Saudi Public Assessment Report

Trazimera ®

Active Pharmaceutical Ingredient(s): Trastuzumab

ATC code/CAS no.: L01XC03

Pharmaceutical/Dosage Form: Powder for concentrate for solution for infusion

Dosage Strength: 150 mg, 440 mg

Marketing Authorization Holder: Pfizer PFE Switzerland GmbH, Switzerland

Shelf life: 48 months

Storage conditions: Store in a refrigerator (2°C -8°C)

Registration No.: 130621078, 2012200344

Decision and Decision Date: Approve 8/4/1442 H

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1. Terms, Definitions, Abbreviations

Terms	Definitions
ADA	Anti-drug Anti-body
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
AUC_{inf}	Area under the serum concentration-time profile from time zero extrapolated to infinite time
AUC_t	Area under the serum concentration-time profile from time zero to the last time point with measurable concentration
CDC	Complement-dependent cytotoxicity
CHO	Chinese hamster ovary
CMA	Critical material attributes
C_{max}	Maximum Serum Concentration
CPP	Critical process parameters
CQAs	Critical quality attributes
DNA	Deoxyribonucleic acid
DOR	Duration Of Response
DP	Drug product
DS	Drug substance
EMA	European Medicines Agency
FC receptor	Fc receptor is a symbol for protein found on the surface of certain cells
FISH	Fluorescent In-Situ Hybridization
GCP	Good Clinical Practice
HER-2	Human Epidermal Growth Factor Receptor 2
IgG1	Immunoglobulin 1
IHC	Immunohistochemistry
IPC	In-process control
ITT	Intention To Treat
IWRS	Interactive Web-Based Response System
MAb	Monoclonal antibody
MBC	Metastatic Breast Cancer
MCB	Master cell bank
NAb	Neutralizing Anti-body
non-CPP	Non-critical process parameters
ORR	Objective Response Rate
PCR	Pathologic Complete Response
PD	Progressive Disease
PFS	Progression Free Survival
PIMS	Phase 1 Management System
PIMS	Phase 1 Management System
PP	Per Protocol

PPQ	Process performance qualification
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
RH	Relative humidity
RMP	Reference medicinal product (
SDI	Saudi Drug Information System
SISH	Silver in-situ hybridization
SWFI	Sterile Water for Injection
TEAE	Treatment Emergent Adverse Events
TGA	Therapeutic Goods Administration
USFDA	US Food and Drug Administration
WCB	Working cell bank

2. Background

2.1 Submission Details

Type of submission: New Biosimilar Drug.

Pharmacological class: Antineoplastics, Anti-Human Epidermal Growth Factor Receptor 2 (HER2); Antineoplastics, Monoclonal Antibody.

Submitted Indication:

Breast cancer

Metastatic breast cancer

Trazimera is indicated for the treatment of tumors overexpressing HER2:

- As monotherapy for the treatment of patients who have received at least one or more chemotherapy regimens for their metastatic disease.
- In combination with paclitaxel or docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- In combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone receptor-positive metastatic breast cancer, not previously treated for their metastatic disease.

Early-stage breast cancer

Trazimera is indicated for the treatment of adult patients with HER2 positive early-stage breast cancer:

- Following surgery, chemotherapy (neoadjuvant or adjuvant) and (if applicable) radiation therapy.
- Following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- In combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumors >2 cm in diameter.

Metastatic gastric cancer or gastro-oesophageal junction cancer

Trazimera in combination with capecitabine or intravenous 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received chemotherapy for their metastatic disease. Trazimera should only be used in patients with metastatic gastric cancer whose tumors overexpress HER2 defined by IHC2+ and confirmed by a positive FISH+ or silver in-situ hybridization result (SISH), or IHC3+ determined by a validated assay.

Submitted Dosage: 150 mg, 440 mg

2.2 Regulatory Background

This product is considered New Biosimilar Drug for Saudi regulatory purposes.

This product qualified for the following regulatory pathway:

☒ Normal submission

☐ Abridged

☐ Verification

☐ Priority

Regulatory status in other countries:

Country	Product name	Dosage form	Strength	Approval Authority	Date of Approval
European Union	Trazimera®	Powder for concentrate for solution for infusion	150 mg 420 mg	EMA	26/07/2018
United States	Trazimera®	Powder for concentrate for solution for infusion	420 mg 150 mg	US-FDA	11/3/2019 30/11/2020
Australia	Trazimera®	Powder for concentrate for solution for infusion	150 mg 60 mg	TGA	19/8/2019

2.3 Product Information

The approved Summary of Product Characteristics (SPC) for this submission can be found in the Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

2. Scientific discussion about the product:

3.1 Quality Aspects

3.1.1 Introduction

PF-05280014 (trastuzumab) is a humanized immunoglobulin 1 (IgG1) monoclonal antibody (mAb) directed against the human epidermal growth factor receptor 2 (HER2/neu receptor) that has been developed as a biosimilar of Herceptin for the treatment of early breast cancer, metastatic breast cancer and metastatic gastric cancer.

PF-05280014 finished product is supplied as a lyophilized powder for concentrate for solution for infusion in a single dose and multi-dose vials, each vial contains L-histidine hydrochloride monohydrate, L-histidine, sucrose, polysorbate 20.

Single-dose vial contains 150 mg Trastuzumab to be reconstituted with 7.2 mL of Sterile Water for Injection (SWFI) to yield a solution containing 21 mg/mL of Trastuzumab at a pH of approximately 6, single-use vial supplied in a 15 mL glass vial sealed with a stopper and an aluminum seal with a flip-off plastic cap.

Single-dose vials contain 440 mg Trastuzumab to be reconstituted with 20 mL of SWFI to yield a solution containing 21 mg/mL of Trastuzumab at a pH of approximately 6. Multi-dose vials are supplied in a 30 mL glass vial sealed with a stopper and an aluminum seal with a flip-off plastic cap.

3.1.2 Drug Substance

- General Information:

Trastuzumab (PF-05280014 as referred by the Applicant) has been developed by Pfizer as a proposed biosimilar product to the reference medicinal product (RMP) Herceptin (Trastuzumab). PF-05280014 is an IgG1 kappa monoclonal antibody with two identical heavy chains and two identical light chains, covalently linked with four inter-chain disulfide bonds. The complete amino acid has been confirmed. The N-linked glycosylation in the CH2 region is essentially fully occupied with asialo, core-fucosylated, complex-type biantennary N-linked glycans with zero and one terminal galactose residues, abbreviated as G0F and G1F, respectively. The known mechanisms of action of trastuzumab are binding to HER2 leading to inhibition of cell proliferation, as well as target cell killing via antibody-dependent cell-mediated cytotoxicity (ADCC) activity.

- Description of the manufacturing process and process control:

The manufacturing process for PF-05280014 drug substance uses a recombinant Chinese hamster ovary (CHO) cell line that contains the DNA encoding the sequence for trastuzumab and is grown in suspension culture. Cells from the working cell bank (WCB) are thawed, and the culture is progressively expanded. A production fed-batch bioreactor culture is harvested and clarified to remove cells and debris. After this harvest step, the product is purified by multiple chromatography steps and virus clearance steps. Lastly, the excipients are added to the product to achieve the final formulation of the drug substance, followed by final filtration and freezing.

The process controls include a combination of critical process parameters (CPP), non-critical process parameters (non-CPP), critical material attributes (CMA), and in-process control (IPC) with defined acceptable ranges. If the results of these controls are outside of the acceptable ranges, an evaluation of the deviation is performed and the disposition decision will be determined based on the outcome of the investigation. The filtered PF-05280014 active substance is filled into a suitable container closure system compliant with required monographs, labeled, frozen, and shipped frozen to the finished product manufacturing site.

- Control of materials:

Information on the materials used in the manufacture of active substance has been provided in sufficient detail. The acceptance criteria for non-compendial raw materials used in the manufacturing process have been provided. The active substance manufacturing process uses a cell culture media that contains no proteins or peptide components of animal, plant, or synthetic origin. The chromatography resins used in the purification process of PF-05280014 are standard materials. A two-tier cell bank system, consisting of a master cell bank (MCB) and Working Cell Bank (WCB) was generated. MCB and WCB were characterized according to ICH requirements. The adventitious agents assays test results indicate that the cell bank is sterile and free of detectable mycoplasma and viruses. Data have been provided to indicate that the cell line is robust with respect to critical parameters MCB and WCB, phenotypic and genotypic stability have been demonstrated, and stability under the defined storage conditions will be monitored.

- Process validation

The validation of the PF-05280014 drug substance manufacturing process has been completed and includes three successful process performance qualification
(PPQ) batches, which are from three independent, consecutive thaws of the WCB. All release results met acceptance criteria in place at the time of process validation and conform to the commercial specifications. In addition, process parameters and in-process test data are within control limits for the commercial process. The active substance is frozen and shipped for finished product manufacture. Shipping validation has been completed and results met the specified acceptance criteria and support shipments of frozen PF-05280014 active substance.

- Manufacturing process development

PF-05280014 development was based on principles outlined in ICH Q8, ICH Q9, ICH Q10 and ICH Q11, a science- and risk-based approach was used to develop the understanding of critical quality attributes (CQAs) and a robust manufacturing process to consistently deliver the desired quality for this product.

- Characterization

A range of state-of-the-art orthogonal methodologies was used to elucidate primary and higher-order structures, posttranslational modifications, glycan structures, extinction coefficient, and charge and size heterogeneity. Several biological assays were employed addressing multiple mechanisms of action of trastuzumab, including functional cell-based assays and binding assays

were developed and applied to characterize PF-05280014. The results demonstrate that PF-05280014 has the expected structure and functional properties.

Forced degradation conditions were used to reveal potential PF-05280014 degradation pathways. The removal of process-related impurities was validated through testing during process validation. Product-related impurities are included in the overall control strategy.

- Control of the drug substance:

Specifications used for drug substance control include test parameters for appearance, protein concentration, glycan profile, identity, purity, potency, and general tests. The justification of specifications and acceptance criteria are provided and found to comply with the ICH Q6B "specifications for release and shelf life".
All in-house analytical procedures were described in sufficient detail, and validated in accordance with ICH Q2 (R1) "Validation of Analytical Procedures: Text and Methodology".
Batch analysis data including several batches have been provided which demonstrate compliance with specification acceptance criteria and batch-to-batch consistency.

- Reference materials:

A two-tiered system for in-house PF-05280014 reference material has been implemented as recommended in ICH Q6B. The current primary reference material (PRM) and working reference material (WRM) have been suitably manufactured and characterized for their purpose.

Protocol for future reference standards is provided. The qualification of future reference standards involves specification parameters at the time of manufacturing and extended characterization tests.

- Stability:

The proposed shelf life and intended storage condition are based on ICH stability guidelines. Stability studies are performed in long-term and accelerated conditions and photostability. The stability data support the proposed shelf life and storage condition. Post-approval stability protocols are provided and considered adequate.

3.1.3 Drug Product

- Description of the product and Pharmaceutical Development:

PF-05280014 finished product is supplied as a lyophilized powder for concentrate for solution for infusion in a single-dose vial each vial contains L-histidine hydrochloride monohydrate, L-histidine, sucrose, polysorbate 20.

The single dose vial contain 150 mg Trastuzumab to be reconstituted with 7.2 mL of Sterile Water for Injection (SWFI) to yield a solution containing 21 mg/mL of Trastuzumab at a pH of

approximately 6. The single-use vial is supplied in a 15 mL glass vial sealed with a stopper and an aluminum seal with a flip-off plastic cap.

The vial contains 440 mg Trastuzumab to be reconstituted with 20 mL of Sterile Water for Injection (SWFI) to yield a solution containing 21 mg/mL of Trastuzumab at a pH of approximately 6. The 440 mg is supplied in a 30 mL glass vial sealed with a stopper and an aluminum seal with a flip-off plastic cap.

Before use, the lyophilized drug product is reconstituted with SWFI diluent to form a solution that is further diluted with sterile 0.9% sodium chloride for administration by intravenous infusion. Lyophilized drug product reconstituted with SWFI contains no preservative.

- Pharmaceutical Development

The manufacturer developed two presentations for Trazimera intended to match the presentations in markets where the corresponding presentation of the Herceptin licensed reference product (150 mg and 440 mg) drug development in alignment with ICH Q8, Pharmaceutical Development and ICH Q9, Quality Risk Management, a variety of risk assessment tools have been utilized in an iterative process to direct process development and characterization.

The excipients of the final formulation are different from the reference product Herceptin. The difference between the two formulations is the substitution of trehalose with sucrose, both of which are disaccharides. When lyophilized PF-05280014 finished product was stored at elevated temperatures, the finished product was observed to be more stable in the sucrose formulation than in the trehalose formulation.

- Manufacture of the product:

The finished product is manufactured at Pfizer Manufacturing Belgium NV, Puurs, Belgium. The frozen PF-05280014 drug substance is thawed and transferred to a manufacturing vessel to begin drug product manufacture. The bulk drug product is then filtered through a sterilizing grade filter into a holding vessel. The bulk drug product is subsequently filtered and aseptically filled into vials. Vials are partially stoppered before lyophilization. Upon completion of the lyophilization cycle, the vials are fully stoppered and capped with a crimp seal. Following this capping operation, the vials are visually inspected. PF-05280014 drug product 150 mg and 440 mg presentations are manufactured using the same process steps and controls. The two presentations are designed to be comparable to one another in that the drug substance and bulk drug product used to make the PF-05280014 drug product is identical for the two presentations, and the only differences between manufacturing processes for the two presentations are (1) the volume filled per vial, (2) the size of the glass vial, and (3) the lyophilization cycle.

The process controls include a combination of CPP, non-CPP, CMA, and IPC with defined acceptable ranges. If the results of these controls are outside of the acceptable ranges, an evaluation

of the deviation is performed and the disposition decision will be determined based on the outcome of the investigation.

The validation of the drug product manufacturing process is provided for both presentations (150 mg and 440 mg), and one additional lot manufactured at the commercial scale for 150 mg. All in-process testing results met the acceptance criteria in place. All release results met acceptance criteria in place at the time of process validation and additionally met the commercial specifications. The validation has demonstrated control, effectiveness and consistency of the drug product manufacturing process, executed within the ranges established.

- Product control:

Specifications used for finished product control include test parameters for appearance, residual moisture, reconstitution time, pH, osmolality, content uniformity, protein concentration, sub-visible particles, charge heterogeneity, identity, impurities, potency, endotoxins and sterility. The justification of specifications and acceptance criteria are provided and found to comply with the ICH Q6B specifications for release and shelf life.

All in-house analytical procedures were described in sufficient detail, and validated in accordance with ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology.

Batch analysis data including several batches have been provided which demonstrate compliance with specification acceptance criteria and batch-to-batch consistency.

- Batch analysis:

Batch analysis data including several batches have been provided which demonstrate compliance with specification acceptance criteria and batch-to-batch consistency.

- Reference materials:

The reference standard used for the analysis of the finished product is the same as that used for the active substance.

- Stability of the product:

Stability studies for lots stored under the recommended long term condition of 5±3° C, the accelerated condition of 30 ± 2 °C/ H 75 ± 5% relative humidity (RH), as well as thermal stress, thermal cycling, and photostability conditions, are provided. The stability program is designed to follow ICH guidelines for the stability of drug product (ICH Guideline Q1A (R2): Stability Testing of New Drug Substances and Products; ICH Guideline Q5C: Quality of Biotechnological Products, Stability Testing of Biotechnological/Biological Products). The results of stability data support the proposed shelf life of 48 months, when stored in a refrigerator (2°C - 8°C), protected from light.

Unopened vials of Trazimera may also be stored at a maximum of 30 ºC for a single period up to 3 months, but not exceeding the original expiration date.

After reconstitution with sterile water for injection, the solution is physically and chemically stable for 48 hours at 2-8 °C (do not freeze). From a microbiological standpoint, the reconstituted solution with Trazimera should be used immediately, unless preparation has been performed under controlled and validated aseptic conditions.

3.1.4 Adventitious agents

The active substance is produced in a serum-free culture medium. No material of bovine origin is added during cell culture. The MCB which has been established is free from TSE-risk substances.

The purification process of PF-05280014 includes several steps for the inactivation/removal of enveloped viruses and the removal of non-enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated.

3.1.5 Comparability studies

The PF-05280014 analytical similarity assessment was comprehensive in both breadth of lot selection and depth of analytics, analyzing sufficient lots by appropriate methods to ensure an understanding of the Herceptin product profile and the PF-05280014 product developed. This assessment included:

- A 3-way comparability exercise was performed comparing PF-05280014 to US-licensed Herceptin, PF-05280014 to EU-approved Herceptin, and US-licensed Herceptin to EU-approved Herceptin.

- 64 drug product lots of trastuzumab-US and 74 drug product lots of trastuzumab-EU were purchased and included as licensed trastuzumab product in the similarity assessment. These licensed drug product lots represent nearly the full 48-month expiry period of the licensed trastuzumab product. A total of 8 drug substance (DS) batches and 13 drug product (DP) lots of PF-05280014 were produced at the commercial scale and included in the similarity assessment. In addition, 3 development scale DS batches representative of the commercial scale and two reference materials of PF-05280014 are also included in the similarity assessment.

- The comparative testing included analysis of the primary structure and post-translational modifications, biological activity, N-linked glycans, charge heterogeneity, product purity, disulfide bonds, higher-order structure, and comparative forced degradation studies of PF-05280014, trastuzumab-US, and trastuzumab-EU.

Primary structure, molecular mass, and posttranslational modifications by application of orthogonal, in-depth mass spectrometric methods support that these attributes of PF-05280014 are highly similar to trastuzumab-EU.

Table 1- Summary of Similarity studies

Quality attribute/s	Findings
Primary Structure and Posttranslational Modifications	Identical amino acid sequence, Similar molecular mass and post-translational modification
Glycan profile	Similar glycan profile
Charge Heterogeneity	Different levels of basic species due to differences in levels of C-terminal lysine, however, C-terminal variants are not considered clinically relevant.
Purity (size variants)	High purity and similar profile
Higher-Order Structure	Similar secondary and tertiary structure and similar thermal stability
Binding to HER2 Target Antigen	Similar binding affinity and relative potency
ADCC Activity	Similar ADCC activity
Antibody-Dependent Cellular Phagocytosis (ADCP)	Similar ADCP activity
Apoptosis	Similar low-level induction of apoptosis
Fcγ Receptors Binding	Similar binding affinity and kinetic
FcRn Binding	Similar binding affinity and kinetic
Complement-dependent cytotoxicity (CDC) Activity	No CDC activity observed for Herceptin nor Trazimera

Forced degradation studies

In addition to the physicochemical and biological comparison, the applicant has conducted comparative forced degradation studies. The treatment conditions include elevated temperature, light exposure, forced deamidation and oxidation. Similar degradation profiles were seen for PF-05280014, trastuzumab-US and trastuzumab-EU thereby confirming the similarity between these products.

The comparability assessment performed by the Applicant is considered adequate to confirm the analytical similarity between Trazimera and approved reference medicinal product Herceptin according to SFDA Guideline on Biosimilar Products.

3.1.6 Discussion on chemical, pharmaceutical and biological aspects

The quality of Trazimera is considered adequate, the manufacturing process and control strategy including physicochemical and biological aspects is expected to produce batches with desired clinical outcome. The comparability study demonstrates a high similarity with the reference medicinal product Herceptin notwithstanding minor clinically irrelevant differences.

3.2 Clinical Aspects

3.2.1 Clinical Pharmacology

Trastuzumab is a recombinant humanized monoclonal IgG1 kappa antibody, this antibody specifically binds to HER2. HER2 overexpression is observed mostly in 15% to 20% of all primary breast cancers. Trastuzumab is shown to inhibit the proliferation of human tumor cells that overexpress HER2. It is a mediator for ADCC. In vitro data show trastuzumab-mediated ADCC, preferably on HER2 overexpressing cancer cells.

4.2.1.1 Pharmacokinetic studies

List of pharmacokinetic studies

Study	Clinical trials identifier	Objectives	Findings
B3271001	NCT01603264	**Primary objectives:** Demonstrate the PK similarity of trastuzumab-Pfizer to trastuzumab-EU and to trastuzumab-US; demonstrate the PK similarity of trastuzumab-EU to trastuzumab-US With a pre-defined bioequivalence limit of 80%-125%. **Secondary objectives:** Evaluate the single-dose safety, tolerability, and immunogenicity of trastuzumab-Pfizer.	**<u>Pharmacokinetics:</u>** <u>90% CI of Trastuzumab-Pfizer vs. EU:</u> • C_{max}: 91.49 (85.32, 98.09) • AUC_t: 92.66 (86.44, 99.34) • AUC_{inf}: 92.15 (86.03, 98.69) <u>90% CI of Trastuzumab-Pfizer vs. US:</u> • C_{max}: 97.41 (90.71, 104.62) • AUC_t: 99.94 (93.08, 107.31) • AUC_{inf}: 99.83 (93.06, 107.09) <u>90% CI of Trastuzumab-Pfizer vs. Average of EU+US:</u> • C_{max}: 94.40 (88.82, 100.34) • AUC_t: 96.23 (90.55, 102.27) • AUC_{inf}: 95.91 (90.32, 101.85) The mean C_{max}, AUC_t, and AUC_{inf} estimates were similar among the 3 study drugs

		In addition, evaluate PK similarity of trastuzumab-Pfizer to the combined groups of Trastuzumab-US and trastuzumab-EU.	

Study 1

Title: Phase I, Double-Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-05280014 and Trastuzumab Sourced From US and EU Administered to Healthy Male Volunteers	
Study identifier	B3271001/ NCT01603264
Design	Phase 1, three arm, double blind (sponsor un-blinded), randomized (1:1:1), parallel group, single dose study.
Hypothesis	Demonstrate the PK similarity
Total study duration including Duration of Run-in phase **And Duration of main phase** **And Duration of Extension phase**	Duration of Run-in phase: 4 weeks Duration of main phase: 10 weeks Duration of extension phase: 71 Days
Treatment arms	PF-05280014 → N = 34 Healthy male volunteers Trastuzumab-EU → N = 35 Healthy male volunteers Trastuzumab-US → N = 32 Healthy male volunteers
Randomization	At screening subjects are given a unique Phase 1 Management System (PIMS) identification number, and this number will correspond to a treatment assignment.
Blinding	This study is double-blinded.
Primary Endpoint	Demonstrate the PK similarity of trastuzumab-Pfizer to trastuzumab-EU and to trastuzumab-US using PK parameters C_{max} and AUC_T (AUC from time zero to time T, the last time point with measurable concentration).
Secondary endpoints	• Safety as measured by type, incidence, severity, timing, seriousness, and relatedness of adverse events, and laboratory abnormalities. • Incidence of anti-trastuzumab antibodies (ADAs), including neutralizing antibodies (Nab).

	• Secondary PK parameters, including $AUC_{0-\infty,}$ serum clearance (CL), $t_{1/2}$, and volume of distribution at steady state (V_{ss}).
Blood samples	Blood samples were taken in the following time-points: At pre-dose (within 1 hour of dose administration), 1.5 (immediately before the end of infusion, but within 0.1 hour prior to the end of infusion is acceptable), 3±0.2, 8±0.5, 24±1, 48±2, 96±4, 168±8, 336±24, 504±48, 672±48, 1008±96, and 1680±168 hours following dose administration.
Statistical analysis	PK similarity will be determined based on the primary PK parameters (C_{max} and AUC_T) using standard bioequivalence testing methods. PK similarity will be shown if the 90% confidence interval of the ratio of the test product to control products is within the acceptance ratio of 80% to 125%. The 90% confidence intervals will be computed on a log scale using the two 1-sided tests procedure. A one-way analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_T, and C_{max} for the test and control products. **Analysis Population:** • The intent-to-treat (ITT) population was defined as all subjects who were randomized to the study treatment. The ITT population was primarily used for subject accountability. • The modified ITT (mITT) population was defined as all subjects who were randomized and received at least 1 dose of study treatment. This population was used for assessment of safety, tolerability and immunogenicity measures. • The per-protocol population was defined as all subjects who were randomized to and received the planned study treatment, and had no major protocol violations. The per-protocol population was used as the primary analysis population for PK analyses.
Study Results	**Pharmacokinetics:** 90% CI of Trastuzumab-Pfizer vs. EU: • C_{max}: 91.49 (85.32, 98.09) • AUC_t: 92.66 (86.44, 99.34) • AUC_{inf}: 92.15 (86.03, 98.69)

	90% CI of Trastuzumab-Pfizer vs. US: • C_{max}: 97.41 (90.71, 104.62) • AUC_t: 99.94 (93.08, 107.31) • AUC_{inf}: 99.83 (93.06, 107.09) 90% CI of Trastuzumab-Pfizer vs. Average of EU+US: • C_{max}: 94.40 (88.82, 100.34) • AUC_t: 96.23 (90.55, 102.27) • AUC_{inf}: 95.91 (90.32, 101.85) The mean C_{max}, AUC_t, and AUC_{inf} estimates were similar among the 3 study drugs

3.2.1.2 Pharmacodynamics studies

The applicant did not submit any pharmacodynamics study. However, HER2 levels were assessed as a biomarker in the main Phase III trial using the per protocol (PP) population which are defined as all subjects who were randomized and received the planned study treatment, and had no major protocol violations (Table 1).

Table 1: Summary of Serum HER2 (ng/ml) - PP Population

Visit	Planned Time Post-Dose	PF-05280014 Treatment Group				Trastuzumab-EU Treatment Group			
		N	NALQ	Mean	SD	N	NALQ	Mean	SD
Cycle 1 Day 1	0 h	280	280	159.83	298.292	282	282	184.42	546.620
Cycle 1 Day 8	0 h	273	272	134.04	267.181	274	274	148.72	483.346
	% CFB	273		-10.95	36.709	273		-11.74	27.737
Cycle 3 Day 1	0 h	253	253	21.23	37.997	266	266	23.82	54.026
	% CFB	253		-60.87	31.187	263		-59.46	34.288
Cycle 5 Day 1	0 h	238	238	17.91	47.535	250	250	13.47	19.005
	% CFB	238		-62.66	33.556	247		-59.04	36.877
Cycle 8 Day 1	0 h	209	209	16.52	52.662	220	220	12.98	14.508
	% CFB	209		-58.88	37.483	217		-59.13	40.000

Assessors' comment on clinical pharmacology

Study B3271001 was designed to demonstrate equivalence in healthy male subjects between the three treatments arms (Trastuzumab-Pfizer, Trastuzumab-EU and Trastuzumab-US).
The study design is considered appropriate as it is performed according to EMA guidelines for similar biological medicinal products containing monoclonal antibodies. Overall, 105 subjects were included in the trial to ensure that at least 93 subjects completed the study, to achieve the targeted sample size that is needed to have at least 81% power to demonstrate PK similarity of the treatment arms. The estimate is based on the assumption that the true ratio between trastuzumab-Pfizer to

trastuzumab-EU and trastuzumab-US for both AUC and C_{max} is 1.00 and assumes inter-subject standard deviations of 0.25 and 0.20 for loge AUC and loge C_{max}, respectively.

Study medication was administered with a dose of 6 mg/kg as a 90-minute IV infusion, as the higher doses of "8 mg/kg" were not tested on healthy subjects. The primary PK parameters were C_{max} and AUC_t, while the $AUC_{(0\text{-}inf)}$ was measured as a secondary endpoint.

The PK sampling time points were as follows: at pre-dose (within 1 hour of dose administration), 1.5 (immediately before the end of infusion, but within 0.1 hours prior to the end of infusion), 3 ± 0.2, 8 ± 0.5, 24 ± 1, 48 ± 2, 96 ± 4, 168 ± 8, 336 ± 24, 504 ± 48, 672 ± 48, 1008 ± 96, and 1680 ± 168 hours following dose administration. A validated Enzyme-linked immunosorbent assay "ELISA" method was used to analyze human serum samples.

PK Analysis performed in the per-protocol population. Demographic and baseline characteristics were generally similar among the three arms (Table 2). Patients were between 18 and 55 years of age.

Table 2: Demographic and Baseline Characteristics – Per Protocol Population

	Trastuzumab-Pfizer	Trastuzumab-EU	Trastuzumab-US
	N=34	N=35	N=32
Gender, n:			
Male	34	35	32
Age (years):			
Mean (SD)	34.5 (10.7)	36.1 (9.5)	35.3 (9.2)
Range	18-55	21-55	21-53
Race, n:			
White	13	7	8
Black	14	22	15
Other	7	6	9
Weight (kg):			
Mean (SD)	79.7 (11.2)	86.3 (11.3)	81.4 (11.0)
Range	61.1-109.8	65.3-111.2	56.9-102.1
Body Mass Index (kg/m^2):			
Mean (SD)	25.8 (3.1)	27.2 (2.6)	25.9 (3.0)
Range	20.3-30.5	21.9-30.5	19.8-30.5
Height (cm):			
Mean (SD)	175.9 (6.7)	177.8 (8.0)	177.3 (7.4)
Range	161-190	154-193	162-193

The ratio of the adjusted means for PK exposure parameters in the comparison of Trastuzumab Pfizer versus Trastuzumab-EU were: C_{max} 91.49 [90% CI: 85.32 - 98.09], AUC_t of 92.66 [90% CI: 86.44 - 99.34], and AUC_{inf} of 92.15 [90% CI: 86.03 - 98.69; Table 3 & 4]. Although the 90% CI for all PK parameters were within the pre-specified equivalence margin of 80% to 125%, the EMA guidance recommends that $AUC_{(0\text{-}inf)}$ to be assigned as a primary endpoint for single dosing trials.

In general, all data provided by the applicant was adequate and have demonstrated similarity between PF-05280014 and reference product "Herceptin" concerning PK parameters.

Table 3: Summary of Statistical Comparisons of Pharmacokinetics Exposure Parameters (C_{max}, AUC_t, and AUC_{inf}) Between Test and Reference Products

Parameter (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test	Reference		
Trastuzumab-Pfizer (Test) versus Trastuzumab-EU (Reference)				
C_{max} (µg/mL)	157	171	91.49	(85.32, 98.09)
AUC_t (µg•hr/mL)	35210	38000	92.66	(86.44, 99.34)
AUC_{inf} (µg•hr/mL)	36650	39770	92.15	(86.03, 98.69)
Trastuzumab-Pfizer (Test) versus Trastuzumab-US (Reference)				
C_{max} (µg/mL)	157	161	97.41	(90.71, 104.62)
AUC_t (µg•hr/mL)	35210	35230	99.94	(93.08, 107.31)
AUC_{inf} (µg•hr/mL)	36650	36710	99.83	(93.06, 107.09)
Trastuzumab-EU (Test) versus Trastuzumab-US (Reference)				
C_{max} (µg/mL)	171	161	106.48	(99.20, 114.30)
AUC_t (µg•hr/mL)	38000	35230	107.85	(100.50, 115.75)
AUC_{inf} (µg•hr/mL)	39770	36710	108.34	(101.05, 116.16)
Trastuzumab-Pfizer (Test) versus Average of Trastuzumab-EU + Trastuzumab-US (Reference)				
C_{max} (µg/mL)	157	171, 161[b]	94.40	(88.82, 100.34)
AUC_t (µg•hr/mL)	35210	38000, 35230[b]	96.23	(90.55, 102.27)
AUC_{inf} (µg•hr/mL)	36650	39770, 36710[b]	95.91	(90.32, 101.85)

Parameter (Units)	Trastuzumab-Pfizer	Trastuzumab-EU	Trastuzumab-US
N, n	34, 34	35, 35	32, 32
C_{max} (µg/mL)	159 ± 26	174 ± 31	164 ± 31
AUC_t (µg•hr/mL)	35700 ± 6287	38510 ± 6569	35870 ± 6878
AUC_{inf} (µg•hr/mL)	37130 ± 6305	40330 ± 6994	37310 ± 6728
CL (mL/hr/kg)	0.166 ± 0.026	0.153 ± 0.025	0.166 ± 0.032
V_{ss} (mL/kg)	56.1 ± 8.2	51.7 ± 6.9	55.7 ± 8.8
$t_{½}$ (hr)	213 ± 42	220 ± 42	212 ± 47

3.2.2 Clinical Efficacy

3.2.2.1 List of submitted clinical efficacy studies

Study ID*	No. of study centres / locations	Design	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
B3271002/ NCT01989676	Multicenter	Double-blind, randomized clinical study	**Primary:** Compare the Objective Response Rate (ORR) in PF-05280014 to trastuzumab-EU in combination with paclitaxel. **Secondary:** • Evaluate the safety of PF-05280014 plus paclitaxel versus trastuzumab-EU plus paclitaxel • Evaluate secondary measures of tumor control • Evaluate the population PK of PF-05280014 and trastuzumab-EU • Evaluate the immunogenicity of PF-05280014 and trastuzumab-EU	N= 707 PF-05280014 = 352 Trasttuzumab-EU = 355	8 cycles (~ 6 months)	Female patients aged 18 years or older	Female patients aged 18 years or older with a confirmed diagnosis of breast cancer and presence of metastatic disease	**Primary:** 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 (RECIST) 1.1.
B3271004/ NCT02187744	Multicenter	Double-blind, randomized clinical study	**Primary:** • Compare the percentage of patients with steady state (Cycle 5) through plasma concentration (C_{trough}) >20µg/ml for PF-05280014 versus trastuzumab-EU **Secondary:** • Evaluate measures of tumor control for PF-05280014 plus paclitaxel versus trastuzumab-EU • Evaluate the safety of PF-05280014 plus paclitaxel versus trastuzumab-EU	N = 226 PF-05280014 = 114 Trastuzumab-EU = 112	6 cycles	Female patients aged 18 years or older	Female patients aged 18 years or older with confirmed HER2 overexpressing invasive breast cancer	**Primary:** Percent of patients with Cycle 5 C_{trough} (Cycle 6 pre-dose) >20 µg/mL.

			• Evaluate the PK of PF-05280014 and trastuzumba-EU • Evaluate the immunogenicity of PF-05280014 and trastuzumab-EU					

* Includes clinical trials registry identifier or sponsor protocol number

3.2.2.2 Data integrity and GCP

The applicant confirmed that all submitted studies were conducted in accordance with Good Clinical Practice (GCP) guidelines. During the conduct of the two phase I studies, the sponsor staff "Pfizer personnel" were un-blinded for detecting any safety issues during the study. In order to minimize the potential for bias, treatment randomization information have been kept confidential by Pfizer personnel and not released to the investigator or investigator site personnel until the study database is locked.

3.2.2.3 Inter-changability studies

NA.

Assessors' comments on the submitted clinical studies

All the submitted studies were registered in "clinicaltrial.gov" and EudraCT. The applicant submitted data from Phase I (B3271001) clinical trial to demonstrate PK similarity of the submitted biosimilar to the reference product approved in the US and EU. In addition, the applicant submitted two Phase III (B3271002 and B3271004) clinical trials that assessed the efficacy and equivalence of the biosimilar product. In addition, a Phase I (B3271006) clinical trial was submitted which was conducted to assess the product's safety with a primary endpoint of estimating the relative risk of an abnormally elevated body temperature after administration of the product.
The design and choice of endpoints for all the submitted studies were in accordance with the requirements of EMA guidance on similar biological medicinal products containing monoclonal antibodies.

Study 1

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Comparative Study of PF-05280014 Plus Paclitaxel Versus Trastuzumab-EU Plus Paclitaxel for the First-Line Treatment of Patients with HER2-Positive Metastatic Breast Cancer to evaluate the efficacy, safety, PK and immunogenicity.		
Study identifier	B3271002	
Design	International, multicenter, parallel assignment, double-blind, randomized, phase 3 clinical study	
	Duration of the main phase:	8 cycles (approximately 6 months)
Hypothesis	Two one-sided hypothesis tests will be carried out in the study for the primary efficacy endpoint of ORR. The hypothesis to be tested was that the risk ratio of ORR of Trazimera versus that of Herceptin by week 25 was falling in the pre-specified equivalent margin of 0.80 to 1.25 in patients with metastatic HER2 positive breast cancer.	
Treatments arms	**Experimental product:** PF-05280014 Initial loading dose of 4mg/kg infused over 90 minutes. And then subsequent weekly infusions on Days 1, 8, 15, and 22 of each 28-day cycle of 2mg/kg were administered over 30 to 90 minutes + Paclitaxel 80 mg/m2 by IV infusion over 60 minutes on Days 1, 8 and 15 of each 28-day cycle	
	Reference product: Trastuzumab EU (Herceptin®) Initial loading dose of 4mg/kg infused over 90 minutes. And then subsequent weekly infusions of 2mg/kg administered over 30 to 90 minutes + Paclitaxel 80 mg/m2 by IV infusion over 60 minutes on Days 1, 8 and 15 of each 28-day cycle **N= 355**	
Randomization	Patients were randomized in a 1:1 ratio using an automated interactive web-based response system (IWRS) to receive either PF-05280014 plus paclitaxel or trastuzumab-EU plus paclitaxel. Randomization was stratified by prior adjuvant trastuzumab exposure (yes versus no), and estrogen receptor (ER) status (ER-positive versus ER-negative).	
Blinding	This study was double-blinded.	
Endpoints and definitions	**Primary endpoints**	• **ORR:**

		Descriptive statistics (frequency and percentage) for patients who reached CR or PR by week 25 of the study and confirmed on week 33 or early discontinuation, in accordance with RECIST 1.1 criteria.
	Secondary endpoints	• **1-Year progression-free survival rate (PFS):** Based on the time from date of randomization to first documentation of PD or death due to any cause. • **Duration of response:** Time from date of the first documentation of objective tumour response (CR or PR) to the first documentation of PD, or to death due to any cause in the absence of documented PD. • **1-Year survival rate:** Time from date of randomization to date of death due to any cause while the patient was on the study. • **Other evaluations:** Including immunogenicity, selected PK samples, and safety evaluations.
Statistical Analysis	A sample size of 630 subjects (315 per treatment arm) provided approximately 85% power for achieving equivalence under the specified margin with 2.5% type I error rate assuming an ORR of 60% in both treatment arms. Considering a possible 10% attrition rate for patients reaching evaluation for ORR, a total sample size of approximately 690 patients (345 per treatment arm) should be randomized to achieve the target sample size of 630. **Analysis Population:** • The intent-to-treat (ITT) population was defined as all subjects who were randomized to the study treatment. The ITT population was used for patient accountability and all efficacy analyses. • The per-protocol population (PP) was defined as all subjects who were randomized and received the planned study treatment, and had no major protocol violations. The per-protocol population was used for drug concentration and biomarker analyses. The primary efficacy endpoint of the study was 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 (window ± 14 days) and confirmed on a follow-up assessment, in accordance with the RECIST 1.1. The denominator in the ORR calculation was the number of ITT patients in each treatment group. Descriptive statistics (frequency and percentage) were done for CR, PR. The 95% confidence interval of these response rates was constructed. These analyses were performed in the ITT population.	
Database lock	17/02/2017	

Results and Analysis

707 patients were randomly assigned into the study to receive either PF-05280014 + paclitaxel or trastuzumab-EU + paclitaxel (Table 5). The PP population was used for sensitivity analyses of the primary and secondary objectives and biomarker analyses. While the ITT population was used as the primary analysis population.

Table 5: Demographic Characteristics – ITT Population

	PF-05280014		Trastuzumab-EU		Total	
Number (%) of Female Patients	352		355		707	
Age (years) [a]:						
<18	0		0		0	
18-44	74	(21.0)	73	(20.6)	147	(20.8)
45-64	212	(60.2)	221	(62.3)	433	(61.2)
≥65	66	(18.8)	61	(17.2)	127	(18.0)
Mean	54.0		54.1		54.1	
SD	10.8		10.9		10.8	
Median	55.0		54.0		54.0	
Range	19-80		25-85		19-85	
Weight at Baseline (kg):						
Mean	69.1		68.1		68.6	
SD	17.1		16.1		16.6	
Median	68.2		66.0		67.0	
Range	29-147		36-139		29-147	
n	352	(100.0)	355	(100.0)	707	(100.0)
Height (cm):						
Mean	158.5		159.3		158.9	
SD	7.0		7.3		7.2	
Median	158.0		159.0		159.0	
Range	137.0-178.0		137.2-178.0		137.0-178.0	
n	352	(100.0)	355	(100.0)	707	(100.0)
Body Mass Index (kg/m^2):						
Mean	27.4		26.8		27.1	
SD	6.3		6.0		6.2	
Median	26.5		25.7		26.1	
Range	15.3-58.9		14.5-56.9		14.5-58.9	
n	352	(100.0)	355	(100.0)	707	(100.0)

Primary endpoint:

Results have demonstrated statistical similarity between the 2 treatment groups with a risk ratio of 0.940 (PF-05280014 over trastuzumab-EU), and a 95% CI of 0.842 to 1.049, which fell within the pre-specified equivalence margin of 0.80 to 1.25.

The primary efficacy endpoint, ORR, in accordance with RECIST 1.1 was 220 (62.5%) patients for those receiving PF-05280014 and 236 (66.5%) patients for those receiving trastuzumab-EU (Table 6).

Table 6: Primary Efficacy Analysis

Analysis description	**Primary Endpoint Analysis**		
Descriptive statistics	**ITT population, Week 33**		
	Treatment group	PF-05280014	Trastuzumab-EU
	Number of subjects	352	355
	Objective Response Rate (ORR)	220 (62.5%)	236 (66.5%)
	95% CI	(57.2, 67.6)	(61.3, 71.4)
Effect estimate	**ORR "week 33"**	**Comparison groups**	PF-05280014 vs. Trastuzumab-EU
		Risk ratio	0.94
		95%-CI	(0.842, 1.049)
	ORR "week 53"	**Risk ratio**	0.948
		95%-CI	(0.848, 1.059)
Sensitivity analysis	**PP population**		
	Treatment group	PF-05280014	Trastuzumab-EU
	Number of subjects	280	285
	ORR	199 (71.1%)	210 (73.7%)
	95% CI	(65.4, 76.3)	(68.2, 78.7)
	ORR "week 33"	**Comparison groups**	PF-05280014 vs. Trastuzumab-EU
		Risk ratio	0.965
		95%-CI	(0.870, 1.068)

Secondary endpoints:

- 1-Year PFS rate:

  There were 144 (40.9%) and 148 (41.7%) patients who had disease progression or had died in the PF-05280014 group and the trastuzumab-EU group, respectively. The 1-year PFS rate was 54% [95%CI: 48% - 60%] compared to 51% [95%CI: 45% - 57%] with a median time to PFS of 12.16 months [95%CI: 11.93 - 12.48] compared to 12.06 months [95%CI: 11.79 - not estimable] in the PF-05280014 and trastuzumab-EU groups, respectively (Table 7).

- Duration of response (DOR):

  There were 151/224 (67.4%) and 157/238 (66.0%) patients who did not have subsequent progression or death up to Week 53 in the PF-05280014 group and the trastuzumab-EU group, respectively. The 9-month DOR rate was 71% [95%CI: 64% - 76%] compared to 68% [95CI%: 61% - 74%], with a median DOR of 11.27 months [95%CI: 10.41 - 11.27] and 10.58 months [95%CI: 10.22 - not estimable] for the PF-05280014 and trastuzumab-EU groups, respectively (Table 7).

- 1-Year survival rate:

  There were 42 (11.9%) and 43 (12.1%) patients who died in the PF-05280014 group and the trastuzumab-EU group, respectively (up to 378 days post-randomization). The median time to death could not be estimated in either treatment group due to the small proportion of deaths observed. The survival probability at 1 year was 89.31% [95%CI: 85.48% - 92.17%] and 87.36% [95%CI: 83.27% - 90.51%] for the PF-05280014 and trastuzumab-EU groups, respectively (Table 7).

Table 7: Secondary Efficacy Analysis

Analysis description	**Secondary Endpoint Analysis**		
Descriptive statistics and estimate variability	**ITT population, Week 53**		
	Treatment group	PF-05280014	Trastuzumab-EU
	Number of subjects	**352**	**355**
	Progressed or died; N **(%)**	144 (40.9)	148 (41.7)
	Censored; N **(%)**	208 (59.1)	207 (58.3)
	1 year PFS rate	0.54	0.51
	95%-CI	(0.48, 0.60)	(0.45, 0.57)
	Median KP estimates of PFS (months)	12.16	12.06
	95%-CI	(11.93, 12.48)	(11.79, not estimable)
	DOR median (months)	11.27	10.58
	95% CI	(10.41, 11.27)	(10.22, -)
	Survival probability at 1 year	89.31	87.36
	95% CI	(85.48, 92.17)	(83.27, 90.51)
Effect estimate		**Comparison groups**	PF-05280014 vs. Trastuzumab-EU
	PFS	**HR**	1
		95% CI	(0.80, 1.26)
	DOR	**HR**	0.92
		95% CI	(0.67, 1.27)
	OS	**HR**	1.004
		95% CI	(0.655, 1.539)
Analysis description	**PK evaluation**		
Mean serum concentration vs. Time		PF-05280014	Trastuzumab-EU
	Cycle 1 Day 1 0 h	1.794	1.822
	Cycle 1 Day 1 2 h 30 min	90.71	91.20
	Cycle 1 Day 8 0 h	27.55	28.78
	Cycle 3 Day 1 0 h	49.25	52.16
	Cycle 4 Day 1 0 h	54.44	56.82
	Cycle 5 Day 1 0 h	59.95	62.73
	Cycle 5 Day 1 1 h 30 min	100.4	100.9
	Cycle 5 Day 8 0 h	60.26	62.32

Study 2

Title: A Phase 3 Randomized, Double-Blind Pharmacokinetic study of PF-05280014 Plus Taxotere® and Carboplatin versus Herceptin® Plus Taxotere® and Carboplatin for the Neo-adjuvant Treatment of Patients with Operable HER2-Positive Breast Cancer	
Study identifier	B3271004
Design	International, double-blind, randomized, phase 3 clinical trial. The blood samples were collected at pre-dose on Day 1 of Cycles 1, 2, 4, 5, and 6 and 1-hour post-dose on Day 1 of Cycle 1 and Cycle 5. Duration of the main phase: From 2014 to March 2016
Hypothesis	The hypothesis to be tested is that the percentage of patients with steady-state (Cycle 5) C_{trough} >20 µg/mL of PF-05280014 is non-inferior to trastuzumab-EU, using a lower limit of -12.5%.
Treatments arms	**Experimental product:** PF-05280014 Initial loading dose of 8mg/kg infused over 90 minutes. And then subsequent every 3 weeks infusions of 6 mg/kg were administered over 30 to 90 minutes + Taxotere 75 mg/m^2 administered IV over 60 minutes on Day 1 of each Cycle + Carboplatin (AUC-based dosing) area under the concentration versus time curve /area under the curve (AUC) is 6, administered IV over 15 minutes on Day 1 of each Cycle **N= 114**
	Reference product: Trastuzumab EU (Herceptin®) Initial loading dose of 8 mg/kg infused over 90 minutes. And then subsequent every 3 weeks infusions of 6 mg/kg were administered over 30 to 90 minutes + Taxotere 75 mg/m^2 administered IV over 60 minutes on Day 1 of each Cycle + Carboplatin area under the concentration versus time curve (AUC) 6, administered IV on Day 1 of each Cycle **N= 112**
Randomization	Patients were randomized in 1:1 ratio to PF-05280014 plus Taxotere and carboplatin or trastuzumab-EU plus Taxotere 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).	
Blinding	This study was double-blinded.	
Endpoints and definitions	**Primary endpoints**	• **PK:** To compare the percentage of patients with steady state (Cycle 5) C_{trough} (Cycle 6 pre-dose) > 20µg in patients with operable HER2- positive breast cancer who received study therapy together with Taxotere and carboplatin in the neo-adjuvant setting.
	Secondary endpoints	• **pathologic complete response (pCR):** Percentage of patient who achieved pCR; which is the absence of invasive neoplastic cells in the breast and lymph nodes following neo-adjuvant therapy. • **ORR:** ORR was the percentage of patients who had CR or PR at Cycle 6 or at the end of treatment. • **Other evaluations:** Including immunogenicity, selected PK samples, and safety evaluations.
Statistical Analysis	Based on the assumption that the percentage of patients reaching steady state in the EU-approved trastuzumab group was 95%, and the percentage of patients reaching steady state in the PF-05280014 group was 93%, then to achieve 85% power with this study design, a minimum of 188 patients (94 per treatment arm) were required. Considering a possible 15% attrition rate for the percentage of patients with the steady state (Cycle 5) C_{trough} >20 µg/mL, a total sample size of 220 randomized patients was planned to provide 85% power to achieve the primary endpoint. The primary objective was to demonstrate that trastuzumab-Pfizer results in a similar percentage of patients with steady-state Cycle 5 C_{trough} >20 µg/mL as EU-approved trastuzumab. The difference in the percentage of patients between the two treatment groups will be estimated using the normal approximation to the binomial distribution, adjusting for the randomization strata mentioned in the randomization section above.	
Database lock	The last data snapshot was on 18/08/2016	

Results and Analysis

226 patients were randomized into the study, of them 215 patients have completed the study (109 patients in the PF-05280014 group and 106 patients in the trastuzumab-EU group; Table 8).

Table 8: Demographic Characteristics – ITT Population

Number (%) of Patients	PF-05280014 (N=114) n (%)	Trastuzumab-EU (N=112) n (%)	Total (N=226) n (%)
Age (years)			
<18	0	0	0
18 to 44	24 (21.1)	37 (33.0)	61 (27.0)
45 to 64	65 (57.0)	58 (51.8)	123 (54.4)
≥65	25 (21.9)	17 (15.2)	42 (18.6)
Mean (SD)	54.0 (11.9)	51.2 (12.7)	52.6 (12.3)
Median	57.0	52.0	55.0
Range	26-77	24-79	24-79
Weight at Baseline (kg)			
Mean (SD)	74.2 (16.5)	73.2 (16.9)	73.7 (16.7)
Median	73.6	70.0	71.0
Range	46.0-140.0	41.0-143.5	41.0-143.5
Height (cm)			
Mean (SD)	162.2 (7.1)	162.8 (6.5)	162.5 (6.8)
Median	162.0	163.0	163.0
Range	149.0-180.0	146.0-180.0	146.0-180.0
Body Mass Index (kg/m^2)			
Mean (SD)	28.2 (5.9)	27.7 (6.2)	27.9 (6.1)
Median	28.1	26.9	27.8
Range	16.8-51.4	16.7-52.1	16.7-52.1
Race			
White	112 (98.2)	109 (97.3)	221 (97.8)
Black	1 (0.9)	0	1 (0.4)
Asian	1 (0.9)	3 (2.7)	4 (1.8)
Ethnicity			
Hispanic/Latino	0	1 (0.9)	1 (0.4)
Not Hispanic/Latino	114 (100.0)	111 (99.1)	225 (99.6)

The primary analysis was performed in the PP population, with a sensitivity analysis being performed in the ITT population using the same methods.

- Pathologic Complete Response (pCR):

  47 patients (46.5%) in the PF-05280014 treatment group had a pCR, 51 patients (50.5%) had a pPR, 2 patients (2.0%) had no pathological response, and 1 patient (1.0%) was not assessed. While in the trastuzumab-EU treatment group, 43 patients (48.3%) had a pCR, 40 patients (44.9%) had a pPR, 3 patients (3.4%) had no pathological response, and 3 patients (3.4%) were not assessed.

  The pCR for PF-05280014 and trastuzumab-EU was 47.0% [95% CI: 36.9% - 57.2%] and 50.0% [95% CI: 39.0% - 61.0%], respectively. The estimated stratified difference between PF-05280014 and trastuzumab-EU was -2.81% [95% CI: -16.58% - 10.96%].

- Objective response rate:

  In the PF-05280014 treatment group, 3 patients (3.0%) had a CR, 86 patients (85.1%) had a PR, 7 patients (6.9%) had stable disease, 2 patients (2.0%) had PD, and 1 patient (1.0%) was non-evaluable. In the trastuzumab-EU treatment group, no patients had CR, 73 patients (82.0%) had a PR, 4 patients (4.5%) had stable disease, 1 patient (1.1%) had PD, and 6 patients (6.7%) were non-evaluable.

  The ORR for PF-05280014 and trastuzumab-EU was 88.1% [95% CI: 80.2% - 93.7%] and 82.0% [95% CI: 72.5% - 89.4%], respectively. The estimated stratified difference was 5.96% [95% CI: -4.01% - 15.94%] (Table 9).

Table 9: Primary Endpoint Analysis

Analysis description	**Primary Endpoint Analysis**		
Descriptive statistics and estimate variability	**PP population**		
	Treatment group	PF-05280014	Trastuzumab-EU
	Number of subjects	101	89
	Cycle 5 C_{trough} ≤20µg/ml	8	6
	Cycle 5 C_{trough} >20µg/ml	93	83
	Percentage with Cycle 5 C_{trough} >20µg/ml	92.1	93.3
	95% CI	(85, 96.5)	(85.9, 97.5)
Effect estimate	**Un-stratified**	**Comparison groups**	PF-05280014 vs. Trastuzumab-EU
		Estimated difference	-1.18
		Standard error for the difference	3.78
		95% CI	(-8.59, 6.23)
	Stratified*	**Estimated difference**	-0.76
		Standard error for the difference	3.7
		95% CI	(-8.02, 6.49)
Analysis description	**Secondary Endpoint Analysis**		
	Treatment group	**PF-05280014**	**Trastuzumab-EU**
	Number of subjects	101	89
	pCR	47.0%	50.0%
	95% CI	36.9% to 57.2%	39.0% to 61.0%
Effect estimate		**Comparison groups**	PF-05280014 vs. Trastuzumab-EU
	pCR	**Estimated Difference**	-2.81%
		95% CI	(-16.58%, 10.96%)
	ORR	**Estimated Difference**	5.96%
		95% CI	(-4.01%, 15.94%)

*Note: Stratified analysis was based on the normal approximation to the binomial distribution, adjusting for the randomization strata of 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).

3.2.3 Overall conclusion of clinical efficacy

The efficacy of the product Trazimera was evaluated in two phase III clinical trials. The main pivotal trial B3271002 has confirmed the similarity between Trazimera and Herceptin in terms of ORR at week 25 and subsequently at week 33 with a pre-defined equivalence margin of (0.8 – 1.25).

The choice of margin was based on a meta-analysis conducted on published literature (three randomized studies) of the reference product to establish the assumption of the ORR for the sample size calculation in this study. Included studies compared taxane and trastuzumab combination versus taxane alone in patients with HER2+ metastatic breast cancer treated in the first-line setting. Using a random effect model, the overall estimated log-transformed risk ratio of ORR of chemotherapy alone over trastuzumab plus

chemotherapy was -0.54 with a 1-sided 90% upper confidence bound of -0.32. A 75% fraction of the upper bound was taken resulting in a numerical value of log risk ratio equal to -0.24. This value of -0.24 was exponentiated to be a risk ratio of 0.79, which corresponded 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. In addition, the applicant used two-sided 95% CI in the analysis instead of 90% CI.

Patients were eligible for enrollment if they had confirmed diagnosis of breast cancer with a metastatic lesion, which in the case of a bio-similarity exercise might affect the homogeneity and sensitivity of the patients' setting. Moreover, the inclusion criteria match the criteria that were used in reference pivotal study

Results of the analysis for the primary endpoint "ORR" showed a risk ratio of 0.94, with a 95% CI of 0.842 to 1.049, which is entirely within the 0.80 to 1.25 equivalence margin.

Results of the secondary endpoints showed a median time to PFS of 12.16 months in the PF-05280014 group and 12.06 months in the trastuzumab-EU group. The median DOR was 11.27 months for the PF-05280014 group and 10.58 months for the trastuzumab-EU group.

Regarding the supportive study B3271004, it was done in patients with operable HER2-positive breast cancer in the neo-adjuvant setting. The study was powered for the primary endpoint which was a PK parameter, comparing the percentage of patients with steady-state (Cycle 5) trough plasma concentration (C_{trough}) >20 µg/mL for PF-05280014 vs. trastuzumab-EU to be non-inferior using a margin of -12.5%.

The applicant justified the use of this margin based on the HannaH study, which was a phase 3 randomized trial in patients with operable HER2-positive breast cancer comparing Subcutaneous with Intravenous (IV) preparations of Herceptin. Their Co-primary endpoints were serum trough concentration (C_{trough}) at pre-dose cycle 8 before surgery (non-inferiority margin for the ratio between groups of 0.80) and pathologic complete response (pCR; the non-inferiority margin for the difference between groups of –12.5%). Therefore, the applicant choose this margin based on clinical considerations rather than statistical considerations, which is considered a new method for selecting margins.

3.2.3 Clinical Safety

The clinical safety data was evaluated through all the previously assessed trials, in addition to the submitted Phase I (B3271006) safety trial.

Pyrexia has been reported in Phase I (B3271001) PK trial in 10 subjects (28.6%) in the trastuzumab-Pfizer, and 3 subjects (8.6%) in the trastuzumab-EU, and 2 subjects (5.7%) trastuzumab-US groups respectively. Therefore, the US.FDA requested from the applicant to conduct a single-dose study with a larger sample size to assess if the numerical imbalance in pyrexia events observed in Phase 1 (B3271001) study was a random event associated with evaluating multiple adverse events in a small study.

Table 10: List of safety studies

Study	Clinical trials identifier	Design	Objective	Findings
B3271006	NCT02015156	Phase I, 2 arms, double-blind (sponsor un-blinded), randomized (1:1), parallel-group, single-dose study	**Primary objectives:** Estimate the relative risk of an abnormally elevated body temperature (defined as body temperature ≥38.0°C) compared to baseline following trastuzumab-Pfizer or trastuzumab-US administration. **Secondary objectives:** Evaluate the safety of trastuzumab-Pfizer versus trastuzumab-US.	**Primary safety assessment:** Pyrexia 95% CI of Trastuzumab-Pfizer: • 0.1791 (0.114, 0.2442) 95% CI of Trastuzumab-US: • 0.1619 (0.0881, 0.2358) 95% CI of Trastuzumab-Pfizer vs. US: 0.0172 (-0.0805, 0.1149)

3.2.3.1 Patient exposure

		Patients enrolled	Patients exposed to adverse event	% of patientsexposed to adverse event	Total number of patients
Study 1 (B3271001)	Trast-Pfizer	35	25	71.4%	35
	Trast-EU	35	24	68.6%	35
	Trast-US	35	23	65.7%	35
Study 2 (B3271002)	PF-05280014	349	337	96.6%	349
	Trast-EU	353	339	96%	353
Study 3 (B3271004)	PF-05280014	113	109	96.5%	113
	Trast-EU	112	106	94.6%	112
Study 4 (B3271006)	Trast-Pfizer	81	5	6.2%	81
	Trast-US	81	11	13.6%	81

3.2.3.2 Immunogenicity studies

The immunogenicity was tested as a secondary endpoint in the studies 1001, 1002 and 1004.

3.2.3.3 Adverse events

Serious adverse events and deaths

B3271001 "Phase I, PK study"

- No death cases or serious adverse events have occurred in the study.

B3271006 "Phase I, Safety study"

- No death cases or drug-related serious adverse events have occurred during this study.

B3271002 "Phase III, the main study"

- In total, the number of patients who died during the study was 73 (10.4%) patients; of them, 34 patients (9.7%) in the PF-05280014 group and 39 patients (11.0%) in the trastuzumab-EU group).
- A further 12 patients (1.7%) died more than 183 days (6 months) after discontinuing the study drug; of them, 8 patients (2.3%) in the PF-05280014 group and 4 patients (1.1%) in the trastuzumab-EU group.
- The most frequent reason for death was due to disease progression.
- Of all death cases, 70 patients (10.0%) were reported to have died from the disease under study (other causes may also have been reported); of them, 38 patients (10.9%) in the PF-05280014 group and 32 patients (9.1%) in the trastuzumab-EU group. However, three patients (0.4%) in the trastuzumab-EU group have been reported died due to study drug toxicity.
- The most frequently reported SAEs were disease progression among 32 patients (9.2%) in the PF-05280014 group and 27 patients (7.6%) in the trastuzumab-EU group, pulmonary embolism in 5 patients (1.4%) in the PF-05280014 group and 3 patients (0.8%) in the trastuzumab-EU group, and pneumonia in 4 patients (1.1%) in the PF-05280014 group and 3 patients (0.8%) in the trastuzumab-EU group.

B3271004 "Phase III, the supportive study"

- Overall, 109 patients (96.5%) in the PF-05280014 group and 106 patients (94.6%) in the trastuzumab-EU group have experienced at least 1 treatment-emergent adverse event (TEAE).
- The most frequently reported TEAEs in both treatment groups were alopecia in 72 patients (63.7%) in the PF-05280014 group and 69 patients (61.6%) in the trastuzumab- EU group.
- Only one patient in the PF-05280014 group died during the study period due to pancytopenia on Cycle 1 Day 6.

Drug Side Effects

In study B3271001, only 72 subjects have experienced treatment-related AE; of them, 25 subjects (71.4%) in the trastuzumab-Pfizer and 24 subjects (68.6%) in the trastuzumab-EU, and 23 subjects (65.7%) in the trastuzumab-US treatment arm. In study B3271002, the most frequent trastuzumab-related TEAEs were ejection fraction decreased, IRR, cardiac failure, and rash; with no notable differences in severity and seriousness.

Cardiac toxicity

In the main Phase 3 study, there were 12 patients (1.7%) who reported a TEAE of cardiac failure; of them, 5 patients (1.4%) in the PF-05280014 group and 7 patients (2.0%) in the trastuzumab-EU group. Grade 2 cardiomyopathy was reported for 2 patients (0.6%) in the trastuzumab-EU group. In addition, 1 patient (0.3%) in the PF-05280014 group and 4 patients (1.1%) in the trastuzumab-EU group reported metabolic cardiomyopathy. Moreover, a Grade 3 event of left ventricular dysfunction was reported in one patient in the PF-05280018 group. There were 74 patients (10.5%) with decreased ejection fraction; of them, 35 patients (10.0%) in the PF-05280014 group and 39 patients (11.0%) in the trastuzumab-EU group.

Overall, all results showed comparable ratios of cardiac disorders between the two products.

Laboratory findings

B3271001 "Phase I, PK study"

Overall, laboratory results were unremarkable (Table 11).

Table 11: Incidence of Laboratory Abnormalities Without Regard to Baseline

			Trastuzumab-Pfizer N=35	Trastuzumab-EU N=35	Trastuzumab-US N=35
Parameters	**Units**	**Criteria**	**n=23 (66%)**	**n=27 (77%)**	**n=25 (71%)**
Hematology					
MCV	10^{-15}L	<0.9× LLN	0	1 (2.9%)	0
MCH	pg	<0.9× LLN	0	1 (2.9%)	1 (2.9%)
MPV	fL	<0.9× LLN	3 (8.6%)	1 (2.9%)	4 (11.4%)
WBC count	10^3/mm^3	>1.5× ULN	0	1 (2.9%)	0
Lymphocytes (abs)	10^3/mm^3	<0.8× LLN	3 (8.6%)	0	1 (2.9%)
Lymphocyte (%)	%	<0.8× LLN	14 (40%)	15 (42.9%)	12 (34.3%)
		>1.2× ULN	0	0	1 (2.9%)
Total neutrophils (abs)	10^3/mm^3	>1.2× ULN	1 (2.9%)	3 (8.6%)	2 (5.7%)
Neutrophils (%)	%	>1.2× ULN	0	1 (2.9%)	0
Basophils (abs)	10^3/mm^3	>1.2× ULN	0	1 (2.9%	0
Basophils (%)	%	>1.2× ULN	4 (11.4%)	5 (14.3%)	1 (2.9%)
Eosinophils (abs)	10^3/mm^3	>1.2× ULN	0	1 (2.9%)	1 (2.9%)
Eosinophils (%)	%	>1.2× ULN	3 (8.6%)	3 (8.6%)	3 (8.6%)
Monocytes (abs)	10^3/mm^3	>1.2× ULN	0	1 (2.9%)	0
Monocytes (%)	%	>1.2× ULN	0	0	1 (2.9%)
Liver Function					
Total bilirubin	mg/dL	>1.5× ULN	1 (2.9%)	0	2 (5.7%)
AST	IU/L	>3.0× ULN	0	2 (5.7%)	0
ALT	IU/L	>3.0× ULN	0	1 (2.9%)	0
Renal Function					
Blood urea nitrogen	mg/dL	>1.3× ULN	1 (2.9%)	1 (2.9%)	1 (2.9%)
Electrolytes					
Potassium	mEq/L	>1.1× ULN	1 (2.9%)	0	0
Calcium	mg/dL	<0.9× LLN	1 (2.9%)	0	0

B3271002 "Phase III, the main study"

Overall, laboratory results were comparable among the treatment groups (Table 12).

Table 12: Incidence of Laboratory Test Abnormalities (Normal Baseline) – Safety Population

Number of patients evaluable for laboratory abnormalities Number (%) with laboratory abnormalities				PF-05280014 347 167 (48%)			Trastuzumab-EU 351 189 (54%)		
Group	**Parameter**	**Units**	**Criteria**	**N**	**n**	**(%)**	**N**	**n**	**(%)**
Hematology	Hemoglobin	g/dL	<0.8 × LLN	277	32	11.6	269	31	11.5
	Platelets	10^3/mm^3	<0.5 × LLN	279	2	0.7	283	7	2.5
			>1.75 × ULN	279	4	1.4	283	1	0.4
	Neutrophils (absolute)	10^3/mm^3	<0.8 × LLN	282	95	33.7	290	95	32.8
			>1.2 × ULN	282	56	19.9	290	68	23.4
Liver Function	Total bilirubin	mg/dL	>1.5 × ULN	334	6	1.8	338	8	2.4
	Aspartate aminotransferase	IU/L	>3.0 × ULN	233	2	0.9	231	10	4.3
	Alanine aminotransferase	IU/L	>3.0 × ULN	267	1	0.4	271	12	4.4
	Alkaline phosphatase	IU/L	>3.0 × ULN	260	2	0.8	242	5	2.1
Renal Function	Creatinine	mg/dL	>1.3 × ULN	319	13	4.1	313	13	4.2

Safety in special populations

Not applicable.

Safety-related to drug-drug interactions and other interactions

Not available.

Discontinuation due to AES

B3271001 "PK study"

Of all the subjects, two subjects have discontinued the study treatment due to infusion related reactions (one subject received trastuzumab-Pfizer, and one subject received trastuzumab-US).

B3271002 "Phase III study"

There were 46 (13.2%) patients in the PF-05280014 group and 41 (11.6%) patients in the trastuzumab-EU group who discontinued from trastuzumab and/or paclitaxel due to AEs. Discontinuation from trastuzumab was in 28 patients in total, and the most frequent reason was due to decreased ejection fraction. While discontinuation from paclitaxel was mostly due to peripheral sensory neuropathy.

Post-marketing experience

This section is not applicable as this product is new to the market.

3.2.3.3 Overall conclusion on clinical safety

In study B3271006, one of the used lots of trastuzumab-Pfizer in this study was the same as the one used in B3271001. The incidence of fever within the first 24 hours was 3.7% in those subjects who received this lot (Lot C/12-000813).

The safety of Trazimera® was evaluated through all the submitted clinical studies. All studies showed a comparable safety profile between the test and the reference product.

The biggest number of death cases was reported in study B3271002, but it was linked with the progression of the disease. Only one case of death was reported in study B3271004 due to a serious AE "pancytopenia" associated with the use of the test product. The most commonly observed AEs were mostly injection-related reactions, neutropenia, and nausea which were comparable among all patients.

Regarding cardiac toxicity, both phase III studies showed comparable rates of cardiac disorders among patients among the two treatment groups. It included cardiac failure, left ventricular dysfunction, and ejection fraction decreased. Overall, the observed data support the similarity of the product to Herceptin® in terms of safety profile.

3.2.4 Discussion on Clinical efficacy and safety aspects

Based on the clinical studies section's review of the submitted dossier, results from analysis of the main studies were within the predefined margins of equivalence. In addition, the confirmed similarity in the mechanism of action, efficacy, PK, and safety profile between PF-05280014 (Trazimera) and Herceptin supports the extrapolation towards all submitted indications, and metastatic breast cancer (MBC) appears to be a sensitive indication. Therefore, the clinical studies section recommends approval of the product for the submitted indications.

4. Risk Management Plan (RMP)

Every newly approved medicinal product in Saudi Arabia has an RMP in place to ensure the medicine or vaccine is used as safely as possible. RMP is a comprehensive document that describes the current knowledge about the safety and efficacy of a medicinal product. In addition, RMP provides information about measures to be undertaken to prevent or minimize risks associated with the use of medicines or vaccines and information on plans for studies and other activities to have more knowledge about the safety and efficacy of the medicinal product. The SFDA has reviewed the RMP Version 1.2, dated 19 April 2018, and concluded the following

- Cardiac dysfunction, administration-related reactions and oligohydramnios were considered as important identified risks during the clinical trials.
- There are no important potential risks during the clinical trials.
- There are no missing information during the clinical trials.

4.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

An exposure during Pregnancy supplemental form for the identified risk Oligohydramnios

4.2 Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities planned or ongoing to assess the effectiveness of risk minimization measures.

4.3 Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Routine risk minimization measures include:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status

There are no additional risk minimization measures applied for the risk of cardiac dysfunction, administration-related reactions and oligohydramnios

4.4. Pharmacovigilance Activities

4.5.1. Artwork and Trade Name assessment (Artwork available in appendix)

Trazimera name and artwork have been evaluated and approved.

Proposed trade Name	**Dosage Form**
Trazimera	Powder for concentrate for solution for infusion

Look–alike/Sound-alike (LA/SA) Error Risk Potential:

Trazimera name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP Confused Drug Name List, INN and USAN STEM) and the pharmaceutical characteristic of the product:

LA/SA for Product name	**SFDA**	**Shared File/ Excel Sheet**	**Martindale**	**Stem Book 2018**
Trazimera	NO	NO	Registered at USA & Poland	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name Trazimera is accepted.

Outer and Inner Package:

Based on the submitted data, the proposed artwork is accepted.

5. Overall Conclusion

Based on a review of data on quality, safety and efficacy, the SFDA considered that the benefit/risk profile of Trazimera is favorable and decided to grant the marketing authorization of Trazimera for the treatment of the following indications:

Metastatic breast cancer
Trazimera is indicated for the treatment of tumors overexpressing HER2:

- As monotherapy for the treatment of patients who have received at least one or more chemotherapy regimens for their metastatic disease.
- In combination with paclitaxel or docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- In combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone receptor-positive metastatic breast cancer, not previously treated for their metastatic disease.

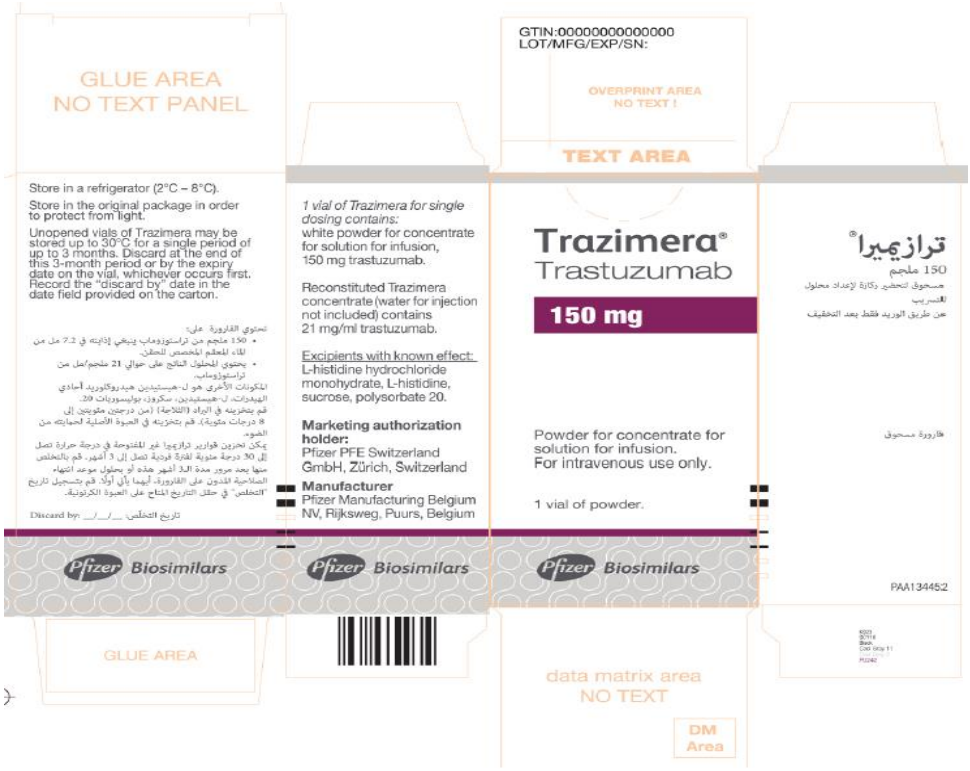
Early-stage breast cancer
Trazimera is indicated for the treatment of adult patients with HER2 positive early-stage breast cancer:

- Following surgery, chemotherapy (neoadjuvant or adjuvant) and (if applicable) radiation therapy.
- Following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- In combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumors >2 cm in diameter.

Metastatic gastric cancer or gastro-oesophageal junction cancer
Trazimera in combination with capecitabine or intravenous 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received chemotherapy for their metastatic disease. Trazimera should only be used in patients with metastatic gastric cancer whose tumors overexpress HER2 defined by IHC2+ and confirmed by a positive FISH+ or silver in-situ hybridization result (SISH), or IHC3+ determined by a validated assay.

7. Appendix


Trazimera®
Trastuzumab
150 mg
Powder for concentrate for solution for infusion.
For intravenous use only.
1 vial of powder.
Pfizer Biosimilars


GLUE AREA
NO TEXT PANEL
GTIN:00000000000000
LOT/MFG/EXP/SN:
OVERPRINT AREA
NO TEXT !
TEXT AREA
Store in a refrigerator (2°C – 8°C).
Store in the original package in order to protect from light.
Unopened vials of Trazimera may be stored up to 30°C for a single period of up to 3 months. Discard at the end of this 3-month period or by the expiry date on the vial, whichever occurs first. Record the "discard by" date in the date field provided on the carton.
1 vial of Trazimera for single dosing contains:
white powder for concentrate for solution for infusion, 150 mg trastuzumab.
Reconstituted Trazimera concentrate (water for injection not included) contains 21 mg/ml trastuzumab.
Excipients with known effect:
L-histidine hydrochloride monohydrate, L-histidine, sucrose, polysorbate 20.
Marketing authorization holder:
Pfizer PFE Switzerland GmbH, Zürich, Switzerland
Manufacturer
Pfizer Manufacturing Belgium NV, Rijksweg, Puurs, Belgium
Trazimera®
Trastuzumab
150 mg
Powder for concentrate for solution for infusion.
For intravenous use only.
1 vial of powder.
ترازيميرا®
150 ملجم
مسحوق لتحضير ركازة لإعداد محلول للتسريب
عن طريق الوريد فقط بعد التخفيف
PAA134452
Pfizer Biosimilars
GLUE AREA
data matrix area
NO TEXT
DM Area


Trazimera®
Trastuzumab
150 mg
ترازيميرا®
150 ملجم
مسحوق لتحضير ركازة لإعداد
محلول للتسريب
عن طريق الوريد فقط بعد التخفيف
Powder for concentrate for solution for infusion.
For intravenous use only.
PAA134453


LOT/EXP:
INDICATIVE DATA MATRIX AREA
PAA134453
Trazimera®
Trastuzumab
150 mg
ترازيميرا®
150 ملجم
مسحوق لتحضير ركازة لإعداد
محلول للتسريب
عن طريق الوريد فقط بعد التخفيف
Powder for concentrate for solution for infusion.
For intravenous use only.
Store in a refrigerator (2°C – 8°C).
Store in the original package in order to protect from light.
A vial of Trazimera reconstituted with water for injection is stable for 48 hours at 2°C – 8°C after reconstitution and must not be frozen.
قم بتخزينه في البراد (الثلاجة)
(من درجتين مئويتين إلى 8 درجات مئوية). قم بتخزينه في العبوة الأصلية لحمايته من الضوء.
Pfizer Biosimilars

6. Appendix

The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not incorporated into the Saudi PAR.

New finding that could impair the quality, efficacy or safety of the medicinal product are recorded and published only at SDI.

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa