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*APPLICATION NUMBER:*

**761081Orig1s000**

**CLINICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	Class 2 Resubmission of BLA, 351(k)
Application Number	761081
Resubmit Date	September 28, 2018
Received Date	September 28, 2018
BSUFA Goal Date	March 28, 2019
Division / Office	DOPI/OHOP
Reviewer Name(s)	Danielle Krol, MD Jennifer Gao, MD Hui Zhang, PhD Shenghui Tang, PhD
Review Completion Date	February 22, 2019
Established Name	Trastuzumab-qyyp
Trade Name	Trazimera*
Therapeutic Class	HER2-binding humanized monoclonal antibody
Applicant	Pfizer
Formulation(s)	IV
Dosing Regimen	8 mg/kg IV loading dose, then 6 mg/kg IV q3 wks
Proposed Indication(s)	<p>TRAZIMERA is a HER2/neu receptor antagonist indicated for:</p> <ul style="list-style-type: none"> <li>• The treatment of HER2-overexpressing breast cancer.</li> <li>• The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.</li> </ul> <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p>
Recommended Indication	<p>TRAZIMERA is a HER2/neu receptor antagonist indicated for:</p> <ul style="list-style-type: none"> <li>• The treatment of HER2-overexpressing breast cancer.</li> <li>• The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.</li> </ul> <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p>

\*In this document, FDA generally refers to the applicant's proposed product by the applicant descriptor "PF-05280014".

This biologics license application (BLA 761081) Class 2 Resubmission seeks approval of the product PF-05280014 (proposed trade name Trazimera), a proposed biosimilar to US-licensed Herceptin (which will be referred to as US-Herceptin for the remainder of this review). The original BLA was submitted on June 22, 2017 and on April 20, 2018, a Complete Response letter was issued due to product quality issues.

The proprietary name TRAZIMERA was conditionally accepted on September 17, 2018 in the original submission. FDA reassessed this with the Class 2 Resubmission, and found it to be acceptable. The 4-letter suffix -qyyp was conditionally accepted during the original submission on February 28, 2018 by the Division of Medication Error Prevention and Analysis (DMEPA). FDA reassessed this proposed suffix with the Class 2 Resubmission and determined the suffix is accepted. Refer to the review by DMEPA in DARRTs from December 28, 2018.

The original BLA submission contained data from 3 completed studies (B3271001, B271004, and B3271006) and 1 ongoing study (B3271002) to support the determination of no clinically meaningful differences between PF-05280014 and US-Herceptin. A scientific bridge between EU-Herceptin, US-Herceptin, and PF-05280014 has been established based in part on the pharmacokinetic (PK) evaluation in study 1001. The comparative clinical study 1002 (B3271002) is a randomized double-blind study in which patients with human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer received either PF-05280014 plus paclitaxel or EU-approved Herceptin (which will be referred to as EU-Herceptin for the remainder of this review) plus paclitaxel in the first-line setting. The primary endpoint was overall response rate (ORR) achieved by Week 25 and subsequently confirmed at Week 33 as assessed by central review in the intent-to-treat (ITT) population. The ratio of ORR was 0.94 with a 95% CI (0.84, 1.05), and a 90% CI (0.86, 1.03), both of which were within the pre-specified equivalence margin of 0.80 to 1.25. The secondary endpoint results for 1-year PFS rate, duration of response (DOR) and 1-year overall survival rate were similar between both arms. The safety findings of studies 1002 and 1004 were reviewed, with special focus on cardiac dysfunction, infusion-related reactions, hematotoxicity, embryo-fetal toxicity and pulmonary adverse reactions and no clinically meaningful differences were found in the safety population. Study 1006 was a supportive comparative safety study to further characterize risk of pyrexia.

With the Class 2 Resubmission, no new patients were enrolled or randomized into study B3271002 since the original BLA submission but was ongoing with patients still on study if they were deriving clinical benefit from therapy. A total of 105 (14.9%) patients remained ongoing in the study with a comparative percent in each treatment group [50 patients in the PF-05280014 group and 55 patients in the EU-trastuzumab group]. The applicant submitted an additional Safety Updates from study B3271002, which included an additional 18 months of safety data from the original submission, based on available data as of July 13, 2018 (data cutoff on January 11, 2017). The number of patients who died was comparable across the 2 treatment groups in both the original submission and the safety update, with disease progression as the most frequent cause of death. The incidence of all categories of treatment-emergent adverse events (TEAEs) and serious TEAEs were comparable across the 2 treatment groups in both the original submission and the safety update. The most frequently reported TEAEs (>20% in either treatment group) were alopecia (189 patients in the PF-05280014 group and 186 patients in the EU-trastuzumab group), anemia (123 patients in the PF-05280014 group and 135 patients in the

EU-trastuzumab group), neutropenia (100 patients in the PF-05280014 group and 94 patients in the EU-trastuzumab group), and peripheral sensory neuropathy (93 patients in the PF-05280014 group and 85 patients in the EU-trastuzumab group). There are no new safety signals identified in the safety update.

Overall there are no new concerning clinical safety findings. Refer to the primary clinical and statistics review dated June 22, 2017 for a full analysis of clinical efficacy and safety.

**Clinical Recommendation:** The recommendation from the clinical and statistics reviewers is approval. The results from completed studies B3271001, B271004 and B3271006, as well as the results from one ongoing study B3271002 support the determination of no clinically meaningful differences between PF-05280014 and US-Herceptin.

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## CLINICAL REVIEW

Application Type	BLA, Original 351(k)
Application Number(s)	761081
Priority or Standard	Standard
Submit Date(s)	June 22, 2017
Received Date(s)	June 22, 2017
PDUFA Goal Date	April 20, 2018
Division / Office	DOP1/OHOP
Reviewer Name(s)	Sara Horton, MD Hui Zhang, PhD
Review Completion Date	4/16/2018
Established Name	Trastuzumab-qyyp
(Proposed) Trade Name	TRAZIMERA*
Therapeutic Class	HER2-binding humanized monoclonal antibody
Applicant	Pfizer
Formulation(s)	IV
Dosing Regimen	8 mg/kg IV loading dose, then 6 mg/kg IV q3 wks
Proposed Indication(s)	<p>TRAZIMERA is a HER2/neu receptor antagonist indicated for:</p> <ul style="list-style-type: none"> <li>• the treatment of HER2 overexpressing breast cancer.</li> <li>• the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.</li> </ul>
Recommended Indication	<p>TRAZIMERA is a HER2/neu receptor antagonist indicated for:</p> <ul style="list-style-type: none"> <li>• the treatment of HER2 overexpressing breast cancer.</li> <li>• the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.</li> </ul> <p>Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.</p>

\*In this document, FDA generally refers to the applicant's proposed product by the applicant descriptor "PF-05280014".

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

This biologics license application (BLA 761081) seeks approval of the product PF-05280014 (proposed proprietary name Trazimera), which is a proposed biosimilar to US-licensed Herceptin (which will be referred to as US-Herceptin for the remainder of this review).

The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

From a clinical standpoint, the data submitted to the 351(k) BLA from the clinical development program of PF-05280014 support a demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin. A demonstration that PF-05280014 is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components together with the clinical data discussed in this review, will support licensure of PF-05280014 as a biosimilar to US-Herceptin under section 351(k) of the PHS Act.

## 1.2 Risk Benefit Assessment

Breast cancer is the number one cancer in women, with more than 200,000 women newly diagnosed in the United States and about 40,000 women dying of breast cancer annually. (1) HER2 is a tyrosine kinase transmembrane receptor that is amplified in about 20-30% of breast cancers. HER2-positive breast cancer is associated with a more aggressive phenotype.

Gastric cancer is much more common in less-developed countries than it is in the United States today. In 2017, about 28,000 new cases of gastric cancer and 11,000 deaths due to it are estimated in the United States, with about 7-34% of them overexpressing HER2. (2,3) Known risk factors for gastric cancer are male sex, increasing age, ethnicity, geography, Helicobacter pylori infection, diet, and smoking

to name a few. As in breast cancer, HER2 positive gastric cancer has been associated with a more aggressive phenotype and resulting poorer prognosis.(3)

Treatment of HER2 positive breast and gastric cancer with targeted therapy such as trastuzumab has led to significant increases in response rates compared to chemotherapy alone. It is one of the key agents used to target these tumor subtypes throughout the world and thus plays a central role in treatment of patients with breast and gastric cancer.

Testing for HER2 status is commonly performed in all new diagnoses of invasive breast cancer and frequently also tested at the time of recurrence. Targeted therapy such as trastuzumab has led to significant increases in response rates compared to chemotherapy alone. For the adjuvant treatment of HER2 positive breast cancer, trastuzumab is given for 1 year, in combination with 4-6 cycles of taxane-based chemotherapy. For the treatment of HER2 positive MBC, trastuzumab is FDA approved in combination with paclitaxel for first-line treatment and as single agent for treatment in patients who have received prior chemotherapy for metastatic disease. For patients who progress on first line treatment, subsequent HER2 targeted treatment options include ado-trastuzumab emtansine (T-DM1, Kadcyła) and lapatinib (Tykerb). For the treatment of metastatic HER2 positive gastric adenocarcinoma, trastuzumab is FDA approved to be used in the first-line setting in addition to chemotherapy with fluoropyrimidine (capecitabine or 5-fluorouracil) and cisplatin.

PF-05280014 is a proposed biosimilar to US-Herceptin (trastuzumab). The Applicant has submitted a BLA for PF-05280014 with proposed indications the same as for US-Herceptin:

1. Adjuvant breast cancer:
  - a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
  - b. With docetaxel and carboplatin
  - c. As a single agent following multi-modality anthracycline based therapy
2. Metastatic breast cancer (MBC):
  - a. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
  - b. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease
3. Metastatic gastric cancer:

- a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease

The clinical team recommends approval of PF-05280014 for the following indications:

1. Adjuvant breast cancer:

- a. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- b. With docetaxel and carboplatin
- c. As a single agent following multi-modality anthracycline based therapy

2. Metastatic breast cancer (MBC):

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

3. Metastatic gastric cancer:

- a. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

The results of the clinical development program support a demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin. The applicant submitted data from a study assessing PF-05280014 when used as first-line treatment in patients with HER2-positive metastatic breast cancer (MBC) in comparison to EU-Herceptin. In the comparative clinical study, Study 1002 (B3271002), the primary endpoint of overall response rate (ORR) ratio between the two treatment groups, as assessed by central radiology review, was 0.940 (95% CI: 0.842, 1.049) (PF-05280014 over EU-Herceptin), which was within the pre-specified 0.80 to 1.25 equivalence margin.

An additional PK and clinical study, Study 1004 (B3271004), was conducted comparing PF-5280014 in combination with Taxotere and carboplatin versus EU-Herceptin in combination with Taxotere and carboplatin in patients with operable HER2-positive breast cancer in the neoadjuvant setting. The primary endpoint was the percentage of patients reporting trough plasma concentration ( $C_{\text{trough}}$ )  $>20 \mu\text{g/mL}$  at Cycle 5 (Cycle 6 pre-dose), and a secondary efficacy endpoint of pathological

complete response (pCR) and ORR. The pathological complete response (pCR) was comparable in both treatment arms (PF-05280014: 46.5% versus EU-Herceptin 48.3%), as was the ORR (PF-05280014: 88.1% versus EU-Herceptin 82.0%) in the per-protocol (PP) population.

The neoadjuvant setting for breast cancer used in study 1004 is an acceptable, homogenous, and sensitive patient population to evaluate for no clinically meaningful differences between PF-05002814 and EU-Herceptin. The patient population receiving HER2-based treatment is the same in the neoadjuvant and adjuvant settings, differing only in the timing of surgery. The mechanism of action of trastuzumab in neoadjuvant breast cancer patients is expected to be the same as the mechanism of action for trastuzumab in the indications for which the applicant is seeking licensure.

The safety findings of studies 1002 and 1004 were reviewed, with special focus on cardiac, pulmonary, infusion reaction, and embryo-fetal toxicities. Overall no meaningful differences were found in the safety populations.

In addition, the applicant submitted data from Study B3271001, a PK similarity study in healthy male volunteers, comparing the PK of PF-05280014, EU-Herceptin, and US-Herceptin after a single intravenous dose at 6 mg/kg. The results showed that the 90% confidence intervals for the test-to-reference ratios of maximum (peak) observed drug concentration ( $C_{max}$ ), area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration ( $AUC_t$ ), and area under concentration-time curve from time 0 to infinite time ( $AUC_{inf}$ ) were within the bioequivalence window of 80% to 125% for the comparisons of PF-05280014 to each of EU-Herceptin and US-Herceptin and of US-Herceptin to EU-Herceptin. These data demonstrate the PK similarity among PF-05280014, EU-Herceptin, and US-Herceptin. The results of this PK similarity study support a demonstration of no clinically meaningful differences between PF-05280014 and US-Herceptin.

The results of Study B3271001 also established the pharmacokinetic (PK) component of the scientific bridge between EU-Herceptin, US-Herceptin, and PF-05280014. Based on analytical and PK data, the applicant has established an adequate scientific bridge between EU-Herceptin, US-Herceptin, and PF-05280014 to justify the relevance of clinical data generated using EU-Herceptin to support a demonstration of biosimilarity of PF-05280014 to US-Herceptin.

The applicant is seeking indications that are the same as those for US-Herceptin. The applicant has provided the following justification for extrapolation of the data and information submitted in the application to support licensure, under section 351(k), as a biosimilar for the conditions of use for which US-licensed Herceptin has been previously approved:

- “PF-05280014 is structurally and functionally similar to Herceptin and shares the same mechanism of action (MoA) across all indications.”
- “The data supports a similar PK profile between PF-05280014 and Herceptin.”
- “The biodistribution/disposition mechanisms for PF-05280014 are expected to be similar to those of Herceptin.”
- “PF-05280014 has demonstrated similar clinical efficacy to Herceptin in MBC, with no clinically meaningful differences in safety and immunogenicity. Efficacy in MBC, adjuvant breast cancer and metastatic gastric cancer is related to the shared MoA. The statutory requirements for biosimilarity have been met, and PF-05280014 is expected to have a similar efficacy, safety, and immunogenicity profile as Herceptin in MBC.”

The Applicant has provided adequate justification for extrapolation. The Applicant has demonstrated that PF-05280014 is highly similar to US-Herceptin based on extensive analytical data and that there are no clinically meaningful differences in safety and efficacy between PF-05280014 and US-Herceptin which supports extrapolating the data to other indications (adjuvant breast cancer and metastatic gastric cancer). The reviewers consider extrapolation to be scientifically justified.

The applicant conducted the following clinical studies to support the application:

- B3271001 (PK bridging similarity study, this study will be referred to as study 1001 for the remainder of this review)
- B3271002 (comparative clinical study in patients with metastatic breast cancer, this study will be referred to as study 1002 for the remainder of this review)
- B3271004 (supportive PK and comparative clinical study in patients with early stage operative breast cancer, this study will be referred to as study 1004 for the remainder of this review)
- B3271006 (supportive comparative safety study to further characterize risk of pyrexia, this study will be referred to as study 1006 for the remainder of this review)

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

No clinical postmarket risk evaluation and mitigation strategies are anticipated at this time.

## **1.4 Recommendations for Postmarket Requirements and Commitments**

At the time of the submission of this BLA, a pregnancy registry and pharmacovigilance program was in place for US-Herceptin. Because the risks of oligohydramnios have been adequately characterized in the Herceptin labeling, FDA has determined that the Herceptin pregnancy registry and pregnancy pharmacovigilance program are no longer necessary for Herceptin and therefore, no registry or pharmacovigilance program is needed for this biosimilar.

No PMRs/PMCs were requested.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

PF-05280014 (proposed proprietary name Trazimera) is a proposed biosimilar to US-Herceptin (trastuzumab). Trastuzumab is a humanized IgG1 monoclonal antibody of the kappa isotype consisting of two identical glycosylated heavy chains and two identical light chains. The target of trastuzumab is the cell surface receptor human epidermal growth factor receptor 2 (HER2). HER2 is part of the HER family of transmembrane tyrosine kinases that have been shown to play a role in the regulation of cellular survival, proliferation, adhesion and differentiation.

### **2.2 Tables of Currently Available Treatments for Proposed Indications**

Table 1 below lists the current FDA approved trastuzumab products.

**Table 1: Summary of FDA Approved Trastuzumab Products**

Name	Indication	Approval	Dosing	Efficacy	Safety and Tolerability
Trastuzuma b-dkst (IV, Ogivri, biosimilar)	Same as Herceptin	2017	Same as Herceptin	Studies conducted to support a finding of biosimilarity	Studies conducted to support a finding of biosimilarity
Trastuzumab (IV, Herceptin)	<p>HER2 overexpressing breast cancer</p> <p>HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma</p>	1998	<p>Adjuvant breast cancer (52 weeks total):</p> <p>1) 4 mg/kg load, then 2 mg/kg weekly with taxane, then 6 mg/kg every 3 weeks;</p> <p>2) after anthracycline-based chemotherapy 8 mg/kg load, then 6 mg/kg every 3 weeks</p> <p>Metastatic breast cancer: 4 mg/kg load, then 2 mg/kg weekly</p> <p>Metastatic gastric cancer: 8 mg/kg load, then 6 mg/kg every 3 weeks</p>	<p>Adjuvant breast cancer: 4 studies showing benefit in DFS and OS with addition of trastuzumab to chemotherapy</p> <p>Metastatic breast cancer: 2 studies showing benefit in TTP and ORR</p> <p>Metastatic gastric cancer: 1 study showing benefit in OS</p>	<p>Cardiomyopathy</p> <p>Infusion reactions</p> <p>Embryo-fetal toxicity</p> <p>Pulmonary toxicity</p> <p>Exacerbation of chemotherapy-induced neutropenia</p>

## 2.3 Availability of Proposed Active Ingredient in the United States

PF-05280014 is not currently marketed in the United States.

Reference Product:

Herceptin was initially licensed in the United States on September 25, 1998.

Subsequently, two additional indications were approved based on supplements to the BLA. The indications for which trastuzumab are licensed are:

- The treatment of HER2 overexpressing breast cancer.
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Boxed warnings from the FDA prescribing information for US-Herceptin include cardiomyopathy, infusion reactions, embryo-fetal toxicity, and pulmonary toxicity. Additional warnings and precautions from the FDA label include exacerbation of chemotherapy-induced neutropenia.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The major clinical regulatory activity with the FDA was as follows:

**February 10, 2012:** Biologics Product Development, Pre-IND Meeting

Discussed FDA's position that, a 3-way scientific bridge between EU-licensed Herceptin (which will be referred to as EU-Herceptin for the remainder of this review), US-Herceptin, and PF-05280014 would need to be incorporated into the 3 arm PK similarity study (B3271001).

Extrapolation would be possible with sufficient scientific justification.

**July 12, 2013:** Biologics Product Development, Type 3 Meeting

Discussed FDA's agreement with the phase 3 study primary endpoint of ORR by week 25. FDA advised Pfizer to recalculate sample size using the risk ratio instead of an absolute difference in response rate. FDA requested an additional study to further evaluate pyrexia finding in the phase 1 PK study. FDA agreed that the phase 3 study could proceed

**June 22, 2017:** BLA 761081 submitted to FDA.

## **2.6 Other Relevant Background Information**

None

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The overall data quality and integrity are acceptable to the reviewers. The submitted datasets are generally consistent and variables are clearly labeled and/or explained. The tumor response datasets included all assessment values and time points. In addition, the applicant responded to numerous information inquiries in a timely manner and resolved identified issues and/or review questions satisfactorily. Based on the submitted data and reports, the reviewers believe that analyses and results are reliable for regulatory decision making.

### **3.2 Compliance with Good Clinical Practices**

The clinical studies were conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Conference on Harmonisation [ICH] 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In study 1002, the final protocol, amendments and informed consent documentation were reviewed and approved by the Institutional Review Board(s) (IRB) or Independent Ethics Committee(s) (IEC) at each of the investigational sites participating in the study. The applicant stated that the study was conducted in compliance with all International Conference on Harmonisation (ICH) GCP Guidelines. In addition, all local regulatory requirements were followed. Safety data were reviewed throughout the study by an external Data Monitoring Committee (DMC). Independent central radiological review of tumor assessment up to Week 33 was performed by Parexel Informatics, who continued to review tumor assessments up to approximately 1-year post randomization (Week 53 assessments). Patient narratives were written and underwent quality review by (b) (4). All other aspects of the CSR were written and quality reviewed by (b) (4).

Quality assurance audits were performed at the study sites by the sponsor's independent quality assurance group or by CRO and/or individual contract personnel under the group's direction. These audits were conducted according to the sponsor's procedures and GCP guidelines.

The clinical study report has been subject to quality control review by the sponsor or the sponsor's designee. The QC processes were reviewed by the sponsor's independent quality assurance group.

### **3.3 Financial Disclosures**

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, the applicant requested statements of financial interest from 860 clinical investigators who participated in studies B3271001, 1002, 1004 and 1006. Two of the 860 clinical investigators listed in the study reports had financial information to disclose that exceeded the disclosure reporting threshold.

***Reviewer Comment: Of the two sites with the clinical investigators that exceeded the disclosure reporting threshold, one site enrolled 3 patients and the other site 1 patient of the 707 patients enrolled on study 1002. Given this small number of patients were enrolled by these two sites, it is unlikely that the study results will be affected.***

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Product Quality**

*Please refer to Dr. Cishan Li and Rachel Novak review for BLA 761081.*

### **4.2 Clinical Microbiology**

*Please refer to Dr. Maria Jose Lopez-Barragan (DS), Virginia Carroll (DP) reviews for BLA 761081.*

### **4.3 Immunogenicity**

*Please refer to Dr. Cishan Li's review for BLA 761081.*

### **4.4 Preclinical Pharmacology/Toxicology**

*Please refer to Dr. Claudia Miller's review for BLA 761081.*

## **4.5 Clinical Pharmacology**

*Please refer to Dr. Christy John's review for BLA 761081.*

### **4.5.1 Mechanism of Action**

Trastuzumab is a humanized IgG1k monoclonal antibody directed against an epitope on the extracellular juxtamembrane domain of HER2. Multiple mechanisms of action have been proposed for trastuzumab, including inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, inhibition of extracellular domain shedding, and activation of cell-mediated immune defenses such as ADCC activity. Trastuzumab has not been shown to inhibit the dimerization of HER2 with the other isoforms; therefore, signaling through the other three receptor isoforms is maintained in the presence of the antibody. Studies have supported a mechanism by which trastuzumab is bound to the HER2 receptor and taken up by the target cell through endocytosis and subsequently degrades the receptor leading to a downregulation of downstream survival signaling, cell cycle arrest and apoptosis. Trastuzumab has also been shown to block the cleavage/shedding of the HER2 receptor extracellular domain thereby preventing the formation of the activated truncated p95, which has been correlated with a poor prognosis based on the detection of the released extracellular domain of HER2 in the serum of metastatic breast cancer patients. (4, 5, 6)

### **4.5.2 Pharmacodynamics**

*Please refer to Dr. Christy John's review for BLA 761081.*

### **4.5.3 Pharmacokinetics**

*Please refer to Dr Christy John's review for BLA 761081.*

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

A listing of clinical trials applicable to this BLA is provided below in Table 2.

**Table 2: Listing Of Clinical Trials**

Protocol No. (Country)	Study Design and Objective(s)	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group)	Duration of Treatment	Study Start/Status	Study Synopsis
<b>Healthy Subject PK and Initial Tolerability Studies</b>							
B3271001 Phase 1: US, single center	<p>Double blind, randomized, parallel-group, single-dose, 3-arm, comparative PK study of PF-05280014 and trastuzumab sourced from US and EU administered to healthy male volunteers.</p> <p><b>Primary Objective:</b></p> <ul style="list-style-type: none"> <li>• Demonstrate the PK similarity of PF-05280014 to trastuzumab-EU.</li> <li>• Demonstrate the PK similarity of PF-05280014 to trastuzumab-US.</li> <li>• Demonstrate the PK similarity of trastuzumab-EU to trastuzumab-US.</li> </ul> <p><b>Secondary Objective:</b></p> <ul style="list-style-type: none"> <li>• Evaluate the single-dose safety and tolerability of PF-05280014 compared to trastuzumab-US and trastuzumab-EU.</li> <li>• Evaluate the immunogenicity associated with a single dose of PF-05280014.</li> </ul>	PF-05280014: 6 mg/kg as a 90-minute IV infusion.	Randomized: 35 Treated: 35 Completed: 34	Sex: M Age (Years) Mean: 34.5 Range: 18-55 Race: W/B/A/O: 13/15/0/7.	Single dose	23 May 2012 / 14 December 2012. Completed.	Module 5.3.3.1 B3271001
		Trastuzumab-EU: 6 mg/kg as a 90-minute IV infusion.	Randomized: 35 Treated: 35 Completed: 35	Sex: M Age (Years) Mean: 36.1 Range: 21-55 Race: W/B/A/O: 7/22/0/6.			
		Trastuzumab-US: 6 mg/kg as a 90-minute IV infusion.	Randomized: 35 Treated: 35 Completed: 35	Sex: M Age (Years) Mean: 35.3 Range: 21-53 Race: W/B/A/O: 8/16/1/10.			

Protocol No. (Country)	Study Design and Objective(s)	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group)	Duration of Treatment	Study Start/Status	Study Synopsis
	<p>trastuzumab-US and trastuzumab-EU.</p> <ul style="list-style-type: none"> <li>• Demonstrate the PK similarity of PF-05280014 to the combined groups of trastuzumab-US and trastuzumab-EU.</li> </ul>						
B3271006 Phase 1: US, single center	<p>Double-blind, randomized, parallel-group, single-dose, 2-arm, safety study of PF-05280014 and trastuzumab sourced from the US administered to healthy male volunteers.</p> <p><b>Primary Objective:</b></p> <p>Estimate the relative risk of abnormal elevated body temperature compared to baseline following PF-05280014 or trastuzumab-US administration.</p> <p><b>Secondary Objective:</b></p> <p>Evaluate the safety of PF-05280014 versus trastuzumab-US.</p>	PF-05280014: 6 mg/kg as a 90-minute IV infusion.	Randomized: 81 Treated: 81 Completed: 63	Sex: M Age (Years) Mean: 34.5 Range: 18-55 Race: W/B/O: 38/43/0.	Single dose	02 January 2014 / 04 April 2014. Completed.	Module 5.3.3.1 B3271006
		Trastuzumab-US: 6 mg/kg as a 90-minute IV infusion.	Randomized: 81 Treated: 81 Completed: 65	Sex: M Age (Years) Mean: 33.6 Range: 18-53 Race: W/B/O: 32/47/2.			
<b>Study Reports of Controlled Clinical Studies in Patients with HER2-Positive, Metastatic Breast Cancer</b>							

Protocol No. (Country)	Study Design and Objective(s)	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group)	Duration of Treatment	Study Start/Status	Study Synopsis
B3271002 Phase 3: Argentina, Brazil, Chile, Czech Republic, Greece, Hungary, India, Japan, Republic of Korea, Latvia, Mexico, Peru, Philippines, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Thailand, Turkey, Ukraine, US.	<p>Randomized, double-blind study of PF-05280014 plus paclitaxel versus trastuzumab plus paclitaxel for the first-line treatment of patients with HER2-Positive metastatic breast cancer.</p> <p><b>Primary Objectives:</b> Compare the ORR in PF-05280014 to trastuzumab-EU in combination with paclitaxel.</p> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>Evaluate the safety of PF-05280014 plus paclitaxel versus trastuzumab-EU plus paclitaxel;</li> <li>Evaluate secondary measures of tumor control;</li> <li>Evaluate the population PK of PF-05280014 and trastuzumab-EU;</li> <li>Evaluate the immunogenicity of PF-05280014 and trastuzumab-EU.</li> </ul>	PF-05280014 Route: IV; Dose Regimen: loading dose: 4 mg/kg; subsequent weekly dose: 2 mg/kg until Week 33, then dosage may have changed to 6 mg/kg every 3 weeks after paclitaxel discontinuation.	Randomized: 352  Treated: 349  Completed: 11	Sex: F Age (Years): Mean: 54.0 Range: 19-80 Race: W/B/A/O: 232/5/104/11.	Multiple dose, until disease progression.	24 February 2014 / TBD. Ongoing.	Module 5.3.3.1 B3271002
		Trastuzumab-EU Route: IV; Dose Regimen: loading dose: 4 mg/kg; subsequent weekly dose: 2 mg/kg until Week 33, then dosage may have changed to 6 mg/kg every 3 weeks after paclitaxel discontinuation.	Randomized: 355  Treated: 353  Completed: 6	Sex: F Age (Years): Mean: 54.1 Range: 25-85 Race: W/B/A/O: 244/8/84/19.			

Protocol No. (Country)	Study Design and Objective(s)	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group)	Duration of Treatment	Study Start/Status	Study Synopsis
B3271004 Phase 3: Belarus, Czech Republic, Hungary, Italy, Poland, Russian Federation, Serbia, Slovakia, Ukraine, US.	<p>A double-blind, randomized, clinical trial evaluating the PK, efficacy, safety, and immunogenicity of PF-05280014 in combination with Taxotere and carboplatin versus trastuzumab-EU in combination with Taxotere and carboplatin in patients with operable HER2-positive breast cancer in the neoadjuvant setting.</p> <p><b>Primary Objective:</b> To compare the percentage of patients with steady state (Cycle 5) trough plasma concentration (<math>C_{50\text{mg}}</math>) <math>\geq 20</math> <math>\mu\text{g/mL}</math> for PF-05280014 versus trastuzumab-EU in patients with operable HER2-positive breast cancer who received study therapy together with Taxotere and carboplatin in the neoadjuvant setting.</p> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>To evaluate measures of tumor control for PF-05280014 versus trastuzumab-EU, when administered in</li> </ul>	PF-05280014 Route: IV; Dose Regimen: loading dose: 8 mg/kg; subsequent dosing (every 3 weeks): 6 mg/kg. Taxotere and carboplatin were administered every 3 weeks (ie, cycled every 21 days) for a total of 6 treatment cycles.	Randomized: 114  Treated: 113  Completed: 109	Sex: F Age (Years): Mean: 54.0 Range: 26-77 Race: W/B/A: 112/1/1.	Multiple dose for 6 cycles (approximately 18 weeks)	23 September 2014 / 09 March 2016. Completed.	Module 5.3.3.2 B3271004
		Trastuzumab-EU Route: IV; Dose Regimen: loading dose: 8 mg/kg; subsequent dosing (every 3 weeks): 6 mg/kg. Taxotere and carboplatin were administered every 3 weeks (ie, cycled every 21 days) for a total of 6 treatment cycles.	Randomized: 112  Treated: 112  Completed: 106	Sex: F Age (Years): Mean: 51.2 Range: 24-79 Race: W/B/A: 109/0/3.			

Protocol No. (Country)	Study Design and Objective(s)	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group)	Duration of Treatment	Study Start/Status	Study Synopsis
	combination with Taxotere and carboplatin in the neoadjuvant setting. <ul style="list-style-type: none"> <li>To evaluate the safety of PF-05280014 versus trastuzumab-EU, administered in combination with Taxotere and carboplatin.</li> <li>To evaluate the immunogenicity of PF-05280014 versus trastuzumab-EU.</li> <li>To evaluate the PK of PF-05280014 and trastuzumab-EU.</li> <li>To explore the relationship between drug exposure and pathologic complete response (pCR) for PF-05280014 versus trastuzumab-EU, administered in combination with Taxotere and carboplatin.</li> </ul>						

Source: Module 5.3.3.1 B3271001; B3271006; Module 5.3.5.1 B3271002; Module 5.3.3.2 B3271004.

Abbreviations: Note: A = Asian; B = Black;  $C_{trough}$  = trough plasma concentration; DB = Double-blind; EU = European Union; F = Female; HER2 = human epidermal growth factor receptor 2; IV = intravenous; M = Male; No. = Number; ORR = objective response rate; O = Other; PK = pharmacokinetics; US = United States; W = White.

Source: eCTD Module 5, Section 5.2

## 5.2 Review Strategy

The efficacy and safety review was conducted by Dr. Sara Horton and the statistical review was conducted by Dr. Hui Zhang. The clinical review included the following:

- Literature review of HER2-positive breast and gastric cancer
- Research of the FDA data base for regulatory history of the PF-05280014 IND 110427 and review of meeting minutes conducted during drug development
- Review of Applicant submitted CSR, protocol, protocol amendments, and selected datasets for Study B3271001, 1002, 1006 and B3271004
- Review of selected case report forms (CRFs) for B3271002 and B3271004
- Review of selected patient narratives for serious adverse events and deaths in B3271002 and B3271004
- Review of response to clinical and biostatistical queries sent to the Applicant
- Review of consultation reports from the Office of Scientific Investigations
- Review of Herceptin label

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Study B3271002

#### Study Design

Study 1002 is a multicenter, double-blind, randomized comparative study evaluating the efficacy, safety, PK, and immunogenicity of PF-05280014 in combination with paclitaxel versus EU-Herceptin with paclitaxel in patients with HER2-positive metastatic breast cancer in the first-line treatment setting. Patients were randomized 1:1 to either PF-05280014 plus paclitaxel or EU-Herceptin plus paclitaxel. Randomization was stratified by prior trastuzumab exposure (yes versus no) and estrogen receptor (ER) status (ER positive versus ER negative).

Trastuzumab was given weekly on Days 1, 8, 15, and 22 of each 28-day cycle. Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the trastuzumab regimen could be changed at the discretion of the investigator to every 3 weeks at a dose of 6 mg/kg infused over 30 to 90 minutes.

Paclitaxel was administered on Days 1, 8, and 15 of each 28-day cycle (i.e., no paclitaxel was administered on Day 22 of each cycle) with a starting dose of 80 mg/m<sup>2</sup> by IV infusion over 60 minutes.

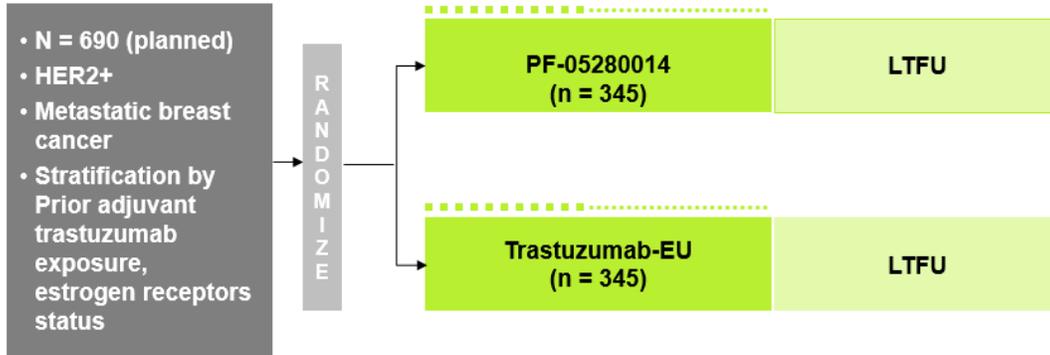
There are two designated treatment periods (Treatment Period 1 and Treatment Period 2) in the study protocol design. The study elements that are required to achieve the study objectives and endpoints (i.e., up through Week 53 visit assessments) are contained within Treatment Period 1. However, since the study population includes patients benefiting from study treatment and who are typically treated beyond attainment of the study objectives and endpoints, Treatment Period 2 was intended solely to provide access to study treatment for patients who continue to receive clinical benefit beyond Treatment Period 1.

1. Treatment Period 1 for a patient began with the first dose of study drug on Cycle 1, Day 1 and ended with the completion of the Week 53 visit assessments and upon providing written, signed and dated informed consent for protocol amendment 4.
2. Treatment Period 2 was for patients benefiting from study treatment at Week 53. These patients who received study treatment beyond Week 53 at the time of amendment 4 approval were consented for and entered Treatment Period 2 no later than 28 days following approval.

The study design is shown in Figure 1 below.

**Figure 1: Study B3271002 Design**

**Study treatment:** Trastuzumab 4 mg/kg IV, then weekly 2 mg/kg; Week 33 changed to 6 mg/kg Q3 weekly  
 Paclitaxel 80 mg/m<sup>2</sup> Days 1, 8, and 15 (during 28-day cycle), 6 cycles



Source: PF-05280014 AOM Meeting August 17, 2017

**Reviewer Comment:** The design of the comparative clinical study is acceptable. The metastatic breast cancer population studied in B327-1002 and the efficacy endpoint of ORR at Week 25, confirmed at Week 33, is appropriate.

The schedule of activities is shown in Table 3 below.

**Table 3: Study 1002 Schedule of Events During Combination Treatment**

Protocol Activity/Cycle	Screen	Treatment period										End of Treatment Visit [18]	Follow-up [19]
		Cycle 1				Subsequent Cycles up through Week 53							
Cycle Week		1	2	3	4	1	2	3	4				
Cycle day	≤28 Prior to Randomization	1	8	15	22	1	8	15	22				
Time (hr) Post-dose		Pre-dose	0										
Study Visit Window (days within cycle)	-10 Days	0	0		±2	±2	±2	±4	±2	±2	±2	+7	±14
<b>Pre-treatment Documentation</b>													
Informed Consent [1]	X												
Demography, Medical History [2]	X												
Physical Examination [3]	X	X			X		X		X		X		X
Vital signs [4]	X	X			X	X	X	X	X	X	X		X
ECOG Performance Status	X												
Inclusion/Exclusion Criteria	X												
<b>Laboratory Studies and Tests</b>													
Tumor HER2 status [7]	X												
Tumor ER testing (only for patients with unknown status) [8]	X												
Hematology [9]	X	X			X	X		X	X	X			X
Blood Chemistry [9]	X	X						X					X
Pregnancy Test (as appropriate) [10]	X	X						X					X
Contraception Check [11]	X		X		X	X	X	X	X	X	X	X	X

Protocol Activity/Cycle	Screen	Treatment period												End of Treatment Visit [18]	Follow-up [19]
		Cycle 1				Subsequent Cycles up through Week 53									
Cycle Week		1	2	3	4	1	2	3	4						
Cycle day	≤28 Prior to Randomization	1	8	15	22	1	8	15	22						
<b>Time (hr) Post-dose</b>		Pre-dose	0												
<b>Study Visit Window (days within cycle)</b>	-10 Days	0	0		±2	±2	±2	±4	±2	±2	±2	±2		+7	±14
Viral disease screen where required by Regulations [12]	X														
12-lead ECG	X													X	
MUGA or ECHO [20]	X	Weeks 9, 17, 25, 33, 41 and 53, and as clinically indicated. Allowable window is ±14 days.											X if not within 12 weeks		
<b>Randomization [13]</b>	X														
Trastuzumab administration		X		X	X	X	X	X	X	X	X	X	X		
Paclitaxel administration		X		X	X		X	X	X						
PK, ADA/Nab and Serum HER2 Sampling		Refer to Study Flowchart 2													
<b>Disease Assessments:</b>															
Tumor Assessment [14]	X	Weeks 9, 17, 25, 33, 41 and 53. Allowable window is ±14 days.											Refer to Study Flowchart 4		
Bone Scan [15]	X	If positive at baseline, Week 33 to confirm partial or complete response if not performed earlier, and as clinically indicated											Refer to Study Flowchart 4		
<b>Other Clinical Assessments:</b>															
Adverse Events [16]	X														Monitored continuously
Prior and Concomitant Medication and Non-drug Treatments [17]	X														Monitored continuously
Survival Follow-up [19]															X

Abbreviations: ADA=Anti-drug Antibodies; β-HCG=Beta Human Chorionic Gonadotropin; CT=Computed Tomography; ECG =Electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ECHO=Echocardiogram; EOT=End of Treatment; HER=Human Epidermal Growth; HBeAg=hepatitis B surface antigen; HBeAb=hepatitis B core antibody; HCVAb=Hepatitis C virus antibody; HIV=human immunodeficiency virus; LVEF=Left Ventricular Ejection Fraction; mAb=monoclonal Antibodies; MUGA=Multi Gated Acquisition Scan; Nab=Neutralizing antibody; PK=pharmacokinetic

Footnotes for Schedule of Activities During Combination Treatment	
1.	<b>Informed Consent.</b> Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
2.	<b>Medical History and Demographics.</b> To include information on prior anti-tumor regimens and last relapse date.
3.	<b>Physical Examination.</b> A complete physical examination to be conducted at Screening and End of Treatment only. All other evaluations will be symptom-directed evaluations. Height will be recorded at screening only.
4.	<b>Vital Signs:</b> Temperature, blood pressure, pulse rate, and respiratory rate will be recorded at all indicated time points. Height will be recorded at screening only. Weight will be recorded at screening, Day 1 of each cycle, and as clinically indicated. The weight from Day 1 of each cycle should be used to calculate the dosage of trastuzumab to be administered on days 1, 8, 15, and 22 of each cycle provided there has not been, in the opinion of the investigator, a clinically significant change in body weight. Of note, if it is a site's standard practice to measure weight weekly, the weight obtained at the previous week/visit can be used to calculate the dosage of trastuzumab to be administered at the current week/visit (eg, the day 22 weight can be used to calculate the dosage for the subsequent cycle day 1) provided there has not been, in the opinion of the investigator, a clinically significant change in body weight. If the patient has experienced a weight change that is considered clinically significant in the opinion of the investigator the patient should be weighed prior to dosing and that weight should be used to calculate the dosage. If the dosage of trastuzumab is calculated using a weight that was NOT collected on day 1 of a cycle that weight should be recorded on an unplanned vital signs eCRF. Vital signs will be taken as follows around trastuzumab infusions:
5.	Cycle 1 Day 1 before, within 10 minutes post-trastuzumab infusion, and within 1 to 2 hours post-trastuzumab infusion, and
6.	On subsequent treatment days - before and within 10 minutes post-trastuzumab infusion.
7.	<b>HER2 Status:</b> Required documentation of HER2 gene amplification or HER2 overexpression as described in Inclusion Criteria, Section 4.1. Sponsor-provided central laboratory is available for screen testing for patients with unknown status.
8.	<b>ER Testing:</b> Only for patients with unknown status. Required documentation of ER status as described in Inclusion Criteria, Section 4.1.
9.	<b>Hematology and Chemistry:</b> Hematology and chemistry assessments will be performed using local laboratories. Parameters required in this study are listed in Table 5. Additional hematology or chemistry assessments may be performed according to standard of care or as clinically indicated. A visit window of -1 day is allowed for the hematology and chemistry assessments required prior to dosing on Cycle 1, Day 1. Note, the hematology and chemistry labs need to be performed once within the screening period and again prior to dosing on Cycle 1, Day 1. If the site is able to have the hematology and chemistry results turned around same day such that they can confirm the patient's eligibility and dose on the same day the same draw, could be used for screening and Cycle 1, Day 1, however it should be noted that adopting such a strategy could be problematic for a patient if the lab results are not favorable on the intended Cycle 1, Day 1.
10.	<b>Pregnancy Test:</b> For patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 10 mIU/mL, will be performed by the local laboratory at screening, within 1 week before study treatment administration. A negative pregnancy result is required before the patient may receive the investigational product. If a negative pregnancy test was not obtained during the screening period within 1 week of the first dose, then the test should be repeated and the patient should not be dosed until it is confirmed the result is negative. If a negative pregnancy test was obtained during the screening period within 1 week of the first dose then the test does not need to be repeated prior to the Cycle 1, Day 1 dose. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), on Day 1 of each dosing cycle, and at the end of treatment visit to confirm the patient has not become pregnant during the study. Additional pregnancy testing may be necessary if required by local practices or regulations.
11.	<b>Contraception Check:</b> At each study visit, for patients who, in the opinion of the investigator, are biologically capable of having children and are sexually active, the investigator will confirm and document consistent and correct use of 2 highly effective methods of contraception consistently and correctly.
12.	<b>Viral disease screening tests:</b> HBsAg, HbcAb, HCVAb, and HIV to be conducted by local laboratory where required by local regulations or if warranted by patient history.
13.	<b>Randomization:</b> All Screening procedures, laboratory results and repeat laboratory results must be completed and reviewed within the screening period prior to randomization. Randomization of eligible patients is preferred no more than 4 business days before administration of first dose of investigational product.
14.	<b>Tumor Assessments:</b> CT or MRI of chest and abdomen and any other site of disease clinically indicated, required at screening for all patients, within 6 weeks prior to randomization. Assessments during treatment must be done every 8 weeks from randomization through Week 41 and at Week 53. Assessments are NOT to be scheduled based on the previous imaging time-point, but rather based on the calendar from date of randomization. The allowable window for disease assessments is ±14 days.
15.	<b>Bone Scans:</b> Required at screening for all patients, within 12 weeks prior to randomization. If positive for breast cancer bone lesions at baseline, subsequent assessments to be performed to confirm partial or complete response at Week 33 if not performed earlier or at any time if patients describe increased bone pain or a new bone pain, or other

signs/symptoms or laboratory abnormalities suggesting progressive bone disease.
16. Adverse Events: Serious adverse events should be monitored and reported from the time that the patient provides informed consent through and including 6 months after the last dose of study treatment. Patients must be followed for non-serious adverse events from the first day of study treatment through and including 6 months after the last dose of study treatment. (See Section 8.14).
17. Prior and Concomitant Medication/Non-Drug Treatments: Medications and non-drug treatments will be verified at screening and monitored continuously by the investigator. (See Sections 5.7, 5.8, 5.9).
18. End of Treatment Visit: Evaluation performed at least 28 days after last dose. Patients that are beyond Week 53 of treatment at the time of Amendment 3 approval must have their End of Treatment visit as soon as possible and no later than 28 days following approval.
19. Follow-up: If study treatment is discontinued before Week 53, patient survival status will be collected by telephone contact every 2 months (±14 days) up to 1 year from patient randomization. Refer to footnote 14 above for AE follow-up requirements.
20. MUGA or ECHO: If a MUGA or ECHO assessment was performed within 7 days prior to the patient providing informed consent as part of the site's standard of care it can be used for the purpose of this study to evaluate the patient's cardiac function during the screening period and does not need to be repeated during the screening period.

Source: B3271002 Protocol Amendment 3

***Reviewer Comment: The schedule of activities is appropriate. Cardiac assessment was performed at baseline and every 8 weeks, which is more frequent than standard of care. Laboratory, EKG AE and PK assessments are also appropriate.***

## Study Objectives and Endpoints

### Primary Objective

To compare the objective response rate (ORR) defined as the percent of patients within each treatment group that achieved Complete Response (CR) or Partial Response (PR) by Week 25 of the study and confirmed on a follow-up assessment, in accordance with the RECIST 1.1., in patients with metastatic HER2-positive breast cancer who receive PF-05280014 in combination with paclitaxel to those who receive EU-Herceptin in combination with paclitaxel.

### Secondary Objectives

- To evaluate the safety of PF-05280014 plus paclitaxel versus EU-Herceptin plus paclitaxel;
- To evaluate secondary measures of tumor control;
- To evaluate the population pharmacokinetics (PK) of PF-05280014 and EU-Herceptin;
- To evaluate the immunogenicity of PF-05280014 and EU-Herceptin.

### Primary Endpoint

Objective Response Rate (ORR), evaluating responses achieved by Week 25 and subsequently confirmed, based on the assessments of the central radiology review in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

### Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events, including cardiotoxicity and infusion-related reactions, and laboratory abnormalities;

- Duration of response (DOR), 1-year progression-free survival (PFS) rate and 1-year survival rate;
- Peak and trough PF-05280014 and EU-Herceptin concentrations at selected cycles;
- Incidence of anti-drug (trastuzumab) antibodies (ADA), including neutralizing antibodies (Nab).

***Reviewer comment: The objectives and endpoints are appropriate, with ORR ratio at Week 25 an appropriate endpoint and agreed upon by the FDA.***

## Eligibility Criteria

### Inclusion Criteria

1. Female patients aged 18 years or older. (Where required by regulations, consent from a legally acceptable representative is required for all patients who are younger than 20 years of age).
2. Histologically confirmed diagnosis of breast cancer.
3. Presence of metastatic disease.
4. Documentation of HER2 gene amplification or overexpression by one of the following:
  - a. Gene amplification by fluorescent in-situ hybridization (FISH), chromogenic in-situ hybridization (CISH), or dual in-situ hybridization (DISH) (as defined by the manufacturer's kit instruction); OR
  - b. Overexpression by immunohistochemistry (IHC) categorized as IHC3+; OR
  - c. Overexpression by immunohistochemistry categorized as IHC2+ with FISH, CISH, or DISH confirmation.If HER2 status is unavailable or was determined using a test other than a Sponsor-approved assay listed in Appendix 1, eligibility must be documented prior to randomization either by:
  - a. the Sponsor-provided central laboratory; OR
  - b. HER2 local testing using both an IHC and an in-situ hybridization analytical test neither of which are considered Sponsor approved. The results from both assays must be unequivocal (i.e., IHC result must be categorized as IHC3+).
5. Available tumor tissue (i.e., formalin fixed-paraffin embedded blocks or unstained slides) for central review of HER2 status. Tumor tissue should be from metastatic disease or, if not obtainable, may be from the primary tumor at the time of initial or current diagnosis.
6. Documentation of ER status (positive or negative) based on local laboratory or Sponsor-identified central laboratory.
7. At least 1 measurable lesion as defined by RECIST 1.1; measurable lesions must be outside prior radiation fields. The following kinds of lesions are not measurable according to RECIST 1.1: ascites, pleural or pericardial effusion, osteoblastic or osteolytic bone metastases, and carcinomatous lymphangitis of

the lung. The site must forward the radiographs to the independent central review laboratory to obtain confirmation of the presence of measurable disease prior to patient randomization.

8. Eastern Cooperative Oncology Group (ECOG) status of 0 to 2.
9. Left ventricular ejection fraction (LVEF) within institutional range of normal, measured by either two-dimensional echocardiogram (ECHO) or multigated acquisition (MUGA) scan.
10. Screening laboratory values within the following limits:
  - a. Absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9$  cells/L (1500/mm<sup>3</sup>);
  - b. Platelet count  $\geq 100 \times 10^9$  cells/L (100,000/mm<sup>3</sup>);
  - c. Hemoglobin  $\geq 9.0$  g/dL (90 g/L);
  - d. Serum creatinine  $\leq 1.5$  x upper limit of normal (ULN);
  - e. Total bilirubin  $\leq 1.5$  x ULN (<3 ULN if Gilbert's disease);
  - f. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)  $\leq 2.5$  x ULN ( $\leq 5$  x ULN if liver metastases are present).
11. Recovery (to Grade 1 or baseline) from all clinically significant adverse effects of prior therapies (excluding alopecia).
12. Patients of childbearing potential must agree to use 2 highly effective methods of contraception, Life Style Guidelines, throughout the study and for 12 months after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active.
13. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
14. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

### Exclusion Criteria

1. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees directly involved in the conduct of the trial.
2. Relapse within 1 year of last dose of previous adjuvant (including neoadjuvant) treatment (except endocrine therapy) and within 1 year before randomization.
3. Prior systemic therapy for metastatic disease (except endocrine therapy).
4. Prior cumulative dose of doxorubicin of  $>400$  mg/m<sup>2</sup>, epirubicin dose  $>800$  mg/m<sup>2</sup>, or the equivalent dose for other anthracyclines or derivatives (eg, 72 mg/m<sup>2</sup> of mitoxantrone).  
If the patient has received more than one anthracycline, then the cumulative dose must not exceed the equivalent of 400 mg/m<sup>2</sup> of doxorubicin.
5. Inflammatory breast cancer.

6. Superficial disease site that cannot be assessed by radiographic method as the only site of measurable disease. Patients with superficial lesions that can be measured by computed tomography (CT) scan or magnetic resonance imaging (MRI) are eligible.
7. Major surgery, radiotherapy, or any investigational agents, within 4 weeks before the administration of the first dose of study treatment.
8. Concurrent administration of other anticancer therapies. Bisphosphonate or Receptor Activator for Nuclear Factor  $\kappa$  B (RANK) ligand inhibition therapy for pre-existing bone metastases or osteoporosis is allowed; prophylactic use to prevent bone metastasis is exclusionary.
9. Active uncontrolled or symptomatic central nervous system (CNS) metastases, as evidenced by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have completed definitive treatment and have not received anticonvulsants or steroids for at least 4 weeks before first dose of study treatment. Patients with newly detected asymptomatic CNS metastases must complete definitive treatment (eg, radiotherapy, stereotactic surgery) before being considered for study entry. Patients with a history of carcinomatous meningitis (leptomeningeal disease) are not eligible.
10. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (CHF) New York Heart Association (NYHA) functional classification of  $\geq 3$ , unstable angina, or myocardial infarction within 12 months before first dose of study treatment.
11. Preexisting grade 2 or greater motor or sensory neuropathy.
12. History of severe hypersensitivity reaction to taxanes, trastuzumab, murine proteins, or excipients in their formulations.
13. Clinical contraindication to treatment with steroids preventing use as part of paclitaxel premedication.
14. Pregnant females; breastfeeding females; females of childbearing potential who are unwilling or unable to use two highly effective methods of contraception as outlined in this protocol for the duration of the study and for 12 months after last dose of investigational product.
15. Known or demonstrated viral infection as listed below. Testing to demonstrate eligibility is required only in countries where regulations mandate testing. In all other countries, testing should be considered if a patient is at risk for having undiagnosed infection (for example due to history of injection drug use or due to geographic location).
  - a. Seropositivity for human immunodeficiency virus (HIV);
  - b. Hepatitis B and/or hepatitis C infection (as detected by positive testing for hepatitis B surface antigen [HbsAg] or antibody to hepatitis C virus [anti HCV] with confirmatory testing).
16. History of another cancer diagnosis (including contralateral breast cancer) within 5 years prior to screening for this study, with the exception of adequately treated ductal carcinoma in situ, cervical carcinoma in situ, or basal or squamous cell

skin cancer.

17. Unwilling or unable to comply with the Life Style Guidelines described in this protocol.
18. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks before randomization and/or during study participation. Patients participating in observational studies not involving an investigational drug(s) and/or long-term follow up of studies involving an investigational drug(s) in which treatment was completed  $\geq 4$  weeks before randomization are not excluded.
19. Other severe acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

**Reviewer comment: The inclusion and exclusion criteria are appropriate.**

### **Drug Administration**

On treatment days when both trastuzumab and paclitaxel were administered, the order of administration was trastuzumab infusion followed by paclitaxel infusion. During the period in which trastuzumab was administered in combination with paclitaxel, and until at least Week 33 of the study, trastuzumab was administered in a weekly regimen on Days 1, 8, 15 and 22 of each 28-day cycle. The first administration on Day 1, Cycle 1 was a loading dose of 4 mg/kg infused over 90 minutes. Subsequent weekly infusions were 2 mg/kg administered over 30 to 90 minutes depending on tolerability. Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the trastuzumab regimen could have changed at the discretion of the investigator to every 3 weeks at a dose of 6 mg/kg infused over 30 to 90 minutes.

Study treatment with trastuzumab continued until objective disease progression in the judgment of the investigator or until the subject completed all Week 53 visit assessments, whichever occurred first.

Paclitaxel was administered in a weekly regimen on Days 1, 8 and 15 of each 28-day cycle. The starting dose of paclitaxel was 80 mg/m<sup>2</sup> by IV infusion over 60 minutes. Dose reductions to 70 mg/m<sup>2</sup> and then 60 mg/m<sup>2</sup> as needed were permitted. In the absence of disease progression or unacceptable toxicity in the judgment of the investigator, patients received treatment with paclitaxel for at least 6 cycles, until maximal benefit of response was obtained, or until the patient completed all Week 53 visit assessments, whichever occurred first.

### **Dose Modifications**

Trastuzumab: for infusion reactions, the infusion rate should be decreased or the infusion should be temporarily or permanently interrupted, depending on severity. For cardiac dysfunction, trastuzumab might either be held or discontinued and consultation with a cardiologist might be warranted.

Paclitaxel: dose reductions to 70 mg/m<sup>2</sup> and then 60 mg/m<sup>2</sup> was allowed for any reason. Patients discontinued paclitaxel if they required more than 2 dose reductions or if they had not recovered from a toxicity related to paclitaxel within 3 weeks.

## Statistical Analysis Plan

**Sample size:** The primary efficacy endpoint was independently assessed best overall response rate (ORR) achieved by week 25 and subsequently confirmed by week 33. To provide approximately 85% power to demonstrate equivalence between PF-05280014 and EU-Herceptin on the primary ORR analysis (ratio of ORR) with the pre-defined equivalence margin of (0.80, 1.25), a sample size of 630 patients (315 per treatment arm) was required. Accounting for a possible 10% attrition rate, the sample size was increased to 690. This sample size calculation assumed that the ORR would be approximately 60% in both treatment arms and the ORR ratio of PF-05280014 to EU-Herceptin was to be analyzed with a two-sided 95% confidence interval (CI). If the 95% CI completely fell in the equivalence region defined as 0.80-1.25, the equivalence would be declared. The equivalence region was derived using a random-effect meta-analysis of historical trastuzumab trials to estimate the treatment effect of trastuzumab with taxane versus taxane alone.

**Equivalence margin:** The applicant evaluated available literature and identified three randomized studies that compared taxane and trastuzumab combination versus taxane alone in patients with HER2+ metastatic breast cancer treated in the first-line setting. The treatment effect of trastuzumab in each historical trial and the results of meta-analysis are summarized in Table 4.

**Table 4: Meta-Analysis Results Based on Data from Three Randomized Trials**

Trial	Trastuzumab + Taxane ORR (n/N)	Taxane ORR (n/N)	ORR Ratio <sup>a</sup> 80% CI
Slamon et al	41% (38/92)	17% (16/96)	0.40 (0.29, 0.56)
Marty et al	61% (56/92)	34% (32/94)	0.56 (0.45, 0.69)
Gasparini et al	75% (45/60)	57% (33/58)	0.76 (0.63, 0.90)
Meta-analysis (Random-effect model)			0.58 (0.47, 0.73)

<sup>a</sup> ORR ratio = ORR<sub>taxane</sub>/ORR<sub>trastuzumab + taxane</sub>

n/N: number of responders/number of total patients

For the meta-analysis, the overall estimated log-transformed ratio of ORR (taxane alone over trastuzumab + taxane) was -0.54 [log(0.58)] with 1-sided 90% upper

confidence bound of -0.32 [log(0.73)]. A 75% fraction of the upper bound was taken and that resulted in a numerical value of log ORR ratio of -0.24. The ORR ratio was 0.79 which would correspond to a margin of 0.79 to 1.27 for equivalence testing. The applicant proposed to use the traditional bioequivalence region of (0.80, 1.25) to be more conservative.

**Analysis population:** The intent-to-treat (ITT) population included all randomized patients. The safety population was defined as all patients who received at least one dose of study treatment. The pharmacokinetics analysis population was defined as all patients who were treated with PF-05280014 or EU-Herceptin, had no major protocol deviations that could influence the pharmacokinetics assessment, and had at least one post-dose concentration measurement.

Primary efficacy analysis was based on the ITT population. Primary safety analysis was based on the safety population. The per-protocol population was a supportive analysis population for efficacy, which was defined as a subset of ITT population who met the following additional criteria:

- had HER2 positive MBC as confirmed by central review,
- had measurable disease at baseline as confirmed by the independent review,
- were randomized and received the study treatment as planned,
- had no major protocol deviation.

**Primary efficacy analysis:** The ratio of ORR and its 95% CI were calculated using the method proposed by Miettinen and Nurminen (1985). Equivalence would be declared if the two-sided 95% CI for the ratio of ORR is completely within the equivalence range of 0.80 - 1.25.

**Secondary efficacy analyses:**

The secondary efficacy endpoints include DoR, 1-year PFS rate, and 1-year survival rate.

- PFS was defined as the time from randomization to the first progression of disease or death due to any cause. The tumor assessment was based on central radiology review in accordance with RECIST 1.1. Patients who were alive and progression-free were to be censored on the date of the last available tumor assessment. Patients without evaluation of disease performed after randomization were to be censored on the date of randomization. Patients without adequate disease assessment at baseline were to be censored on the date of randomization. Patients who used radiotherapy or surgery to manage breast cancer lesions or started a new anti-cancer therapy prior to documented PD were to be censored on the date of the last available tumor assessment prior to the start of new therapy. Patients who had death or PD identified after 2 or more missed tumor assessments were to be censored on the day following the date of the previous tumor assessment. The Kaplan-Meier method was used to

estimate the PFS rate at 1-year with the 2-sided 95% confidence interval of the rate obtained using the Greenwood's formula. PFS was to be compared using a stratified log-rank test.

- DoR was defined as the time from date of the first documented objective tumor response to the first documented progression of disease or to death due to any cause. DoR was to be analyzed the same way as PFS.
- Time to death was defined as the time from the date of randomization to death due to any cause. Patients last known to be alive were to be censored on the date of the last contact. Time to death was to be analyzed the same way as PFS.

**Sensitivity analyses:** Sensitivity analyses were performed on the primary endpoint of ORR in the PP population. The Miettinen and Nurminen method with the stratification variables was conducted to assess whether prior adjuvant trastuzumab exposure and/or estrogen receptor status would affect the ratio of ORR. A descriptive summary table for CR and PR based on investigator's assessment was created.

The primary efficacy analyses for the primary and secondary endpoints were planned to be performed when the last patient had completed week-25 tumor assessment and had the opportunity to subsequently confirm response at week 33, or discontinued early. When all patients had completed week-53 assessment or discontinued early, analyses for the primary and secondary endpoints were planned to be repeated.

***Reviewer Comment: In general, biosimilar comparative clinical studies use a two-sided 90% CI in the primary analysis so that alpha is controlled  $\leq 0.05$ . This study was designed to use a two-sided 95% CI in the primary analysis, which is more conservative.***

## Independent Review Charter

Imaging performed up to Week 53 was forwarded to the independent central review laboratory for retrospective documentation of eligibility, disease response and progression in accordance with RECIST 1.1.

Materials forwarded for independent review on study B3271002 were preferably in digital format in DICOM format. Original films could be forwarded for review if necessary.

Available tumor tissue (i.e., formalin fixed-paraffin embedded blocks or unstained slides) was to be sent for central review of HER2 status. Tumor tissue was from metastatic disease or, if not obtainable, from the primary tumor at the time of initial or current diagnosis. Central review to confirm tumor HER2 status was planned to be performed for all patients enrolled in the study.

Central review could be performed retrospectively for patients who were determined to be HER2-positive by use of either a Sponsor approved assay or two different analytical test methods that were not considered Sponsor approved.

If a patient's tumor HER2 status could not be determined by using either a Sponsor approved assay or two different HER2 assays performed locally, a tissue sample was sent to the Sponsor-provided central laboratory early in the study screen period; results of the assessment will be returned to the investigator for inclusion in patients' source documents.

### **Study B3271002 Protocol Amendments**

The following protocols were available for review:

- Original protocol, Mar 28, 2013
- Amendment 1, July 29, 2013 – Added HER2-positive status confirmation for full study population, including entry criteria requiring specimen availability for testing. Elaborated safety endpoint to specify cardiotoxicity and infusion related reactions as special interests
- Amendment 2, July 10, 2014 – Updated HER2 status testing requirements. Added requirement that sites must forward radiographs to the central imaging vendor to obtain confirmation of the presence of measurable disease prior to patient randomization.
- Amendment 3, September 27, 2016: Updated study design to end patient treatment after the completion of Week 53 visit assessments.
- Amendment 4, March 16, 2017: Updated study design to delineate two treatment periods (Treatment Period 1 and Treatment Period 2) to allow for continued treatment beyond Week 53, but with limited protocol required assessments.

### **5.3.2 Study B3271004**

#### Study Design

Study 1004 is a noninferiority, double-blind, randomized study evaluating the PK, efficacy, safety, and immunogenicity of PF-05280014 in combination with docetaxel and carboplatin versus EU-Herceptin in combination with docetaxel and carboplatin in patients with operable HER2-positive breast cancer in the neoadjuvant setting. Patients were randomized 1:1 to either PF-05280014 plus docetaxel and carboplatin or EU-Herceptin plus docetaxel and carboplatin. Randomization was stratified by primary tumor size (<5 cm, or ≥5 cm), ER status (ER positive versus ER negative) and by progesterone receptor status (progesterone receptor positive versus progesterone receptor negative).

The first administration of PF-05280014 or EU- Herceptin on Day 1, Cycle 1 was a loading dose of 8 mg/kg infused over 90 minutes. Subsequent infusions were every 3 weeks (i.e., cycled every 21 days) with a dose of 6 mg/kg administered over 30 to 90 minutes depending on tolerability. In the absence of objective disease progression or prohibitive toxicity, patients received PF-05280014 or EU- Herceptin for 6 cycles.

Taxotere and carboplatin was administered every 3 weeks (i.e., cycled every 21 days) for a total of 6 treatment cycles as follows:

- Taxotere® 75 mg/m<sup>2</sup> Day 1 of each Cycle.
- Carboplatin AUC 6 IV Day 1 of each Cycle.

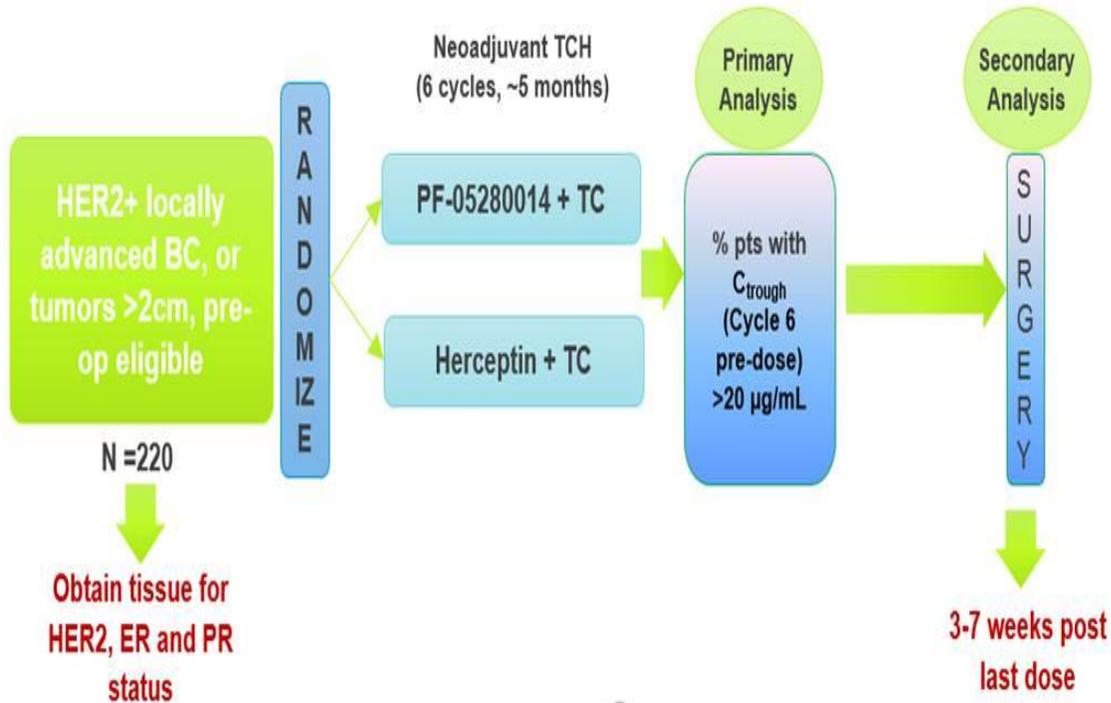
In the absence of objective disease progression or prohibitive toxicity, patients received the treatment regimen for 6 cycles.

Patients underwent a definitive surgical resection of their primary tumor, as part of their standard of care, such as a lumpectomy or mastectomy with sentinel node (SN) biopsy or axillary lymph node dissection (ALND). Surgery was performed within 3 to 7 weeks after completion of the last dose at Cycle 6. Pathology of tumor sample and pathologic response was assessed by an investigator designated qualified pathologist. No central review was performed on the post-surgical pathology specimens

Central radiology review was performed for all disease assessments performed at screening, at the end of Cycle 3 and at the End of Treatment (EOT) visit, as well as restaging performed as clinically indicated.

The study design is shown in Figure 2 below.

**Figure 2: Study B3271004 Design**



Source: PF-05280014 AOM Meeting August 17, 2017

### **Primary Objective**

To compare the percentage of patients with steady state (Cycle 5)  $C_{\text{trough}} >20 \mu\text{g/mL}$  between PF-05280014 versus EU- Herceptin in patients with operable HER2-positive breast cancer who receive therapy together with Taxotere and carboplatin in the neoadjuvant setting.

### **Secondary Objectives**

- To evaluate measures of tumor control for PF-05280014 versus EU- Herceptin, when administered with combination with Taxotere and carboplatin in the neoadjuvant setting (pCR).
- To evaluate the safety of PF-05280014 versus EU- Herceptin, administered in combination with Taxotere and carboplatin.
- To evaluate the immunogenicity of PF-05280014 versus EU- Herceptin.
- To evaluate the PK of PF-05280014 versus EU- Herceptin.

- To explore the relationship between drug exposure and pCR for PF-05280014 versus EU- Herceptin, administered in combination with Taxotere and carboplatin

### **Study B3271004 Study endpoints**

The primary endpoint was the percentage of patients with steady state (Cycle 5)  $C_{\text{trough}}$  (Cycle 6 pre-dose)  $>20 \mu\text{g/mL}$ . Secondary efficacy endpoints included pathologic complete response (pCR) and ORR. Other secondary endpoints included safety, PK, and immunogenicity.

**Reviewer Comment: The design and endpoints of the clinical study 1004 are acceptable.**

## **6 Review of Efficacy**

### **Efficacy Summary**

The results of Study 1002, together with other information in the application, support the determination of no clinically meaningful differences between PF-05280014 and US-Herceptin. Specifically, the 90% confidence intervals for the overall response rate ratio between PF-05280014 and EU-Herceptin in Study B3271002 are within the equivalence margins. A scientific bridge between EU-Herceptin, US-Herceptin, and PF-05280014 has been established based in part on the pharmacokinetic (PK) evaluation in Study 1001.

#### **6.1 Indication**

The Applicant-proposed indications are the same as those for US-licensed Herceptin.

#### **6.2 Method**

Similarity in clinical efficacy was assessed in Study B3271002 comparing PF-05280014 with EU-Herceptin in patients with MBC. The primary efficacy analysis was based on the ratio of objective response rate per central review by week 25 (and subsequently confirmed by week 33) in the ITT population. Sensitivity analyses were performed as appropriate. Analyses of the primary endpoint, secondary endpoints, and safety are included in this review.

### 6.3 Demographics

This was an international study with patients enrolled from 24 countries in the ITT population as seen in Table 5. The top five countries for enrollment were Russia, Ukraine, Philippines, India, and Korea. There was only one patient enrolled from the United States.

**Table 5: Study B3271002 Enrollment by Country for ITT Population**

Country	PF-05280014 (N=352) n (%)	EU-Herceptin (N=355) n (%)
Russian Federation	97 (27.6)	102 (28.7)
Ukraine	83 (23.6)	77 (21.7)
Philippines	41 (11.6)	28 (7.9)
India	23 (6.5)	16 (4.5)
Korea	18 (5.1)	19 (5.4)
South Africa	14 (4.0)	22 (6.2)
Japan	18 (5.1)	14 (3.9)
Poland	13 (3.7)	15 (4.2)
Brazil	8 (2.3)	10 (2.8)
Chile	7 (2.0)	9 (2.5)
Romania	11 (3.1)	4 (1.1)
Turkey	3 (0.9)	8 (2.3)
Thailand	2 (0.6)	7 (2.0)
Peru	2 (0.6)	6 (1.7)
Serbia	2 (0.6)	3 (0.8)
Argentina	1 (0.3)	4 (1.1)
Mexico	2 (0.6)	2 (0.6)
Hungary	3 (0.9)	1 (0.3)
Slovakia	2 (0.6)	1 (0.3)
Portugal	1 (0.3)	2 (0.6)
Greece	0	3 (0.8)
United States	1 (0.3)	0
Latvia	0	1 (0.3)
Czech Republic	0	1 (0.3)

[Source: Study B3271002 demog.xpt and popflg xpt]

The demographics by treatment arm are shown in Table 6.

**Table 6: Demographic Characteristics for Study B3271002 in ITT Population**

	PF-05280014 (N=352)	EU-Herceptin (N=355)
Age, years		
Mean (SD)	54.0 (10.8)	54.1 (10.9)
Median (range)	55 (19 – 80)	54 (25 – 85)
Age group, n (%)		
18-44	74 (21.0)	73 (20.6)
45-64	212 (60.2)	221 (62.3)
≥65	66 (18.8)	61 (17.2)
Gender, n (%)		
Female	352 (100)	355 (100)
Race, n (%)		
White	232 (65.9)	244 (68.7)
Black	5 (1.4)	8 (2.3)
Asian	104 (29.5)	84 (23.7)
Other	11 (3.1)	19 (5.4)
Racial designation, n (%)		
Indian Subcontinent	24 (6.8)	17 (4.8)
Asian		
Japanese	18 (5.1)	14 (3.9)
Korean	18 (5.1)	19 (5.4)
Other	55 (15.6)	54 (15.2)
Unspecified	237 (67.3)	251 (70.7)
Ethnicity, n (%)		
Hispanic/Latino	19 (5.4)	26 (7.3)
Not Hispanic/Latino	333 (94.6)	329 (92.7)
Height, cm		
Mean (SD)	158.5 (7.0)	159.3 (7.3)
Median (range)	158 (137 – 178)	159 (137 – 178)
Weight, kg		
Mean (SD)	69.1 (17.1)	68.1 (16.1)
Median (range)	68.2 (29.3 – 146.5)	66.0 (36.1 – 139.0)
BMI, kg/m <sup>2</sup>		
Mean (SD)	27.4 (6.3)	26.8 (6.0)
Median (range)	26.5 (15.3 – 58.9)	25.7 (14.5 – 56.9)

[Adapted from Study B3271002 CSR Table 14]

**Reviewer Comment:** All patients were female and over 18 years of age. Majority of patients were White. Baseline demographics were well balanced between the two treatment arms.

The baseline disease characteristics by treatment arm are shown in Table 7.

**Table 7: Baseline Disease Characteristics for Study B3271002 in ITT Population**

	<b>PF-05280014 (N=352)</b>	<b>EU-Herceptin (N=355)</b>
Duration since diagnosis, months		
n	343	348
Mean (SD)	24.8 (37.8)	22.4 (29.8)
Median (range)	6.7 (0.3 – 283.7)	6.1 (0.3 – 157.4)
Histology (Histopathological Classification), n (%)		
Ductal	278 (79.0)	277 (78.0)
Lobular	14 (4.0)	17 (4.8)
Unknown	4 (1.1)	3 (0.8)
Other	56 (15.9)	58 (16.3)
Baseline disease site, n (%)		
Visceral (lung and/or liver)	259 (73.6)	269 (75.8)
Non-visceral	93 (26.4)	86 (24.2)
Prior systemic therapy, n (%)		
Yes	152 (43.2)	156 (43.9)
No	200 (56.8)	199 (56.1)
Prior radiation therapy, n (%)		
Yes	115 (32.7)	117 (33.0)
No	237 (67.3)	238 (67.0)
Prior surgery		
Yes	173 (49.1)	180 (50.7)
No	179 (50.9)	175 (49.3)
Prior trastuzumab, n (%)		
Yes	33 (9.4)	39 (11.0)
No	319 (90.6)	316 (89.0)
Estrogen receptor (ER) status, n (%)		
Positive	184 (52.3)	184 (51.8)
Negative	168 (47.7)	171 (48.2)

***Reviewer Comment: Baseline disease characteristics were generally balanced between the two treatment arms.***

## 6.4 Subject Disposition

In total, 707 patients were randomized onto study B3271002. Three hundred fifty-two patients were randomized to the PF-05280014 arm and 355 patients were randomized to the EU-Herceptin arm. Patient disposition is shown in Table 8. Reasons for discontinuation from treatment are summarized in Table 9.

**Table 8: Study B3271002 Patient Disposition**

	<b>PF-05280014</b>	<b>EU-Herceptin</b>
Number (%) of patients randomized	352	355
Treated	349 (99.1)	353 (99.4)
Treated until progression	123 (34.9)	127 (35.8)
Treated stopped before progression	42 (11.9)	46 (13.0)
Study		
Completed	11 (3.1)	6 (1.7)
Ongoing at date of cutoff	279 (79.3)	279 (78.6)
Withdraw	62 (17.6)	70 (19.7)
Subject died	38 (10.8)	38 (10.7)
Lost to follow-up	7 (2.0)	11 (3.1)
Other	3 (0.9)	1 (0.3)
No longer willing to participate in study	14 (4.0)	20 (5.6)

[Source: Study B3271002 CSR Table 9]

**Table 9: Study B3271002 Discontinuation from Treatment (ITT Population)**

	PF-05280014 (N=352) n (%)	EU-Herceptin (N=355) n (%)
Primary reason for discontinuation from trastuzumab	165 (46.9)	173 (48.7)
Objective progression or relapse	123 (34.9)	127 (35.8)
Adverse event(s)	15 (4.3)	11 (3.1)
Patient no longer willing to continued treatment for reasons other than adverse event	9 (2.6)	9 (2.5)
Other	10 (2.8)	6 (1.7)
Patient died	3 (0.9)	10 (2.8)
Global deterioration of health status	3 (0.9)	4 (1.1)
Protocol violation	1 (0.3)	4 (1.1)
Lost to follow-up	1 (0.3)	2 (0.6)
Primary reason for discontinuation from paclitaxel	147 (41.8)	140 (39.4)
Objective progression or relapse	75 (21.3)	70 (19.7)
Adverse event(s)	36 (10.2)	32 (9.0)
Patient no longer willing to continued treatment for reasons other than adverse event	6 (1.7)	7 (2.0)
Other	21 (6.0)	8 (2.3)
Patient died	3 (0.9)	10 (2.8)
Global deterioration of health status	4 (1.1)	7 (2.0)
Protocol violation	1 (0.3)	4 (1.1)
Lost to follow-up	1 (0.3)	2 (0.6)

[Source: Study B3271002 CSR Table 10]

***Reviewer Comment: Trastuzumab was discontinued in 46.9% of patients in the PF-05280014 arm and 48.7% of patients in the EU-Herceptin arm, with objective progression or relapse being the most common reason in both treatment arms.***

**Protocol violations/Deviations**

The most common reason for exclusion from the PP population was no measurable disease at baseline per central review (according to RECIST 1.1) with 31 (8.8%) patients in the PF-05280014 arm and 25 (7.0%) patients in the EU-Herceptin arm.

**Table 10: Study B3271002 Major Criteria for Exclusion for Per-Protocol Population**

	<b>PF-05280014 (N=352)</b>	<b>EU-Herceptin (N=355)</b>
Total patients excluded	72 (20.5)	70 (19.7)
No histologically confirmed diagnosis of breast cancer	0	1 (0.3)
No presence of metastatic disease	0	1 (0.3)
No measurable disease at baseline per Central Review	31 (8.8)	25 (7.0)
Active uncontrolled or symptomatic CNS metastases	0	1 (0.3)
Missing, not evaluable, or equivocal HER2 status by Central Laboratory	27 (7.7)	25 (7.0)
Prior systemic therapy for metastatic disease	0	1 (0.3)
Randomized but not dosed	3 (0.9)	2 (0.6)
Negative HER2 status by Central Laboratory	10 (2.8)	15 (4.2)
Study treatment under-dosing by 25% before Week 33	7 (2.0)	4 (1.1)
Inadvertent study treatment unblinding before Week 33	0	1 (0.3)
Incorrect study treatment administered for at least one dose	0	1 (0.3)

Patients could be excluded from the PP population for more than 1 reason.  
[Source: Study B3271002 CSR Table 13]

***Reviewer Comment: The number of patients who were excluded from the PP population was comparable between the two treatment arms. ORR results observed from the PP population are consistent to those from the ITT population.***

## 6.5 Analysis of Primary Endpoint(s)

Overall response rate (ORR) per central review by week 25 (and subsequently confirmed by week 33) was the primary efficacy endpoint of Study B3271002. The primary analysis of ORR was based on the ratio of ORRs between the PF-05280014 and EU-Herceptin in the ITT population. The results of the primary analysis are summarized in Table 11.

**Table 11: Study B3271002 ORR per Central Review (ITT Population)**

	<b>PF-05280014 (N=352) n (%)</b>	<b>EU-Herceptin (N=355) n (%)</b>
Complete response (CR)	10 (2.8)	13 (3.7)
Partial response (PR)	210 (59.7)	223 (62.8)
Stable disease (SD)	76 (21.6)	74 (20.8)
Progressive disease (PD)	18 (5.1)	11 (3.1)
Indeterminate	38 (10.8)	34 (9.6)
Overall response rate (ORR)	220 (62.5)	236 (66.5)
Ratio of ORR (PF-05280014 vs. EU-Herceptin)	0.94	
95% CI	(0.84, 1.05)	
90% CI	(0.86, 1.03)	

[Adapted from Study B3271002 CSR Tables 15 and 16]

***Reviewer Comment:*** *The ratio of ORR between the two treatment arms was 0.94 with a 95% CI of (0.84, 1.05) and a 90% CI of (0.86, 1.03), both of which were within the pre-defined equivalence margins of 0.80 and 1.25. The difference in ORR between the two arms was -4.0% (95% CI: -11.0%, 3.1%; 90% CI: -9.9%, 1.9%). ORR per central review was also evaluated in the PP population. The ORR was 71.1% in the PF-05280014 arm and 74.4% in the EU-Herceptin arm. The ratio of ORR is 0.96 (95% CI: 0.86, 1.06; 90% CI: 0.88, 1.04). The ratio was within the pre-defined equivalence margins. Results from the PP population are consistent with those from the ITT population.*

### **Sensitivity Analyses for ORR**

Results of ORR sensitivity analyses are shown in Table 12.

**Table 12: Study B3271002 Sensitivity Analyses of ORR**

	<b>PF-05280014 # of responders/# of pts (ORR)</b>	<b>EU- Herceptin # of responders/# of pts (ORR)</b>	<b>ORR Ratio (95% CI) <sup>a</sup></b>	<b>ORR Ratio (90% CI) <sup>a</sup></b>
ORR per central review, PP population	199/280 (71.1%)	212/285 (74.4%)	0.96 (0.86, 1.06)	0.96 (0.88, 1.04)
ORR per INV, ITT population	232/352 (65.9%)	236/355 (66.5%)	0.99 (0.89, 1.10)	0.99 (0.91, 1.08)
ORR per INV, PP population	199/280 (71.1%)	205/285 (71.9%)	0.99 (0.89, 1.10)	0.99 (0.90, 1.08)
ORR per central review, ITT population, adjusted for stratification factors	220/352 (62.5%)	236/355 (66.5%)	0.94 (0.84, 1.04)	0.94 (0.85, 1.03)

<sup>a</sup> ORR ratio: ORR<sub>PF-05280014</sub>/ ORR<sub>EU-Herceptin</sub>

***Reviewer Comment: Results of ORR sensitivity analyses per central review or investigator assessment in different analysis populations are consistent with the primary findings.***

Primary endpoint ORR was re-analyzed at week 53 cutoff with additional information that resulted in updates to the central radiology assessments. The ratio of ORR between the two treatment arms was 0.95 with a 95% CI of (0.85, 1.06) and a 90% CI of (0.86, 1.04). The results at week 53 cutoff are consistent with those at week 33 cutoff.

## **6.6 Analysis of Secondary Endpoint(s)**

Secondary efficacy endpoints included DoR, 1-year PFS rate and 1-year OS rate. Analyses for the secondary endpoints included all available radiology data up to week 53 and all available data up to 378 days post randomization (i.e., randomization date + 365 + 14 days window -1).

### **Duration of Response**

As of week 33 cutoff time, 57 patients (25.1%) out of the 220 responders in the PF-05280014 arm and 57 patients (24.2%) out of the 236 responders in the EU-Herceptin arm had either progressed or died. The median time of response duration couldn't be

estimated in either the PF-05280014 arm or the EU-Herceptin arm due to lack of events and length of follow-up.

**Reviewer Comments:**

- ***At the week 33 analysis, the applicant’s DoR analysis included 5 patients as responders who had the first PR/CR on week 33 assessment and a confirmed response at a later tumor assessment. The applicant’s DoR results are consistent with those presented above.***
- ***The results of DoR analysis at week 53 cutoff are consistent with those at week 33 cutoff. The median time of response duration was 11.3 months in the PF-05280014 arm and 10.6 months in the EU-Herceptin arm.***

**1-year Progression-free Survival Rate**

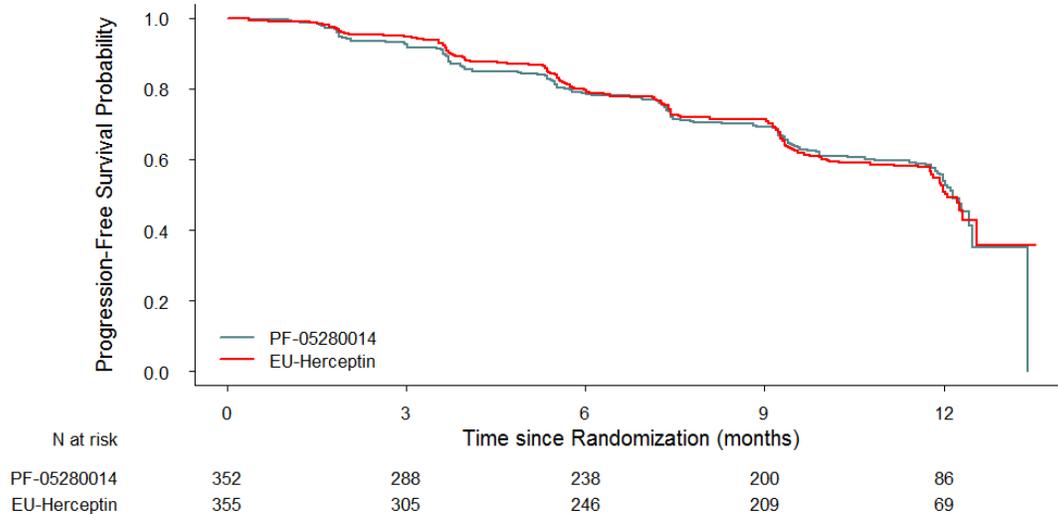
Table 13 presents PFS per central review for the ITT population at week 33 and at week 53. The 1-year PFS rate was 56% and 52% in the PF-05280014 arm and the EU-Herceptin arm in the week 33 analysis, and 54% and 51% in the PF-05280014 arm and the EU-Herceptin arm in the week 53 analysis, respectively. The stratified hazard ratio of PF-05280014 vs. EU-Herceptin was 1.07 in the week 33 analysis and 1.00 in the week 53 analysis. Kaplan-Meier plot for PFS at week 53 is shown in Figure 3.

**Table 13: Study B3271002 Analysis of Progression-free Survival based on Central Radiology Assessments**

	<b>PF-05280014 (N=352)</b>	<b>EU-Herceptin (N=355)</b>
<b>Week 33 cutoff</b>		
Number of PD or deaths	121 (34.4%)	120 (33.8%)
Median (95% CI), months	12.2 (11.9, 13.4)	12.2 (11.8, -)
1-year PFS rate (95% CI)	0.56 (0.49, 0.62)	0.52 (0.45, 0.59)
Stratified hazard ratio (95% CI) <sup>a</sup>	1.07 (0.83, 1.37)	
<b>Week 53 cutoff</b>		
Number of PD or deaths	144 (40.9%)	148 (41.7%)
Median (95% CI), months	12.2 (11.9, 12.5)	12.1 (11.8, -)
1-year PFS rate (95% CI)	0.54 (0.48, 0.60)	0.51 (0.45, 0.57)
Stratified hazard ratio (95% CI) <sup>a</sup>	1.00 (0.80, 1.26)	

<sup>a</sup> Stratified by prior trastuzumab exposure and ER status.

**Figure 3: Study B3271002 Kaplan-Meier Curves of Progression-free Survival**



***Reviewer Comment: PFS HR was close to 1. There was no apparent difference in PFS between the two arms.***

### **1-year Survival Rate**

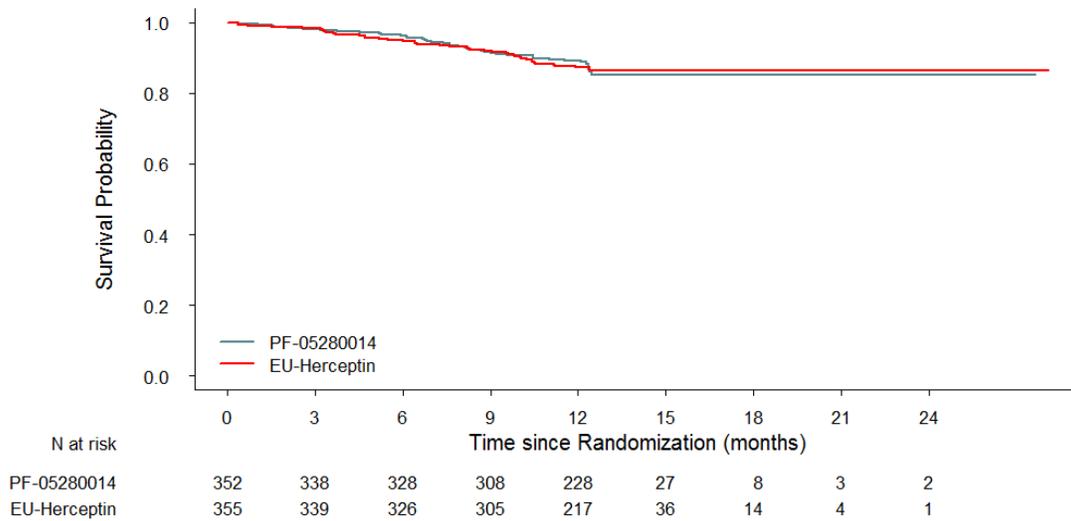
Overall survival results at week 33 and at week 53 are summarized in Table 14. The stratified hazard ratios of PF-05280014 vs. EU-Herceptin were 1.05 in the week 33 analysis and 1.00 in the week 53 analysis. Kaplan-Meier plot for OS at week 53 is shown in Figure 4.

**Table 14: Study B3271002 Analysis of Overall Survival**

	<b>PF-05280014 (N=352)</b>	<b>EU-Herceptin (N=355)</b>
<b>Week 33 cutoff</b>		
Number of deaths	39 (11.1%)	38 (10.7%)
Median (95% CI), months	–	–
1-year OS rate (95% CI)	0.89 (0.85, 0.92)	0.88 (0.84, 0.91)
Stratified hazard ratio (95% CI) <sup>a</sup>	1.05 (0.67, 1.64)	
<b>Week 53 cutoff</b>		
Number of deaths	42 (11.9%)	43 (12.1%)
Median (95% CI), months	–	–
1-year OS rate (95% CI)	0.89 (0.85, 0.92)	0.87 (0.83, 0.91)
Stratified hazard ratio (95% CI) <sup>a</sup>	1.00 (0.66, 1.54)	

<sup>a</sup> Stratified by prior trastuzumab exposure and ER status.

**Figure 4: Study B3271002 Kaplan-Meier Curves of Overall Survival**



***Reviewer Comment: The OS results are immature. The median time to death could not be estimated in either treatment arm due to the small number of deaths observed. OS HR was close to 1. There was no apparent difference in OS between the two arms.***

## 6.7 Other Endpoints

There were no other efficacy endpoints for Study B3271002 other than those discussed above.

## 6.8 Subpopulations

### Subgroup Analyses of ORR

Subgroup analyses of ORR per central review in the ITT population were performed by age, race, geographic region, stratification factors (prior trastuzumab exposure, and estrogen receptor status) and ECOG status. As shown in Table 15, in all subgroups the 90% CI of the ORR ratio (PF-05280014: EU-Herceptin) included 1 except the subgroup of Asian patients.

**Table 15: Study B3271002 Subgroup Analyses of ORR per Central Review (ITT Population)**

	<b>PF-05280014 n/N (ORR%)</b>	<b>EU-Herceptin n/N (ORR%)</b>	<b>ORR Ratio (90% CI) <sup>a</sup></b>
Overall	220/352 (62.5%)	236/355 (66.5%)	0.94 (0.86, 1.03)
Age			
<65	177/286 (61.9%)	199/294 (67.7%)	0.91 (0.83, 1.01)
≥65	43/66 (65.2%)	37/61 (60.7%)	1.07 (0.86, 1.36)
Race			
White	141/232 (60.8%)	152/244 (62.3%)	0.98 (0.87, 1.10)
Asian	70/104 (67.3%)	66/84 (78.6%)	0.86 (0.74, 0.99)
Black	3/5 (60.0%)	7/8 (87.5%)	0.69 (0.29, 1.22)
Other	6/11 (54.5%)	11/19 (57.9%)	0.94 (0.50, 1.61)
Region			
America & West Europe	29/53 (54.7%)	35/62 (56.5%)	0.97 (0.73, 1.28)
East Europe	110/180 (61.1%)	117/179 (65.4%)	0.93 (0.82, 1.07)
Other	81/119 (68.1%)	84/114 (73.7%)	0.92 (0.80, 1.06)
ECOG PS			
0	122/186 (65.6%)	137/194 (70.6%)	0.93 (0.83, 1.04)
1	91/150 (60.7%)	89/146 (61.0%)	1.00 (0.85, 1.16)
2	7/16 (43.8%)	10/15 (66.7%)	0.66 (0.36, 1.14)
Prior trastuzumab exposure			
Yes	17/33 (51.5%)	18/39 (46.2%)	1.12 (0.74, 1.67)
No	203/319 (63.6%)	218/316 (69.0%)	0.92 (0.84, 1.01)
ER status			
Positive	116/184 (63.0%)	116/184 (63.0%)	1.00 (0.88, 1.14)
Negative	104/168 (61.9%)	120/171 (70.2%)	0.88 (0.77, 1.00)

<sup>a</sup> ORR ratio: ORR<sub>PF-05280014</sub>/ ORR<sub>EU-Herceptin</sub>

## 6.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this application.

## 6.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

See duration of response results described in the section of secondary endpoints. Persistence of effect is addressed by the secondary endpoints of duration of response and PFS which are time to event endpoints.

## 6.11 Additional Efficacy Issues/Analyses

### Treatment Compliance

Study treatment was delivered in the clinic by site personnel; therefore, no measurement of treatment compliance was required.

### Concomitant Medications

All patients used concomitant medications (100.0% in both the PF-05280014 and the EU-Herceptin arms). The most commonly used concomitant medications in both treatment groups were part of pre- or post-chemotherapy treatment: corticosteroids for systemic use (100.0% and 99.7% in the PF-05280014 and EU-Herceptin groups, respectively), antiemetics (64.2% versus 60.6%), drugs for acid-related disorders (57.3% versus 52.4%), and antihistamines for systemic use (97.7% versus 96.3%).

## 6.12 Efficacy Results of Supportive Study 1004

Pathologic complete response (pCR) was a secondary endpoint in Study 1004. The analysis of pCR was conducted in the per-protocol population. Forty-seven patients (46.5%) out of 101 patients in the PF-05280014 arm and 43 patients (48.3%) out of 89 patients in the EU-Herceptin arm had a pCR.

***Reviewer Comment: The pCR rates were comparable between the two treatment arms.***

## 7 Review of Safety

### Safety Summary

The results of Study 1002, together with other information in the application, support a determination of no clinically meaningful differences between PF-05280014 and US-Herceptin. The safety analyses in B3271002, which compared PF-05280014 and EU-Herceptin in HER2 positive metastatic breast cancer patients, and in B3271004, which compared PF-05280014 and EU-Herceptin in the neoadjuvant setting, did not show any meaningful differences in safety between arms.

### 7.1 Methods

### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

The safety evaluation for this application is primarily based of study B3271002. Details of the design for B3271002 and B3271004 are presented in Section 5.3 above. Key features of two additional PK similarity studies utilizing PF-05280014 (B3271001 and B3271006) are summarized in Section 5.1.

Efficacy results for B3271002 are presented in Section 6.

The Applicant is seeking approval of PF-05280014 for the same indications as US-Herceptin: 1) adjuvant and metastatic treatment of patients with HER2 positive breast cancer and 2) HER2 positive metastatic gastric adenocarcinoma.

Studies 1001 and 1006 were conducted in a different population of healthy volunteers than the intended population of certain cancer patients. These two studies are not included in the overall safety assessment of PF-05280014.

Study 1001 is a single-dose PK study conducted in healthy male subjects using PF-05280014, EU-Herceptin and US-Herceptin. In this study, there were no meaningful differences among the 3 groups in the incidence of adverse events (AEs) reported, with the exception of pyrexia, an abnormally elevated body temperature. A higher incidence of pyrexia was reported in the PF-05280014 (n=10, 28.6 %) compared to US-Herceptin (n=2, 5.7%) and EU-Herceptin (n=3, 8.6%).

At the request of the Food and Drug Administration (FDA), Pfizer conducted another single-dose study (study 1006) with a larger sample size to estimate the relative risk of pyrexia (defined as body temperature  $\geq 38.0^{\circ}\text{C}$ ) compared to baseline following PF-05280014 or US-Herceptin administration to healthy subjects. The incidence of pyrexia in the per-protocol (PP) population was 6.2% (n=5) in the PF-05280014 group and 13.6 % (n=11) in the US-Herceptin group. The difference was not statistically significant. It was concluded that the differences in the incidence of pyrexia previously observed in study 1001 were most likely caused by chance differences due to small sample size.

The safety assessments for 1002 and 1004 are adequate. Particular attention was paid to the assessment of cardiac adverse events (AEs) due to the known cardiac effects of trastuzumab. Twelve-lead ECGs were obtained at screening, as clinically indicated, and at the End of Treatment Visit. An echocardiogram (preferred) or MUGA Scan was performed at screening, weeks 9,17,25,33,41 and 53, and as clinically indicated. The method used for individual patients was to be consistent throughout study participation. Imaging was repeated at least monthly if there was a 16% absolute decrease in LVEF from pre-treatment levels or LVEF below institutional level of normal and a 10% absolute decrease in LVEF.

### **7.1.2 Categorization of Adverse Events**

The applicant defined an adverse event as any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage.

A treatment-emergent adverse event (TEAE) was defined as any event that occurred after the beginning of the study treatment or any pre-existing adverse event that worsened after the beginning of the study treatment.

A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose resulted in death, is life-threatening, resulted in persistent or significant disability/incapacity, is a congenital anomaly, is an important medical event, or requires inpatient hospitalization or prolongation of existing hospitalization. Progression of the malignancy under study was not to be reported as an SAE unless the outcome was fatal within the safety reporting period.

AEs were collected from the time the patient had taken at least 1 dose of study treatment through and including 6 months after the last dose of the study drug. SAEs were recorded from the time that the patient provided informed consent through and including 6 months after the last dose of the study drug.

Adverse events were classified based on the Medical Dictionary for Regulatory Activities (MedDRA) (Version 15.1 for Study B3271001 and Version 17.0 for B3271006). AEs were graded (Grade 0 to 5) in accordance with NCI CTCAE Version 4.03.

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

Applicant combined patient data from Studies B3271002 and B3271004 for pooled analysis. Overall, the pooled safety population included 462 patients in the PF-05280014 group and 465 patients in the EU-Herceptin group. The incidence of TEAEs, AEs of CTCAE Grade 3 or higher, and SAEs were comparable across treatment groups, and there were no notable discrepancies between the pooled PF-05280014 group and the pooled EU-Herceptin group.

***Reviewer Comment: Agree with the applicant that the utility of these pooled analyses was limited by differences in study designs, dosing, and study populations.***

## **7.2 Adequacy of Safety Assessments**

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

The safety population of study 1002 consisted of 702 total patients, 349 in the PF-05280014 arm and 353 in the EU-Herceptin arm and is defined as all patients who received at least 1 dose of study drug. This is the primary population for the overall safety analysis in this safety assessment.

Table 16 and Table 17 below list the mean number of cycles, mean duration of exposure, and mean cumulative dose, actual dose intensity and relative dose intensity for PF-05280014 and EU-Herceptin, and paclitaxel in study 1002.

**Table 16: Summary of Exposure to Trastuzumab Product – Safety Population (Study B3271002)**

	<b>PF-05280014 N=349</b>	<b>EU-Herceptin N=353</b>
Mean (SD) number of cycles	11.1 (4.7)	11.1 (4.4)
Mean (SD) duration of exposure, weeks	33.9 (12.7)	34.4 (12.3)
Mean (SD) cumulative dose, mg	5717.3 (2682.0)	5635.4 (2576.7)
Mean (SD) actual dose intensity, mg /weeks	166.8 (44.9)	163.3 (45.2)
Mean relative dose intensity <sup>a</sup> %	100.5	101.3
Source dataset: intensity.xpt		
a: Relative dose intensity was defined as actual dose intensity (cycle 1-8) / intended dose intensity (cycle 1-8) * 100%, because data of intended dose were only available for cycles between 1 and 8.		

**Reviewer Comment:** *The Sponsor used a different method in calculating Mean (SD) duration of exposure (weeks). They did not exclude cycles that were missed. In FDA analysis of calculating Mean (SD) duration of exposure (weeks), the cycles that were missed were excluded. Both analyses lead to similar results.*

**Table 17: Summary of Exposure to Paclitaxel – Safety Population (Study B3271002)**

	<b>PF-05280014 N=349</b>	<b>EU-Herceptin N=352<sup>a</sup></b>
Mean (SD) number of cycles	7.6 (2.9)	7.9 (3.0)
Mean (SD) duration of exposure, weeks	22.2 (8.8)	23 (8.8)
Mean (SD) cumulative dose, mg	2992.4 (1245.4)	3073.3 (1267.1)
Mean (SD) actual dose intensity, mg /weeks	134.8 (18.0)	133.2 (17.6)
Mean relative dose intensity <sup>b</sup> %	97.1	96.5

Source dataset: intnsity.xpt  
a: Patient (Subject ID of (b) (6)) was included in the Safety population but not included in the summary of treatment exposure for paclitaxel, as the patient had a Grade 4 IRR during her Cycle 1, Day 1 administration of EU-Herceptin that resulted in discontinuation from study drug.  
b: Relative dose intensity was defined as actual dose intensity (cycle 1-8) / intended dose intensity (cycle 1-8) \* 100%, because data of intended dose were only available for cycles between 1 and 8.

***Reviewer Comment: The Sponsor used a different method in calculating Mean (SD) duration of exposure (weeks). They did not exclude cycles that were missed. In FDA analysis of calculating Mean (SD) duration of exposure (weeks), the cycles that were missed were excluded. Both analyses lead to similar results.***

Of the 702 patients treated, the mean duration of exposure to a trastuzumab product was similar in both arms. The mean number of cycles was 11 in both groups.

***Reviewer Comments: The exposure was well balanced between the two arms.***

The safety population consisted of all patients who received at least 1 dose of study drug. This is a subset of the intention to treat population (ITT – all patients who were randomized to study drug.). The trial was conducted at 168 sites in 24 countries (Argentina, Brazil, Chile, Czech Republic, Greece, Hungary, India, Japan, Korea, Latvia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russia Federation, Serbia, Slovakia, South Africa, Thailand, Ukraine and the United States). Table 18 below provides an overview of the demographic characteristics of the safety population.

**Table 18: Summary of Demographic Characteristics – Safety Population (Study B3271002)**

	<b>PF-05280014 (N=349)</b>	<b>EU-Herceptin (N=353)</b>
<b>Age</b>		
Mean (SD)	54.0 (10.9)	54.1 ± (10.9)
Median (Min - Max)	55 (19 – 80)	54 (25 – 85)
<b>Age Group</b>		
< 65	283 (81.1%)	292 (82.7%)
≥ 65	66 (18.9%)	61 (17.3%)
<b>ECOG</b>		
0	184 (52.7%)	192 (54.4%)
1	149 (42.7%)	146 (41.4%)
2	16 (4.6%)	15 (4.2%)
<b>Race</b>		
Asian	103 (29.5%)	83 (23.5%)
Black	5 (1.4%)	8 (2.3%)
White	231 (66.2%)	243 (68.8%)
Other	10 (2.9%)	19 (5.4%)
<b>Ethnicity</b>		
Hispanic/Latino	17 (4.9%)	26 (7.4%)
Not Hispanic/Latino	332 (95.1%)	327 (92.6%)
<b>Country</b>		
Argentina	1 (0.3%)	4 (1.1%)
Brazil	7 (2%)	10 (2.8%)
Chile	6 (1.7%)	9 (2.5%)
Czech Republic	0 (0%)	1 (0.3%)
Greece	0 (0%)	3 (0.8%)
Hungary	3 (0.9%)	1 (0.3%)
India	23 (6.6%)	16 (4.5%)
Japan	18 (5.2%)	14 (4%)
Korea, Republic of	18 (5.2%)	18 (5.1%)
Latvia	0 (0%)	1 (0.3%)
Mexico	2 (0.6%)	2 (0.6%)
Peru	2 (0.6%)	6 (1.7%)
Philippines	40 (11.5%)	28 (7.9%)
Poland	13 (3.7%)	15 (4.2%)
Portugal	1 (0.3%)	2 (0.6%)
Romania	11 (3.2%)	4 (1.1%)
Russian Federation	97 (27.8%)	102 (28.9%)
Serbia	2 (0.6%)	2 (0.6%)

Slovakia	2 (0.6%)	1 (0.3%)
South Africa	14 (4%)	22 (6.2%)
Thailand	2 (0.6%)	7 (2%)
Turkey	3 (0.9%)	8 (2.3%)
Ukraine	83 (23.8%)	77 (21.8%)
United States	1 (0.3%)	0 (0%)
<b>Previous Treatment (Antineoplastic Agents)</b>		
Anthracyclines and related substances	1 (0.3%)	0 (0%)
Capecitabine	16 (4.6%)	19 (5.4%)
Carboplatin	7 (2%)	11 (3.1%)
Celecoxib	2 (0.6%)	7 (2%)
Cisplatin	4 (1.1%)	3 (0.8%)
Clarithromycin	2 (0.6%)	7 (2%)
Cyclophosphamide	145 (41.5%)	133 (37.7%)
Cyclophosphamide w/doxorubicin	1 (0.3%)	0 (0%)
Cyclophosphamide w/doxorubicin/fluorouracil	1 (0.3%)	0 (0%)
Cyclophosphamide w/epirubicin/fluorouracil	0 (0%)	1 (0.3%)
Cyclophosphamide w/fluorouracil/methotrexate	1 (0.3%)	0 (0%)
Docetaxel	48 (13.8%)	40 (11.3%)
Doxifluridine	1 (0.3%)	0 (0%)
Doxorubicin	122 (35%)	116 (32.9%)
Epirubicin	27 (7.7%)	22 (6.2%)
Fluorouracil	93 (26.6%)	87 (24.6%)
Gemcitabine	4 (1.1%)	3 (0.8%)
Lapatinib	8 (2.3%)	7 (2%)
Lomustine	1 (0.3%)	1 (0.3%)
Methotrexate	9 (2.6%)	8 (2.3%)
Mitoxantrone	0 (0%)	5 (1.4%)
Paclitaxel	28 (8%)	33 (9.3%)
Taxanes	1 (0.3%)	1 (0.3%)
Trastuzumab	46 (13.2%)	52 (14.7%)
Tretinoin	1 (0.3%)	0 (0%)
Vincristine	0 (0%)	1 (0.3%)
Vinorelbine	2 (0.6%)	7 (2%)
Bevacizumab	1 (0.3%)	0 (0%)
Irinotecan	0 (0%)	1 (0.3%)
Mitomycin	0 (0%)	1 (0.3%)

Pertuzumab	3 (0.9%)	2 (0.6%)
Trastuzumab emtansine	2 (0.6%)	0 (0%)
<b>Estrogen Receptor (ER)</b>		
Positive	183 (52.4%)	183 (51.8%)
Negative	166 (47.6%)	170 (48.2%)
<b>HER2</b>		
Positive	348 (99.7%)	352 (99.7%)
Negative <sup>a</sup>	1 (0.3%)	0 (0%)
Equivocal <sup>b</sup>	0 (0%)	1 (0.3%)
Source datasets: discon.xpt, popflg.xpt, demog.xpt, ther2v.xpt, cnmedp1.xpt, and cnmedp2.xpt		
a: Subject (USUBJID: (b) (6) and PID: (b) (6)) had a negative HER2 test result.		
b: Subject (USUBJID: (b) (6) and PID: (b) (6)) had an equivocal HER2 test result.		

***Reviewer Comments:*** *The demographics for the safety population are well balanced. In study 1002, one patient, USUBJID (b) (6) had a negative HER2 test and unknown ISH result, and one patient, USUBJID (b) (6), had an equivocal HER2 test result. Patient (b) (6) was removed from the per-protocol population. This reviewer does not believe that this had an impact on the overall outcome.*

### **7.2.2 Explorations for Dose Response**

Not applicable.

### **7.2.3 Special Animal and/or In Vitro Testing**

Not applicable.

### **7.2.4 Routine Clinical Testing**

The schedule of safety evaluations for 1002 was described in the Schedule of Activities, Study Flowchart 1 of the study protocol. The frequency of monitoring was considered adequate within the context of the study. ECG and left ventricle ejection fraction monitoring were adequate.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

Not applicable.

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

Not applicable.

## 7.3 Major Safety Results

### 7.3.1 Deaths

The number of deaths in each treatment group is shown in Table 19 below. These deaths reflect patients who died during the study as of the cutoff date and within 183 days (6 months) of discontinuing study drug.

**Table 19: Summary of Deaths (Study B3271002)**

	<b>PF-05280014 (N=349)</b>	<b>EU-Herceptin (N=353)</b>
<b>Total Deaths</b>	34 (11.2%)	36 (10.8%)
Due to disease progression	30 (10.0%)	25 (7.7%)
Due to adverse events	1 (0.3%)	3 (0.9%)
Due to other reasons	3 (0.9%)	8 (2.3%)

Source: Table 37, B3271002 CSR wk 33

A total of 14 patients, 10 receiving EU-Herceptin and 4 receiving PF-05280014, progressed due to events other than disease progression. The narratives for these patients were reviewed. Cardiac disease, infection and disease progression are the most common causes of death. After review, the deaths do not appear to be related to study drug. One patient received study drug PF-05280014, and had limited data for assessment of causality:

- (b) (6): 60-year-old Asian female patient assigned to PF-05280014. She was diagnosed with breast cancer (b) (6). Her medical history included hypertension. She received 2 doses of the first cycle of weekly PF-05280014 on Days 1 and 8, November 20 and November 26, 2015 in combination with Paclitaxel. The patient also received a transfusion of packed RBCs for anemia on Study Day 8. Screening ECG was normal and LVEF fraction was 66% on Day -13. On November 28, 2015 (Study Day 9), the patient was hospitalized with Grade 3 proctalgia. While hospitalized, on (b) (6) the patient was found unconscious and pulseless. The family refused resuscitative measures

and no autopsy was performed. It is unknown if the patient underwent relevant tests for the event of cardio-respiratory arrest.

***Reviewer Comments: The causes of death are well balanced between the two arms and do not have a meaningful safety impact. Overall there are no concerning safety findings in the patients who died.***

- ***Patient (b) (6) had only received 2 doses of study drug prior to cardiopulmonary arrest. She had a history of hypertension and had recent anemia requiring a blood transfusion. No resuscitation nor autopsy was performed, and clinical data is limited. Her cause of death is unclear, possibly related to underlying cardiac disease exacerbated by anemia, and less likely due to study drug.***

### 7.3.2 Nonfatal Serious Adverse Events

All SAEs were to be reported regardless of treatment group or suspected relationship to study drug.

Serious TEAEs from study 1002 are listed below in Table 20.

**Table 20: Summary of Serious TEAEs (Study B3271002)**

<b>Serious TEAE</b>	<b>PF-05280014 (N=349)</b>	<b>EU-Herceptin (N=353)</b>
Acute kidney injury	1 (0.3%)	1 (0.3%)
Acute respiratory failure	0 (0.0%)	1 (0.3%)
Affective disorder	0 (0.0%)	1 (0.3%)
Alveolitis allergic	1 (0.3%)	0 (0.0%)
Anaemia	3 (0.9%)	1 (0.3%)
Angioedema	0 (0.0%)	1 (0.3%)
Atrial fibrillation	2 (0.6%)	0 (0.0%)
Back pain	0 (0.0%)	1 (0.3%)
Bacteraemia	1 (0.3%)	0 (0.0%)
Bronchospasm	1 (0.3%)	0 (0.0%)
Cardiac arrest	0 (0.0%)	1 (0.3%)
Cardiac failure	0 (0.0%)	3 (0.9%)
Cardiac failure acute	0 (0.0%)	1 (0.3%)
Cardio-respiratory arrest	2 (0.6%)	0 (0.0%)
Cardiovascular insufficiency	0 (0.0%)	1 (0.3%)
Cellulitis	1 (0.3%)	4 (1.1%)
Cerebral infarction	0 (0.0%)	1 (0.3%)
Cholecystitis	1 (0.3%)	0 (0.0%)

Chronic obstructive pulmonary disease	1 (0.3%)	0 (0.0%)
Cyst rupture	1 (0.3%)	0 (0.0%)
Cystitis	1 (0.3%)	0 (0.0%)
Death	0 (0.0%)	1 (0.3%)
Deep vein thrombosis	2 (0.6%)	0 (0.0%)
Dehydration	0 (0.0%)	1 (0.3%)
Dermatitis contact	0 (0.0%)	1 (0.3%)
Device related infection	1 (0.3%)	0 (0.0%)
Device related sepsis	0 (0.0%)	1 (0.3%)
Diarrhoea	1 (0.3%)	1 (0.3%)
Disease progression	12 (3.4%)	12 (3.4%)
Drug hypersensitivity	1 (0.3%)	0 (0.0%)
Duodenal ulcer haemorrhage	0 (0.0%)	1 (0.3%)
Dyspepsia	0 (0.0%)	1 (0.3%)
Ejection fraction decreased	0 (0.0%)	2 (0.6%)
Embolism	0 (0.0%)	1 (0.3%)
Endometrial hyperplasia	0 (0.0%)	2 (0.6%)
Fall	0 (0.0%)	1 (0.3%)
Fatigue	1 (0.3%)	1 (0.3%)
Hydronephrosis	0 (0.0%)	1 (0.3%)
Hyperglycaemia	2 (0.6%)	0 (0.0%)
Hypernatraemia	1 (0.3%)	0 (0.0%)
Hypersensitivity	1 (0.3%)	0 (0.0%)
Hypertension	0 (0.0%)	1 (0.3%)
Hypokalaemia	4 (1.1%)	0 (0.0%)
Hypovolaemic shock	0 (0.0%)	1 (0.3%)
Infusion related reaction	1 (0.3%)	1 (0.3%)
Injury	0 (0.0%)	1 (0.3%)
Intracranial venous sinus thrombosis	1 (0.3%)	0 (0.0%)
Ischaemic stroke	0 (0.0%)	2 (0.6%)
Laceration	0 (0.0%)	1 (0.3%)
Leukopenia	1 (0.3%)	1 (0.3%)
Lower respiratory tract infection	0 (0.0%)	1 (0.3%)
Macular degeneration	1 (0.3%)	0 (0.0%)
Malignant pleural effusion	2 (0.6%)	0 (0.0%)
Mastitis	1 (0.3%)	0 (0.0%)
Metrorrhagia	1 (0.3%)	0 (0.0%)
Neuropathy peripheral	2 (0.6%)	0 (0.0%)
Neutropenia	3 (0.9%)	1 (0.3%)

Osteomyelitis	1 (0.3%)	0 (0.0%)
Ovarian germ cell teratoma benign	1 (0.3%)	0 (0.0%)
Pathological fracture	1 (0.3%)	0 (0.0%)
Pericardial effusion	1 (0.3%)	0 (0.0%)
Peritonitis	1 (0.3%)	0 (0.0%)
Pneumonia	4 (1.1%)	3 (0.9%)
Pneumonia aspiration	0 (0.0%)	1 (0.3%)
Pneumonitis	1 (0.3%)	0 (0.0%)
Proctalgia	1 (0.3%)	0 (0.0%)
Pulmonary embolism	5 (1.4%)	2 (0.6%)
Pulmonary oedema	2 (0.6%)	0 (0.0%)
Pyrexia	0 (0.0%)	3 (0.9%)
Rectal cancer	1 (0.3%)	0 (0.0%)
Respiratory tract infection	0 (0.0%)	1 (0.3%)
Sepsis	0 (0.0%)	2 (0.6%)
Septic shock	1 (0.3%)	0 (0.0%)
Small intestinal obstruction	1 (0.3%)	0 (0.0%)
Spinal compression fracture	1 (0.3%)	1 (0.3%)
Staphylococcal sepsis	0 (0.0%)	1 (0.3%)
Suicide attempt	1 (0.3%)	0 (0.0%)
Thrombocytopenia	1 (0.3%)	1 (0.3%)
Tumour lysis syndrome	0 (0.0%)	1 (0.3%)
Urinary tract infection	1 (0.3%)	2 (0.6%)
Uterine leiomyoma	0 (0.0%)	1 (0.3%)
Uterine prolapse	1 (0.3%)	0 (0.0%)
Vertigo	1 (0.3%)	0 (0.0%)
Vocal cord paralysis	1 (0.3%)	0 (0.0%)
Wound infection	1 (0.3%)	0 (0.0%)
Source dataset: advers.xpt		

The FDA analysis identified several discrepancies compared with the sponsor's data in the Summary of Serious AEs, Table 36, Module 5.3.5.1 B3271002 Report Body. An IR to the sponsor was sent February 2, 2018 for clarification:

Anemia **Sponsor:** PF-4, EU-1 vs **FDA:** PF-3, EU-1

Back pain **Sponsor:** PF-0, EU-2 vs **FDA:** PF-0, EU-1

Disease progression **Sponsor:** PF-32, EU-24 vs **FDA:** PF-12, EU-12

Pulmonary embolism **Sponsor:** PF-5, EU-3 vs **FDA:** PF-5, EU-2

The sponsor clarified that their Table 36 reflects all serious AE's, including those prior to treatment as well as treatment emergent SAEs, where the FDA analysis included treatment emergent SAEs only. This sufficiently accounted for the discrepancies noted for anemia, back pain, disease progression and pulmonary embolism.

***Reviewer Comments: There were discrepancies in the incidences of SAEs anemia, back pain, disease progression and pulmonary embolism that were small and explained by the differences in the AE reporting periods (treatment emergent versus all AEs). Overall the Serious TEAEs were infrequent with the exception of disease progression and did not pose any concerning safety findings.***

### 7.3.3 Dropouts and/or Discontinuations

The pre-specified safety withdrawal criteria are reasonable and included infusion reaction with dyspnea, clinically significant hypotension or severe or life threatening, cardiotoxicity with specified LVEF decline or symptomatic cardiac failure.

Table 21 below lists TEAEs leading to permanent withdrawal from the study.

**Table 21: Summary of Withdrawal from Study due to TEAEs (Study B3271002)**

Adverse Events	PF-05280014 (N=349)		EU-Herceptin (N=353)	
	Trastuzumab	Paclitaxel	Trastuzumab	Paclitaxel
Acute respiratory failure	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Altered state of consciousness	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Alveolitis allergic	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Anaemia	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)
Anaphylactic reaction	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)
Arthralgia	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Aspartate aminotransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Atrial fibrillation	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood alkaline phosphatase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Bronchospasm	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Cardiac failure	1 (0.3%)	1 (0.3%)	1 (0.3%)	0 (0.0%)
Chest discomfort	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

Chills	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)
Chronic kidney disease	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Cough	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Cyst rupture	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Drug hypersensitivity	0 (0.0%)	2 (0.6%)	0 (0.0%)	1 (0.3%)
Dyspnoea	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)
Ejection fraction decreased	5 (1.4%)	1 (0.3%)	4 (1.1%)	2 (0.6%)
Erysipelas	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Hepatobiliary disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Hyperbilirubinaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Hypersensitivity	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Infusion related reaction	0 (0.0%)	0 (0.0%)	1 (0.3%)	2 (0.6%)
Ischaemic stroke	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Myalgia	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Nephrotic syndrome	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Neuropathy peripheral	0 (0.0%)	3 (0.9%)	1 (0.3%)	4 (1.1%)
Neutropenia	0 (0.0%)	2 (0.6%)	0 (0.0%)	1 (0.3%)
Oedema peripheral	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Ovarian germ cell teratoma benign	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Pain	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)
Paronychia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Pathological fracture	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pericardial effusion	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Peripheral sensorimotor neuropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Peripheral sensory neuropathy	0 (0.0%)	16 (4.6%)	0 (0.0%)	11 (3.1%)
Peritonitis	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Pleural effusion	2 (0.6%)	2 (0.6%)	0 (0.0%)	0 (0.0%)
Polyneuropathy	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)

Pulmonary embolism	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Rectal cancer	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Vertigo	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Wheezing	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Source dataset: discon.xpt				

The FDA analysis identified several discrepancies compared with the sponsor's data in the Summary of Permanent Discontinuation from Treatment due to AEs, Table 31, Module 5.3.5.1 B3271002 Report Body. An IR was sent to the sponsor February 2, 2018 for clarification:

*Ejection Fraction decreased  
Pain*

**Sponsor:** PF-6, EU-4 vs **FDA:** PF-5, EU-4

**Sponsor:** PF-0, EU-Paclitaxel-0 vs **FDA:** PF-0, EU-Paclitaxel-1

*Peripheral sensory neuropathy*

**Sponsor:** PF-Paclitaxel-17, EU-0 vs **FDA:** PF-Paclitaxel-16, EU-0

*Pleural Effusion*

**Sponsor:** PF-Paclitaxel-1, EU-0 vs **FDA:** PF-Paclitaxel-2, EU-0

The sponsor clarified that their Table 31 Summary of Permanent Discontinuation from Treatment due to Adverse Events - Safety Population is based on treatment-emergent adverse events (TEAEs) from the data source *advers.xpt* with a data cutoff date of 24 August 2016. The data source used for the numbers in the FDA analysis is from a dataset *discon.xpt*, which is comprised of subject summary data (End of Treatment for Trastuzumab, Paclitaxel, and End of Study data) merged with corresponding AE data.

***Reviewer Comments:*** *The discrepancies in the incidences of TEAEs resulting in permanent withdrawal were explained by the different data sets employed and the differences in their respective data cutoff points. Overall the TEAEs resulting in permanent discontinuation were infrequent and well balanced between the two arms. There were no concerning safety findings.*

### 7.3.4 Submission Specific Primary Safety Concerns

#### 7.3.4.1 Adverse Events of Special Interest

Major events of interest which are listed as Black Box Warnings in the prescribing information for US-Herceptin include cardiomyopathy, pulmonary toxicity, infusion reactions, and embryo-fetal toxicity. There were no pregnancies reported on study 1002. AEs of special interest identified in study 1002 prior to the data cutoff date

included: infusion reactions, anaphylactic reaction, chills, pyrexia, pruritus, dyspnea, cardiac failure, left ventricular dysfunction, ejection fraction decreased, and interstitial lung disease. Cardiac toxicities, pulmonary toxicities, and infusion reactions are discussed below.

### 7.3.4.1.1 Cardiac Toxicity

Table 22 below lists the cardiac TEAEs in study 1002. There were 5 patients (1.4%) on the PF-05280014 and 7 patients (2%) on the EU-Herceptin arm who experienced cardiac failure. The majority were grade 1-2 in severity.

**Table 22: Summary of Cardiac TEAEs (Study B3271002)**

Cardiac TEAEs	PF-05280014 (N=349)		EU-Herceptin (N=353)	
	Total	Grade 3 - 4	Total	Grade 3 - 4
Angina pectoris	1 (0.3%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Aortic valve sclerosis	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Arrhythmia	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Atrial fibrillation	3 (0.9%)	2 (0.6%)	2 (0.6%)	0 (0.0%)
Bradyarrhythmia	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Bradycardia	3 (0.9%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Bundle branch block right	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac aneurysm	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Cardiac failure	5 (1.4%)	1 (0.3%)	7 (2%)	1 (0.3%)
Cardiac failure acute	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Cardiac tamponade	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardio-respiratory arrest	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiomyopathy	0 (0.0%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Cardiovascular insufficiency	1 (0.3%)	1 (0.3%)	1 (0.3%)	0 (0.0%)
Conduction disorder	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diastolic dysfunction	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Extrasystoles	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Intracardiac thrombus	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Left ventricular dysfunction	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Metabolic cardiomyopathy	1 (0.3%)	0 (0.0%)	4 (1.1%)	0 (0.0%)
Mitral valve disease	2 (0.6%)	1 (0.3%)	1 (0.3%)	0 (0.0%)
Mitral valve incompetence	1 (0.3%)	0 (0.0%)	3 (0.9%)	0 (0.0%)
Myocardial fibrosis	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Myocardial ischaemia	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Palpitations	3 (0.9%)	0 (0.0%)	4 (1.1%)	0 (0.0%)
Pericardial effusion	4 (1.1%)	2 (0.6%)	1 (0.3%)	0 (0.0%)
Rheumatic heart disease	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sinus bradycardia	1 (0.3%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Sinus tachycardia	4 (1.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Tachycardia	8 (2.3%)	0 (0.0%)	7 (2%)	0 (0.0%)
Ventricular arrhythmia	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Ventricular hypokinesia	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Source dataset: advers.xpt				

***Reviewer Comments: More patients in the PF-05280014 arm experienced cardiac arrhythmias and more patients on the EU-Herceptin arm experienced cardiac failure, but both were within the expected incidence of cardiotoxicities based on the US-Herceptin label. The majority of all cardiac TEAEs were grade 1-2. Overall the differences do not impact our conclusion that the study supports a finding of no clinically meaningful differences.***

#### 7.3.4.1.2 Pulmonary Toxicity and Infusion Related Reactions

Table 23 below lists the frequency of pulmonary toxicities and infusion reactions. The majority were grade 1-2 with infusion related reactions being the most common.

**Table 23: Summary of Pulmonary Toxicities and Infusion Reactions (Study B3271002)**

TEAEs	PF-05280014 (N=349)			EU-Herceptin (N=353)	
	Total	Grade 3 - 4		Total	Grade 3 - 4
Drug hypersensitivity	3 (0.9%)	2 (0.6%)		5 (1.4%)	1 (0.3%)
Infusion related reaction	34 (9.7%)	0 (0.0%)		30 (8.6%)	3 (0.9%)
Interstitial lung disease	0 (0.0%)	0 (0.0%)		1 (0.3%)	0 (0.0%)
Pulmonary fibrosis	0 (0.0%)	0 (0.0%)		1 (0.3%)	0 (0.0%)
Respiratory disorder	3 (0.9%)	0 (0.0%)		3 (0.9%)	0 (0.0%)

Source dataset: advers.xpt

***Reviewer Comments:*** *There are no safety concerns noted for pulmonary toxicities and infusion reactions.*

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

#### 7.4.1.1 Treatment Emergent Adverse Events (TEAEs)

Table 24 below lists a summary of TEAEs, which was balanced between the two study arms. Almost all of the patients experienced at least one TEAE, the majority being grade 1-2 in severity.

**Table 24: Summary of TEAEs (Study B3271002)**

	<b>PF-05280014 (N=349)</b>	<b>EU-Herceptin (N=353)</b>
Patients with all grade TEAEs	337 (96.6%)	338 (95.8%)
Patients with Grade ≥3 TEAEs	118 (33.8%)	128 (36.3%)
Patients with serious TEAEs	51 (14.6%)	54 (15.3%)
Patients with TEAEs leading to withdrawal from study	45 (12.9%)	41 (11.6%)
Source dataset: advers.xpt and discon.xpt		

The FDA analysis identified a discrepancy when compared with the sponsor’s data in their Treatment-Emergent Adverse events table, Table 25, Module 5.3.5.1 B3271002 Report Body. An IR to the sponsor was sent February 2, 2018 for clarification:

*Pts with Gr ≥3 TR-TEAEs*

**Sponsor:** PF-117, EU-127 vs **FDA:** PF-118, EU-128

The sponsor clarified that their Table 25 “Treatment-Emergent Adverse Events (All Causality) - Safety Population” is based on treatment-emergent adverse events (TEAEs) from the data source advers.xpt alone. The FDA analysis is from the advers.xpt dataset along with the dataset discon.xpt, which is comprised of subject summary data (End of Treatment for Trastuzumab, Paclitaxel, and End of Study data) merged with corresponding AE data.

***Reviewer Comments:*** *The TEAEs were well balanced between the two arms and the majority were grade 1-2 in severity. The small discrepancy in the incidence of TEAEs ≥ Grade 3 was explained by the different data sets employed. Overall the TEAEs were well balanced between the two arms. There were no concerning safety findings.*

#### 7.4.1.2 Treatment-Related TEAEs

Table 25 below lists a summary of treatment-related TEAEs, which was balanced between the two study arms. The majority were grade 1-2 in severity.

**Table 25: Summary of Treatment-related TEAEs (Study B3271002)**

	<b>PF-05280014 (N=349)</b>	<b>EU-Herceptin (N=353)</b>

Patients with all grade treatment-related TEAEs	315 (90.3%)	313 (88.7%)
Patients with Grade $\geq 3$ treatment-related TEAEs	73 (20.9%)	91 (25.8%)
Patients with serious treatment-related TEAEs	17 (4.9%)	15 (4.2%)
Patients with treatment-related TEAEs leading to withdrawal from study	39 (11.2%)	38 (10.8%)
Source dataset: advers.xpt and discon.xpt		

The FDA analysis identified several discrepancies compared with the sponsor's data in their Treatment-Emergent Adverse events table, Table 25, Module 5.3.5.1 B3271002 Report Body. An IR to the sponsor was sent February 2, 2018 for clarification:

*Pts with all grade TR-TEAEs*                      **Sponsor:** PF-337, EU-338 vs **FDA:** PF-315, EU-313  
*Pts with Gr  $\geq 3$  TR-TEAEs*                      **Sponsor:** PF-117, EU-127 vs **FDA:** PF-73, EU-91

The sponsor clarified that their Table 25 "Treatment-Emergent Adverse Events (All Causality) - Safety Population" is based on treatment-emergent adverse events (TEAEs) from the data source advers.xpt alone. The FDA analysis is from the advers.xpt dataset along with the dataset discon.xpt, which is comprised of subject summary data (End of Treatment for Trastuzumab, Paclitaxel, and End of Study data) merged with corresponding AE data.

***Reviewer Comments: The treatment-related TEAEs were well balanced between the two arms and the majority were grade 1-2 in severity. The discrepancies in the incidences of treatment-related TEAEs were explained by the different data sets employed. Overall the treatment-related TEAEs were well balanced between the two arms. There were no concerning safety findings.***

#### 7.4.1.3 TEAEs With Incidence $\geq 5\%$

Common TEAEs seen in  $\geq 5\%$  of patients in any group in study 1002 are shown in Table 26 below. The most frequently reported TEAEs with an incidence of  $\geq 5\%$  were alopecia (PF-05280014 group 189 [54%] and EU-Herceptin 184 [52%]) and neutropenia (PF-05280014 98 [28%] and EU-Herceptin 91 [26%]). Adverse events of special interest were discussed in Section 7.3.5.1 above.

**Table 26: Summary of TEAEs with Incidence  $\geq$  5% in any Group (Study B3271002)**

<b>MedDRA Preferred Terms</b>	<b>PF-05280014 (N=349)</b>	<b>EU-Herceptin (N=353)</b>
Abdominal pain	0 (0.0%)	28 (8%)
Alanine aminotransferase increased	29 (8.3%)	41 (11.7%)
Alopecia	189 (54.2%)	184 (52.7%)
Anaemia	119 (34.1%)	130 (37.2%)
Arthralgia	39 (11.2%)	35 (10%)
Aspartate aminotransferase increased	25 (7.2%)	26 (7.4%)
Asthenia	50 (14.3%)	43 (12.3%)
Back pain	0 (0.0%)	30 (8.6%)
Blood alkaline phosphatase increased	0 (0.0%)	24 (6.9%)
Bone pain	19 (5.4%)	0 (0.0%)
Constipation	20 (5.7%)	26 (7.4%)
Cough	29 (8.3%)	29 (8.3%)
Decreased appetite	21 (6%)	0 (0.0%)
Diarrhoea	57 (16.3%)	66 (18.9%)
Dizziness	30 (8.6%)	0 (0.0%)
Dyspnoea	19 (5.4%)	18 (5.2%)
Ejection fraction decreased	30 (8.6%)	36 (10.3%)
Epistaxis	0 (0.0%)	22 (6.3%)
Fatigue	43 (12.3%)	49 (14%)
Headache	40 (11.5%)	51 (14.6%)
Hypertension	34 (9.7%)	26 (7.4%)
Infusion related reaction	34 (9.7%)	30 (8.6%)
Leukopenia	34 (9.7%)	41 (11.7%)
Myalgia	21 (6%)	33 (9.5%)
Nausea	54 (15.5%)	63 (18.1%)
Neuropathy peripheral	31 (8.9%)	33 (9.5%)
Neutropenia	98 (28.1%)	91 (26.1%)
Oedema peripheral	23 (6.6%)	41 (11.7%)
Pain in extremity	19 (5.4%)	19 (5.4%)
Peripheral sensory neuropathy	93 (26.6%)	83 (23.8%)
Pruritus	0 (0.0%)	18 (5.2%)
Pyrexia	39 (11.2%)	28 (8%)
Rash	24 (6.9%)	24 (6.9%)

Respiratory tract infection viral	20 (5.7%)	0 (0.0%)
Stomatitis	23 (6.6%)	0 (0.0%)
Upper respiratory tract infection	30 (8.6%)	40 (11.5%)
Vomiting	26 (7.4%)	24 (6.9%)
Weight increased	0 (0.0%)	20 (5.7%)
Source dataset: advers.xpt		

***Reviewer Comments:*** *The TEAEs with an incidence of  $\geq 5\%$  were well balanced, without meaningful differences. The majority of TEAEs are likely attributable to chemotherapy.*

#### **7.4.2 Laboratory Findings**

Trastuzumab is not known to cause significant laboratory abnormalities, but chemotherapy is. The reported changes in laboratory values for studies 1002 and 1004 were reviewed and overall well balanced between the treatment arms in hematology labs and chemistries for the safety population.

***Reviewer Comments:*** *No safety concerns noted. Trastuzumab is not known to cause significant laboratory findings.*

#### **7.4.3 Vital Signs**

Changes in vital signs for the safety population reported were reviewed and overall well balanced between the treatment arms for temperature, blood pressure, heart rate, and respiratory rate.

***Reviewer Comments:*** *No safety concerns noted.*

#### **7.4.4 Electrocardiograms (ECGs)**

Trastuzumab is not known to cause clinically significant ECG changes. The reported ECG findings for study 1002 were reviewed. A 12 lead ECG was obtained at Screening, as clinically indicated, and at the End Of Treatment visit. Echocardiogram (preferred) or MUGA was performed every 8-12 weeks as per protocol and as needed. The number of patients with clinically significant abnormal ECGs (based on the investigator's assessment) was comparable for both treatment groups (7 [2.0%] in the PF-05280014 group and 4 [1.1%] in the EU-Herceptin group).

**Reviewer Comments: Very few patients had clinically significant ECG changes at baseline. No safety concerns.**

#### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted

#### 7.4.6 Immunogenicity

Immunogenicity results were reviewed for study 1002. Forty-four patients had positive ADA results at baseline (30 PF-05280014 and 14 EU-Herceptin) with 24 positive neutralizing antibody (16 PF-05280014 and 8 EU-Herceptin). NAb samples were only analyzed for patients with a positive ADA test. Those with a negative ADA test were automatically assigned a negative NAb test result.

**Table 27: Summary of Positive Anti-Drug Antibody (Study B3271002)**

Visit	Immunogenicity Test	PF-05280014 N=349		EU-Herceptin N=353	
		Sample Size	N (%)	Sample Size	N (%)
Cycle 1 Day 1	Positive Anti-Drug Antibody	346	30 (8.7%)	342	14 (4.1%)
	Positive Neutralizing Antibody	26	16 (4.6%)	13	8 (2.3%)
Cycle 3 Day 1	Positive Anti-Drug Antibody	307	0 (0%)	321	0 (0%)
	Positive Neutralizing Antibody	0	0 (0%)	0	0 (0%)
Cycle 5 Day 1	Positive Anti-Drug Antibody	287	0 (0%)	303	0 (0%)
	Positive Neutralizing Antibody	0	0 (0%)	0	0 (0%)
Cycle 8 Day 1	Positive Anti-Drug Antibody	253	0 (0%)	260	0 (0%)
	Positive Neutralizing Antibody	0	0 (0%)	0	0 (0%)

Cycle 11 Day 1	Positive Anti-Drug Antibody	214	0 (0%)	214	0 (0%)
	Positive Neutralizing Antibody	0	0 (0%)	0	0 (0%)
Cycle 14 Day 1	Positive Anti-Drug Antibody	156	0 (0%)	141	0 (0%)
	Positive Neutralizing Antibody	0	0 (0%)	0	0 (0%)
Cycle 17 Day 1	Positive Anti-Drug Antibody	107	0 (0%)	100	1 (1%)
	Positive Neutralizing Antibody	0	0 (0%)	0	0 (0%)

Source datasets: ada.xpt (SDTM) and nab.xpt (SDTM)

Note: on Page 106 of Study B3271002 CSR, the sponsor claimed that NAb samples were only analyzed for patients with a positive ADA test. Those with a negative ADA test were automatically assigned a negative NAb test result. At Baseline (Cycle 1, Day 1,) there were 26 patients in the PF-05280014 group and 13 patients in the EU-Herceptin group with a sample analyzed for NAb. The analysis for NAb for the remaining 5 Baseline ADA-positive samples (4 in the PF-05280014 group and 1 in the EU-Herceptin group) will be conducted and the results presented in a subsequent report.

Following initiation of study drug, all patients with the exception of 1 patient in the EU-Herceptin group, tested negative for ADA (titer <1.00) from Cycle 1, Day 1 through Cycle 17, Day 1. Anti-drug antibody positivity occurred infrequently overall and there were no positive ADA results at post-baseline visits until the one patient tested positive for a low tier (1.00) of ADA at Cycle 17, Day 1.

Please also refer to Dr. Cishan (Kevin) Li's review for BLA 761081 for further details regarding immunogenicity

**Reviewer Comments:**

***The observed rate of immunogenicity was overall low, with comparable treatment-emergent immunogenicity observed for the 2 treatment groups. Treatment-emergent ADA or NAb were not associated with IRRs. There are no safety concerns.***

## 7.5 Other Safety Explorations

None

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

Trastuzumab is not known to cause secondary malignancies. An evaluation of second primary malignancies found one patient on the PF-05280014 arm that developed rectal cancer. This is unlikely related to study drug.

**Reviewer Comments: No safety concerns noted.**

### **7.6.2 Human Reproduction and Pregnancy Data**

There has been no reported PF-05280014 exposure in pregnant women in studies 1002 and 1004. There have been no reported embryo-fetal toxicities.

**Reviewer Comments: No safety concerns noted.**

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

There has been no PF-05280014 exposure in pediatric patients in studies 1002 or 1004.

**Reviewer Comments: No safety concerns noted.**

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

There was no experience of overdose in studies 1002 and 1004.

**Reviewer Comments: No safety concerns noted.**

## **7.7 Additional Submissions / Safety Issues**

The Day 120 Safety Update was submitted on October 16, 2017 for study 1002. TEAEs and deaths were included through January 11, 2017 (Data cutoff date for Week 53 analysis). As of the cutoff date the incidence of deaths (all causalities) was comparable between the 2 treatment groups (42 [11.9%] and 43 [12.1%] patients in the PF-05280014 group and the EU-Herceptin group, respectively). In the PF-05280014 group, there were 70 (20.1%) patients who experienced SAEs and the corresponding number of patients in the EU-Herceptin group was 73 (20.7%). The most frequently reported SAE was disease progression (32 [9.2%] patients in the PF-05280014 group and 27 [7.6%] patients in the EU-Herceptin group). The most frequently reported TEAEs of special interest in both treatment groups was ejection fraction decreased (35 [10.0%] patients in the PF-05280014 group and 39 [11.0%] patients in the EU-

Herceptin group), followed by IRR (34 [9.7%] patients in the PF-05280014 group and 30 [8.5%] patients in the EU-Herceptin group), and pyrexia (26 [7.4%] patients in the PF-05280014 group and 21 [5.9%] patients in the EU-Herceptin group). There were no statistically significant treatment differences for any of the events.

***Reviewer Comments: Overall, there were no clinically significant safety findings in the Day 120 Safety Update.***

## **8 Postmarket Experience**

PF-05280014 is not marketed in any country. There is no postmarket safety data.

## 9 Appendices

### 9.1 Literature Review/References

- 1: NCI: SEER, Cancer Stat Facts: Breast Cancer, <https://seer.cancer.gov/statfacts/html/breast.html>, Accessed June 30, 2017.
- 2: NCI: SEER, Cancer Stat Facts: Stomach Cancer, <https://seer.cancer.gov/statfacts/html/stomach.html>, Accessed June 30, 2017.
- 3: Bang, et al., The Lancet, 2010, 376, 687-697
- 4: Nahta, et al., Oncogene, 2007, 26, 3637-3643
- 5: Pupa, et al., Oncogene, 1993, 8, 2917-2923
- 6: Hayes, et al., Clinical Cancer Research, 2001, 7, 2701-2711
- 7: Arnould, et al., British Journal of Cancer, 2006, 94, 2559-2267
- 8: Wen, et al., Oncogene, 2006, 25, 6986-6996
- 9: Gasparini, et al., Breast Cancer Research and Treatment, 2007, 101, 355-365
- 10: Marty, et al., Journal of Clinical Oncology, 2005, 4265-4274
- 11: Slamon, et al., New England Journal of Medicine, 2001, 365, 783-792

### 9.2 Labeling Recommendations

The following changes were recommended to the TRAZIMERA label:

1. Per guidance for biosimilars, throughout the label:
  - a. “trastuzumab” refers to US-Herceptin
  - b. “trastuzumab product(s)” refers to US-Herceptin and biosimilars
  - c. “TRAZIMERA” refers to PF-05280014
2. Highlights of Prescribing Information
  - a. Product name changed to “TRAZIMERA”
  - b. Full product title changed to “TRAZIMERA (trastuzumab-xxxx)”
  - c. Added description of biosimilar and biosimilarity of TRAZIMERA
3. Section 1 Indications and Usage wording changed to: “Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.”
4. Section 8 Use in Specific Populations

(b) (4)

### 9.3 Advisory Committee Meeting

No Oncology Advisory Committee Meeting (ODAC) was necessary for this BLA submission.

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/s/  
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