: NEOSPHERE (WO20697): Asymptomatic Left Ventricular Dysfunction (Reviewer Table)

Asymptomatic LV Dysfunction	H+T N=107	P+H+T N=107
Total	**2%**	**8%**
-Neoadjuvant Phase	**1%**	**3%**
-Adjuvant Phase	**1%**	**6%**
-Follow up Phase	**0**	**3%**

H=Herceptin; P=Pertuzumab; T=Docetaxel

There was one case of symptomatic LV dysfunction on NEOSPHERE. This occurred in the arm with dual anti-HER2 treatment in the neoadjuvant setting with pertuzumab and trastuzumab but without docetaxel (Treatment Arm C). This patient became symptomatic after cycle 3 of treatment in the neoadjuvant period and was withdrawn from treatment. Of note, this patient had a significant cardiac history with

hypercholesterolemia and a cardiac stent placement 5 yrs prior. This case highlights the importance of careful patient selection for treatment with anti- Her2 targeted agents Treatment discontinuation due to a cardiac Adverse Event was highest in the experimental arm of interest with pertuzumab + trastuzumab + docetaxel. All discontinuations in this arm occurred in the adjuvant setting.

All patients in NEOSPHERE have recovered their LV function to greater than 50%, indicating that the cardiac toxicity seen with this therapy maybe reversible.

In TRYPHAENA (BO22280), pertuzumab was administered in the neoadjuvant period for all three treatment arms; therefore, the effect of pertuzumab could not be isolated. In contrast to NEOSPHERE, where the chemotherapy regimen was divided before and after surgery, all chemotherapy in TRYPHAENA was administered prior to surgery. The primary endpoint for this study was cardiac safety. LVEF was assess locally and reviewed centrally. The results presented in Table 41 are based on local readings.

Table 41: TRYPHAENA (BO22280): Cardiac Safety Profile (Reviewer Table)

	P+H+FEC/ P+H+T N=72	FEC/P+H+T N=75	P+TCH N=76
Asymptomatic LV Dysfunction*	**7%**	**8%**	**8%**
Symptomatic LV Dysfunction	**0**	**4%***	**1%**
Total pts with LV Dysfunction	**7%**	**12%**	**9%**
Tx discontinuation due to Cardiac AE	**4%**	**5%**	**1%**

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel; *Based on local readings

All but one patient in the TRYPHAENA study have recovered their LV function to greater than 50%.

Reviewer Comments: *There was a higher rate of left ventricular dysfunction with the addition of pertuzumab in the neoadjuvant setting as seen in NEOSPHERE (WO20697). This is in contrast to the results from the metastatic breast cancer study CLEOPATRA (WO20698) which had a higher rate of patients with LVEF decline in the control arm which lacked pertuzumab. The difference for these results may due to the addition of an anthracycline to the treatment regimen in NEOSPHERE (WO20697). Most of the cases left ventricular dysfunction were asymptomatic and did appear to be reversible.*

In TRYPHAENA (BO22280), the highest rate of patients with LV dysfunction including symptomatic LV dysfunction and discontinuation due to cardiac AE occurred in the sequential anthracycline, pertuzumab and trastuzumab treatment arm (FEC/P+H+T) and not the treatment arm where this was given concurrently (P+H+FEC/P+H+T) as one might have predicted. However, it is difficult to make any conclusions based on these findings from this small study which did not isolate the effect of pertuzumab. These treatment regimens are being studied further in ongoing and proposed trials.

The optimal treatment regimen and duration of pertuzumab for a curative intent population are not known and are currently being investigated, results of which may impact the cardiac safety profile. Much of the information needed to better characterize the cardiac toxicity of pertuzumab in an early breast cancer population will be gained from the large adjuvant APHINITY trial which has now completed accrual. Also, further information will be gained from a study proposed by the Applicant as a PMR after discussion with the Agency. In that study, neoadjuvant pertuzumab will be given in combination with two different anthracycline treatment regimens. The two treatment arms would include one arm of concurrent FEC administration with pertuzumab and trastuzumab as in Arm A of TRYPHAENA (BO22280) and the other arm would include dose dense doxorubicin/cyclophosphamide followed by paclitaxel + pertuzumab+ trastuzumab. The second anthracycline regimen is commonly used in the United States.

Neutropenia, neutropenic infection and febrile neutropenia:

In NEOSPHERE (WO20697), the rate of neutropenia was highest in the control arm (H+T) in the neoadjuvant period. However, the rate of febrile neutropenia and SAE neutropenia was higher in the experimental arm in the neoadjuvant period. Growth factor support with granulocyte-colony stimulating factor (G-CSF) was allowed in the protocol. Results are shown in Table 42.

Table 42: NEOSPHERE (WO20697): Rates of all grades Neutropenia and Febrile Neutropenia in the neoadjuvant period (Reviewer Table)

	H+T N=107	P+H+T N=107
Neutropenia	**64%**	**51%**
Febrile Neutropenia	**7%**	**8%**
SAE Neutropenia	**1%**	**4%**

H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comments: *The higher rate of neutropenia in the control arm (H+T) was likely due to a slightly higher dose intensity of docetaxel received by patients in the control arm as compared to the experimental arm (P+H+T).*

In TRYPHAENA (BO22280), the highest rate of neutropenia for the neoadjuvant period was in the TCH+P treatment arm. As in NEOSPHERE, growth factor support with G-CSF was allowed. Results are shown in Table 43.

Table 43: TRYPHAENA (BO22280): Rates of Neutropenia and Febrile Neutropenia in the Neoadjuvant Period (Reviewer Table)

	P+H+FEC/ P+H+T N=72	FEC/P+H+T N=75	P+TCH N=76
Neutropenia	**51%**	**47%**	**49%**
Febrile Neutropenia	**18%**	**9%**	**17%**

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel

7.3.5 Submission Specific Primary Safety Concerns

This section will summarize the information from the application that pertains to these additional "adverse events to monitor" for studies NEOSPHERE (WO20697) and TRYPHAENA (BO 22280) pre-specified by the applicant and based on the known pertuzumab safety profile or mechanism of action. (See section 7.3.4 for discussion of cardiac and febrile neutropenia concerns.)

- Diarrhea
- Rash
- Interstitial lung disease
- Hypersensitivity/anaphylaxis
- Mucositis
- Venous thromboembolic events

Diarrhea:

In NEOSPHERE (WO20697), the incidence of diarrhea ranged from 27.8%-54.3% in the four treatment arms for the neoadjuvant setting. More patients experienced diarrhea in the treatment arms containing docetaxel. In the two treatment arms of most interest, H+T and P+H+T, the incidence of all grade diarrhea and grade 3-4 was higher in the P+H+T treatment arm (45.8% vs 33.6% and 5.6% vs 3.7% respectively). For the overall treatment period, the incidence of all grade diarrhea was still higher in the

P+H+T treatment arm compared to H+T (51.4% vs 38.3%). No patients discontinued therapy due to diarrhea.

In TRYPHAENA (BO22280), the incidence of diarrhea ranged from 61.1%-72.4% in the three treatment arms for the neoadjuvant setting. The incidence of all grade and grade 3-4 diarrhea was highest in the TCH+P arm (72.4% and 11.8% respectively). No patients discontinued therapy due to diarrhea.

Rash:

In NEOSPHERE (WO20697), the incidence of rash ranged from 11.1% to 28.7% in the four treatment arms for the neoadjuvant setting. More patients experienced rash in the treatment arms containing docetaxel. In the two treatment arms of most interest, H+T and P+H+T, the incidence of all grade rash was higher in the P+H+T treatment arm (26.2% vs 21.5%); however, grade 3-4 rash was higher in the H+T treatment arm (1.9% vs 0.9%). For the overall treatment period all grade rash was still higher in the P+H+T treatment arm compared to T+D (28% vs 24.3%). No patients discontinued therapy due to rash.

In TRYPHAENA (BO22280), the incidence of rash ranged from 10.7%-21.1% in the three treatment arms for the neoadjuvant setting. The incidence of all grade and grade 3-4 rash was highest in the TCH+P arm (21.1% and 1.3% respectively). One patient in the P+H+FEC/P+H+T treatment arm did discontinue treatment in the neoadjuvant setting due to a grade 2 rash that developed on Day 7. The rash resolved without sequelae on Day 57.

Interstitial lung disease:

The incidence of interstitial lung disease (ILD) was low in both neoadjuvant studies. In NEOSPHERE study (WO20697), one patient on the P+T treatment arm developed grade 2 ILD on Day 8 of treatment after just one cycle of therapy. The AE reportedly resolve without sequelae on Day 163. Patient had no change in pertuzumab and docetaxel due to this event. Of note, the patient also has a clinical history of systemic lupus erythematous, Raynaud's phenomenon and scleroderma.

In the TRYPHAENA study (BO22280), one patient on the FEC/P+H+T treatment arm was diagnosed with pneumonitis in the neoadjuvant setting. The patient was diagnosed with pneumonitis on Day 79 with last study treatment on Day 67 (cycle 4). The patient discontinued treatment due to the event and the SAE resolved on Day 89. A second patient on treatment arm TCH+Px6 developed radiation pneumonitis in the adjuvant setting.

In the ISS there are 26 cases of ILD reported in 25 patients. Twenty of the cases occurred in treatment arms including pertuzumab and all 20 cases are being reported as having resolved.

Hepatic Disorders:

In the neoadjuvant period of NEOSPHERE (WO20697), the highest rate of patients experiencing a hepatic disorder adverse event according to the Standardized MedDRA Queries (SMQ) “Drug Related Hepatic Disorder” was highest in the control arm (H+T) at 5.6% and was 3.7% in the experimental arm of interest (P+H+T). No patients in the P+H no patients experienced a hepatic disorder adverse event in this treatment period and in the P+T treatment arm it was 3.2%. In addition, on death due to fulminant hepatitis did occur in the neoadjuvant period on the P+H+T treatment arm as detailed in Section 7.3.1. None of the other events led to treatment discontinuation.

In the neoadjuvant period of TRYPHAENA (BO22280), one patient on the FEC/P+H+T treatment arm had a hepatic disorder AE. This patient was withdrawn from treatment due to grade 3 hepatotoxicity. Three patients on the TCH+P treatment arm had a hepatic disorder adverse event. All three of these patients experienced an increased ALT and one patient also had an elevated AST and GGT. None of these events led to treatment discontinuation.

Hypersensitivity/anaphylaxis:

Anaphylaxis and Hypersensitivity at any time point were captured; it was not restricted to a particular time window as with infusion reaction. Anaphylaxis or hypersensitivity reactions were analyzed using the Roche standard AEGT ‘Anaphylaxis and Hypersensitivity’ containing the MedDRA SMQ (narrow) ‘Anaphylactic reaction’ plus all MedDRA preferred terms containing the term ‘hypersensitivity’. There is some overlap with the AEGT/SMQ used to identify infusion-related reactions.

In NEOSPHERE study (WO20697), the incidence of all grade drug hypersensitivity/anaphylaxis ranged from 1.9%-6.4% in the four treatment arms for the neoadjuvant setting where pertuzumab was administered. More patients experienced hypersensitivity reactions in the treatment arms containing pertuzumab. Six events occurred during the pertuzumab infusion. The incidence of drug hypersensitivity is as follows: H+T (1.9%), P+H+T (5.6%), P+H (5.6%), and P+T (6.4%). One of the cases was considered a SAE and occurred in the treatment arm of T+P. The SAE was thought to be due to either pertuzumab or trastuzumab. Treatment was interrupted and then continued without incidence. One patient in treatment arm P+H+T had a hypersensitivity reaction to docetaxel and all treatment was discontinued after cycle 2 of therapy.

In the TRYPHAENA study (BO22280), the incidence of all grade drug hypersensitivity/anaphylaxis ranged from 2.7%-18.4% in the three arms for the neoadjuvant setting. The incidence was as follows: FEC+P+H/P+H+T (15.3%), FEC/P+H+T (2.7%), and TCH+Px6 (18.4%). Four cases were considered to be SAEs with discontinuation of treatment in 3 cases. Two of the cases were on the FEC+P+T/D+P+T treatment arm and two cases were on the TCH+Px6 treatment arm.

No deaths occurred due to anaphylaxis or hypersensitivity events.

Mucositis:

In NEOSPHERE study (WO20697), the incidence of all grade mucositis ranged from 1.9% -26.2% in the four treatment arms for the neoadjuvant setting. More patients experienced mucositis in the treatment arms containing docetaxel. In the two treatment arms of most interest, H+T and P+H+T, the incidence of all grade mucositis and grade 3-4 mucositis was higher in the P+H+T treatment arm (26.2% vs 21.5% and 1.9% vs 0% respectively). No patients discontinued therapy due to mucositis.

In the TRYPHAENA study (BO22280), the incidence of all grade mucositis ranged from 17.1%-23.6% in the three arms for the neoadjuvant setting. Grade 3-4 mucositis was only seen in the TCH+Px6 treatment arm at a rate of 1.3%. No patients discontinued therapy due to mucositis.

Pertuzumab Infusion Related Reactions:

Infusion related reactions were defined adverse reactions that occurred during, or on the day of or day after (for a 24 hours period) pertuzumab infusion. Pertuzumab was administered only in the neoadjuvant period for NEOSPHERE and TRYPHAENA.

In NEOSPHERE study (WO20697), the sequence of administration was trastuzumab followed by pertuzumab followed by docetaxel. In TRYPHAENA (BO22280) the sequence of administration was trastuzumab followed by pertuzumab followed by chemotherapy. The majority of AEs were Grade 1-2 and occurred during the first or second cycle of infusion. The most common infusion related reactions included infusion related reaction, chills, headache, pyrexia, and drug hypersensitivity.

Reviewer Comments: *Since pertuzumab was administered on the same day as all of the other study drugs in both NEOSPHERE and TRYPHAENA, it is difficult to determine causality for the infusion related reactions.*

Venous thromboembolic events:

In NEOSPHERE study (WO20697), 4 patients experienced a venous thromboembolic event (VTE) during the study overall. All four cases occurred in treatment arms including pertuzumab (2 patients in P+H+T and 2 patients in P+T). Two events occurred in the neoadjuvant setting when pertuzumab was administered and the other two occurred in the adjuvant setting.

In the TRYPHAENA study (BO22280), 4 patients experience a VTE. Three events occurred in the neoadjuvant setting (2 patients in the P+T+FEC/P+H+T arm and one

patient in the TCH+P arm) and one event occurred in the adjuvant period (FEC/P+H+T treatment arm).

No deaths resulted from a VTE event in either study.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the NEOSPHERE study (WO20697), the most common adverse reactions (≥ 25%) were alopecia, neutropenia, diarrhea, rash; mucosal inflammation, fatigue, and nausea on the pertuzumab treatment arm of interest (P+H+T) in the neoadjuvant setting. Adverse events of all grades in the neoadjuvant period of NEOSPHERE that had a greater than 5% incidence and were more common in the experimental arm are shown in Table 44.

Table 44: NEOSPHERE (WO20697): AEs (all grades) ≥5% and more common in P+H+T vs H+T (Reviewer Table)

	H+T N=107	P+H+T N=107
Diarrhea	**34%**	**46%**
Nausea	**37%**	**39%**
Mucosal Inflammation	**22%**	**26%**
Rash	**22%**	**26%**
Stomatitis	**8%**	**18%**
Vomiting	**12%**	**13%**
Febrile Neutropenia	**7%**	**8%**
Infusion Related Reactions	**5%**	**7%**

H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comments: *These are all known toxicities of pertuzumab and have previously been reported in the metastatic breast cancer study CLEOPATRA. However, the long term safety of pertuzumab in an early breast cancer setting is unknown. The short term toxicity of neoadjuvant pertuzumab is largely similar to the already known safety profile of this drug and appears to be manageable. But if and what long term toxicities may arise in this curative intent population are not known at this time.*

In TRYPHAENA, the most common adverse reactions (≥ 25%) on any treatment arm in the neoadjuvant period were diarrhea, neutropenia, alopecia, fatigue, nausea, vomiting, thrombocytopenia. Grade 3-4 adverse events ≥2% in the neoadjuvant period of TRYPHAENA (BO22280) are shown in Table 45.

Table 45: TRYPHAENA (BO2228) Grade 3-4 Adverse Events ≥2% in Neoadjuvant Period (Reviewer Table)

	P+H+FEC/P+H+T N=72	FEC/P+H+T N=75	TCH+P N=76
Neutropenia	**47%**	**43%**	**46%**
Anemia	**1%**	**4%**	**17%**
Febrile Neutropenia	**18%**	**9%**	**17%**
Diarrhea	**4%**	**5%**	**12%**
Leukopenia	**19%**	**12%**	**12%**
Thrombocytopenia	**0**	**0**	**12%**
Vomiting	**0**	**3%**	**5%**
ALT Increased	**0**	**0**	**4%**
Fatigue	**0**	**0**	**4%**
Drug Hypersensitivity	**3%**	**0**	**3%**
Dyspnea	**0**	**2%**	**1%**
Nausea	**0**	**2%**	**0**

FEC=5-FU, epirubicin, and cyclophosphamide; H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comments: *The rate of all grade and grade 3-4 adverse events are higher in the treatment arms for the neoadjuvant period of TRYPHAENA, as compared to NEOSPHERE, as all the chemotherapy was given prior to surgery. Grade 3-4 anemia, diarrhea, and thrombocytopenia are much higher in the TCH+P treatment arm compared to the other two treatment arms. Rates for these Grade 3-4 adverse events are higher than reported in the BCIRG 006 study using the TCH regimen in the adjuvant setting.[17] It is not clear why there is significantly more hematologic toxicity with the addition of pertuzumab to the TCH regimen in TRYPHAENA (BO22280).*

7.4.2 Laboratory Findings

In the NEOSPHERE and TRYPHAENA, hematology and chemistry were evaluated prior to each new cycle of therapy and on Day 8 of treatment cycles in which included chemotherapy. The most common laboratory abnormalities throughout the overall treatment period were decreased neutrophil, total white blood cell count (WBC) and lymphocyte counts.

7.4.3 Vital Signs

Vital signs were obtained at screening and during each follow up visit. No clinically meaningful vital sign changes were observed in the treatment arm as compared to the control arm.

7.4.4 Electrocardiograms (ECGs)

For full details, see QT sub study results from Section 7.4.4 review in BLA 125409.

7.4.5 Special Safety Studies/Clinical Trials

See Clinical Pharmacology review from BLA 125409 for more information.

7.4.6 Immunogenicity

Anti-therapeutic antibodies (ATA) were not collected in either NEOSPHERE or TRYPHAENA. See Section 7.4.6 from the BLA 125409 Clinical Review.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The doses administered in NEOSPHERE and TRYPHAENA were approved doses of 840 mg IV loading followed by 420 mg IV every 3 weeks. In both neoadjuvant clinical studies pertuzumab was limited to 3-6 cycles of administration. No new information regarding dose dependency was submitted with this application.

7.5.2 Time Dependency for Adverse Events

Cardiac safety was the primary endpoint for the TRYPHAENA (BO22280) study. Endpoints included incidence of symptomatic cardiac events as assessed by the investigator (grade 3,4 or 5 left ventricular systolic dysfunction) and clinically significant LVEF declines over the course of the neoadjuvant period (LVEF decline of $\geq$10% from baseline and to a value of < 50%). LVEF was measured locally and reviewed centrally.

The median time to first LVEF decrease as reported in the Updated Clinical Study Report for TRYPHAENA (BO22280) was 92 days in Arm A, 184 days in Arm B and 333.5 days in Arm C. The mean maximum change in LVEF measurement from baseline was -6.6, -8.4 ad -7.0 by in Arms A, B and C, respectively based on local readings. In general, the decline was greatest at Cycle 6.

7.5.3 Drug-Demographic Interactions

All patients in NEOSPHERE and TRYPHAENA were female. In NEOSPHERE, 95 patients were identified as Asian. The incidence of all grade and grade 3-4 neutropenia,

diarrhea and rash were higher in the Asian population as compared to the overall population as seen in Table 46.

Table 46: NEOSPHERE (WO20697) Select Grade 3-4 AEs higher in Asian population (Reviewer Table)

	H+T (%) n=25	P+H+T (%) n=24	P+H (%) n=22	P+T (%) n=24
Neutropenia	**59**	**45**	**1**	**57**
Asian	**84**	**83**	**5**	**88**
Diarrhea	**4**	**6**	**0**	**4**
Asian	**12**	**17**	**0**	**13**
Rash	**2**	**2**	**0**	**1**
Asian	**8**	**4**	**0**	**0**

H=Herceptin; P=Pertuzumab; T=Docetaxel

Reviewer Comment: *This increased toxicity in the Asian population was also seen in CLEOPATRA. Rates for these AEs were higher in the arms including docetaxel. The treatment arm of pertuzumab and trastuzumab arm which lacked docetaxel in the neoadjuvant setting had a low rate of grade 3-4 adverse events in both the overall and Asian population. This supports the fact that the increased toxicity was likely due to docetaxel in this population.*

7.5.4 Drug-Disease Interactions

Pertuzumab is not cleared by the kidneys and is not metabolized by cytochrome P450 isoenzymes; therefore, drug-disease interactions are not anticipated for co-morbidities.

7.5.5 Drug-Drug Interactions

No drug-drug interactions have been observed between pertuzumab, trastuzumab and docetaxel as investigated in a sub study of CLEOPATRA (WO20698-PK-DDI-substudy). This was confirmed by PK data from NEOSPHERE (Exposure-Response Analysis Report 13-0285).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The carcinogenic potential of pertuzumab has not been evaluated in long-term studies in animals.

7.6.2 Human Reproduction and Pregnancy Data

For full details, see Section 7.6.2 review in BLA 125409.

Two patients did become pregnant while on treatment in NEOSPHERE study (WO20697). One patient on treatment Arm C (P+T) became pregnant after cycle 4 of neoadjuvant treatment and chose to have an abortion, which was induced on study day 85. Treatment resumed with cycle 5 of treatment on study day 124. Another patient, also on treatment Arm C (P+T), became pregnant after cycle 9 of treatment and chose to withdraw from all study medication. Last dose of study medication was with trastuzumab and FEC for cycle 9 on study day 202 (b) (6) The baby was born on (b) (6) without abnormality.

There were no pregnancies reported in the TRYPHAENA study (BO22280).

7.6.3 Pediatrics and Assessment of Effects on Growth

Pertuzumab has not been studied in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no overdoses reported with pertuzumab. There is no experience with drug abuse or withdrawal and rebound phenomena with pertuzumab.

7.7 Additional Submissions / Safety Issues

There are no additional submissions or safety issues.

8 Postmarket Experience

Pertuzumab (PERJETA®) was approved by the FDA on June 8, 2012 for use in combination with trastuzumab and docetaxel for the first line treatment of Her2 positive MBC. As of August 1, 2013, pertuzumab has received regulatory approval for the MBC indication in 53 countries. More than 4500 patients are estimated to have received pertuzumab in ongoing and completed clinical trials sponsored by Genentech/Roche and more than 5300 patients have received pertuzumab in the post-marketing setting.

A review of the post marketing experience by the Applicant has identified no new safety signals. This was summarized in the ISS based on results from the Scheduled Periodic

Adverse Drug Experiences Reports (PADERs) for the period of June 8, 2013 to December 7, 2012. In addition, a Periodic Benefit Risk Evaluation Report (PBRER) for the period of June 8, 2012 to June 7, 2013 for the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) by the Marketing Authorization Holder (Roche and Genentech) identified no new safety signal.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

There was extensive internal labeling discussion regarding revisions to the PERJETA label to include the neoadjuvant indication. Key clinical labeling recommendations based on internal discussions and from Oncologic Drug Advisory Committee (ODAC) discussion include:

- Add a “boxed warning” regarding cardiac toxicity.
- In section 1.2, add language referring to the accelerated approval status: “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.”

- In section 1.2, add indication for 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 containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin.
- In section 1.2, add limitations of Use: The safety of doxorubicin-containing regimens in combination with PERJETA has not been established. The safety of PERJETA administered in the adjuvant setting has not been established.
- In section 2.1, add postoperative treatment recommendation of three cycles of FEC chemotherapy and completion of one year of trastuzumab treatment.
- In section 6.1, add a table summarizing the adverse reactions from Study 2.
- In section 14.2, add a table summarizing the efficacy from Study 2 in ITT population and subgroup pCR data on hormone receptor positive and negative patients.

9.3 Advisory Committee Meeting

This application was presented at the ODAC meeting on September 12, 2013. ODAC voted 13 to 0, with one abstention, that pertuzumab demonstrated a favorable benefit to risk profile for the neoadjuvant treatment of early breast cancer. In summary FDA reviewers and the Agency's ODAC members stated that they considered the pertuzumab application was favorable based on the totality of evidence. These evidence included:

- Data from the CLEOPATRA trial in a metastatic disease setting, which showed a statistically significant and robust clinical effect on overall survival.
- A fully-accrued adjuvant therapy APHINITY trial.
- Evidence that trastuzumab, a similar agent, can improve disease-free survival.
- The NEOSPHERE study isolates the effect of pertuzumab with an improvement in pathological complete response rate.
- A large database reflecting extensive exposure of patients to pertuzumab in a variety of breast cancer settings, with an acceptable safety profile.

A summary of the minutes from the discussion at ODAC regarding this application are as follows:

Many committee members described their consideration of this benefit to risk evaluation as being primarily based on the "totality of evidence," including the significant amount of data from the use of pertuzumab in the metastatic setting. Several members expressed some lack of confidence in the results of the NEOSPHERE study when taken alone, but an understanding of safety and efficacy in the metastatic setting helped to contribute to the comfort when interpreting the study results from the neoadjuvant setting. Some members of the committee cited this reasoning in suggesting that the results from

NEOSPHERE should not be used as precedent for approval in this area of treatment, and instead should be viewed as a unique situation due to the robust overall clinical development of this product.

In evaluating the NEOSPHERE study, members cited several issues which create challenges in applying the results to clinical practice. Many members talked about the problems of pCR as an endpoint, and uncertainty over whether this translates to long term clinical benefit for patients. Several committee members were unsure on the appropriate chemotherapy regimen to use with this targeted therapy. One member described uncertainty about the appropriate duration of treatment as well. Additional concerns that were highlighted by members included cardiac toxicities, the need for appropriate patient selection, the small size of the trial, and the lack of patients from the United States.

Many members of the committee explained that the completion of enrollment for the APHINITY confirmatory trial increased the comfort with the accelerated approval of pertuzumab. ODAC members described this as a “well-designed” study, and expressed hope that this trial would ultimately support the clinical benefit of this product. Several members went further to encourage the sponsor – in the event that the confirmatory trial does not support the clinical benefit of pertuzumab after its accelerated approval – to voluntarily withdraw the indication at that time.

The committee member who abstained cited the “black and white” nature of the question, and a feeling that the issue was “gray” instead. This member detailed a feeling that it is “okay to go ahead” in this area, but that careful monitoring is necessary.

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/s/

LALEH AMIRI KORDESTANI
09/25/2013

SUPARNA B WEDAM
09/25/2013

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