31 May 2018
EMA/414095/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trazimera

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/004463/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse events of special interest
AUC	area under the serum drug concentration-time curve
AUCinf	area under the serum drug concentration-time curve from 0 to infinite time
AUCt	area under the serum concentration-time curve from time 0 to time of last quantifiable concentration
CD	chemically-defined
CDC	complement-dependent cytotoxicity
% CFB	percent change from baseline
CHO	Chinese hamster ovary
CI	confidence interval
CISH	chromogenic in-situ hybridization
CMA	critical material attributes
Cmax	maximum observed drug concentration
Cmin	trough minimum concentration
CPP	critical process parameters
CQA	critical quality attributes
CR	complete response
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
DISH	dual in-situ hybridization
DOR	duration of response
EBC	early breast cancer
ECG	electrocardiogram
ECL	electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of treatment
ER	estrogen receptor
EU	European Union
Fab	fragment antigen-binding
Fc	fragment crystallizable
FcRn	fragment crystallizable receptor neonatal
FISH	fluorescent in-situ hybridization
GCP	Good Clinical Practice
HCP	host cell proteins
HER2	human epidermal growth factor receptor 2
HMMS	high molecular mass species
IHC	immunohistochemistry

IIV	interindividual variability
ITT	intent-to-treat
IV	intravenous
LIVCA	limit of in vitro cell age for production
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MAA	Marketing Authorization Application
mAb	monoclonal antibody
MAH	Marketing Authorisation Holder
MBC	metastatic breast cancer
MCB	master cell bank
MGC	metastatic gastric cancer
MVOF	minimum value of objective function
NAb	neutralizing antibodies
ORR	objective response rate
OS	overall survival
pCR	pathologic complete response
PD	pharmacodynamic(s)
PD	progressive disease
PK	pharmacokinetic(s)
PP	per-protocol
PPQ	process performance qualification
PR	partial response
SD	stable disease
SISH	silver in situ hybridization
SmPC	Summary of Product Characteristics
SOC	system organ class
SWFI	sterile water for injection
t1/2	half-life
TEAE	treatment-emergent adverse event
US	United States
WCB	working cell bank
WFI	water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 27 June 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Trazimera, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication

Metastatic breast cancer

Trazimera is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with 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 MBC, not previously treated with trastuzumab.

Early breast cancer

Trazimera is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).
- 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 Trazimera therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Trazimera should only be used in patients with metastatic or early breast cancer whose tumours have either

HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

Metastatic gastric cancer

Trazimera in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Trazimera should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Herceptin, 150 mg, powder for concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 28-08-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/145/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Herceptin, 150 mg, powder for concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 28-08-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/145/001

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Herceptin, 150 mg, powder for concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 28-08-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/145/001

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	**date**	**Area**
EMEA/CHMP/SAWP/95041/2011	17 February 2011	Quality, non-clinical and clinical
EMEA/CHMP/SAWP/352933/2013	27 June 2013	Quality and clinical

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Sol Ruiz

The application was received by the EMA on	27 June 2017
The procedure started on	13 July 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	2 October 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	10 October 2017
The PRAC Rapporteur's first Assessment Report was circulated to all	13 October 2017

PRAC members on	
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 February 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	3 April 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 April 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 April 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 April 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	24 May 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Trazimera on	31 May 2018

2. Scientific discussion

2.1. Problem statement

This application concerns a centralised procedure for the marketing authorisation of Trazimera (PF-05280014, trastuzumab), developed as a similar biological medicinal product to the innovator product Herceptin for intravenous (IV) use, which was approved in the European Union (EU) in August 2000 (EMEA/H/C/000278).

Pfizer developed PF-05280014 as a potential biosimilar to the trastuzumab products marketed globally as Herceptin (reference product) for the same indications as the reference product, including HER2-positive early breast cancer (EBC), metastatic breast cancer (MBC) and metastatic gastric cancer (MGC).

About the product

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Trastuzumab selectively binds to the extracellular domain of HER2 and thereby preventing HER2 signalling. In addition trastuzumab binds to fragment crystallizable (Fc) receptors on immune effector cells, facilitating immune destruction of HER2-expressing cancer cells.

PF-05280014 is provided as a lyophilized drug product in a dosage strength of 150 mg. The Applicant claimed the same therapeutic indications and posology for the proposed biosimilar as granted for Herceptin in the EU:

Breast cancer

Metastatic breast cancer:

Herceptin is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments. Assessment report EMA/CHMP/9855/2018 Page 12/118
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with 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 MBC, not previously treated with trastuzumab.

Early breast cancer:

Herceptin is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC).

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see Summary of Product Characteristics (SmPC, section 5.1).
- 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 Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see SmPC sections 4.4 and 5.1).

Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see SmPC sections 4.4 and 5.1).

Metastatic gastric cancer

Herceptin in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herceptin should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see SmPC sections 4.4 and 5.1).

Type of Application and aspects on development

The marketing authorisation application of Trazimera is an abridged application for a biosimilar under Article 10 (4) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The applicant received Scientific Advice from the CHMP on 17/02/2011 pertaining to quality, non-clinical and clinical aspects of the dossier, and on 27/06/2013 pertaining to quality and clinical aspects.

2.2. Quality aspects

2.2.1. 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 for Herceptin for the treatment of early breast cancer, metastatic breast cancer and metastatic gastric cancer.

The PF-05280014 finished product is supplied as a lyophilized powder for concentrate solution for infusion in a dosage strength of 150 mg. Reconstitution with 7.2 mL of sterile water for injection (SWFI) yields a solution containing 21 mg/mL of PF-05280014 at a pH of approximately 6 with the excipients L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20 and sucrose. The finished product is supplied in a 15 mL glass vial sealed with a stopper and an aluminium seal with flip-off plastic cap.

2.2.2. Active Substance

General information

PF-05280014 (trastuzumab) active substance is a humanised monoclonal antibody of the IgG1 subclass. It is a glycoprotein with one N-linked glycosylation site on the Asn300. Trastuzumab selectively binds to the extracellular domain of HER2 and thereby preventing HER2 signalling. 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.

PF-05280014 is an IgG1 kappa monoclonal antibody with two identical 450 amino acid (aa) heavy (H) chains and two identical 214 aa light (L) chains, covalently linked with four inter-chain disulfide bonds. The N-linked glycosylation consensus sequence, NST, 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. C-terminal lysine (K) is encoded by the H chain expression vector cDNA sequence, but is observed only at low levels in the mature, secreted form of PF-05280014, presumably due to intracellular processing by Chinese hamster ovary (CHO) cellular proteases. Therefore, the penultimate glycine (G) residue is the predominant H chain C terminus in PF-05280014.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The trastuzumab active substance manufacturing process has been adequately described. The manufacturing process for PF-05280014 active substance uses a recombinant CHO cell line. Cells are grown in suspension culture using chemically-defined (CD), animal-derived component-free (ACF) media. The main steps of the manufacturing process are cell culture, recovery and purification. The process begins with the thawing of cells from the working cell bank (WCB) followed by expansion. The purification of PF-05280014 comprises several chromatography steps and orthogonal dedicated virus clearance steps

Active substance is provided in appropriate container closure systems which are compliant with required monographs.

Cells from the working cell bank (WCB) are thawed, and the culture is progressively expanded. During culture expansion and maintenance in seed bioreactors critical process parameters and critical material attributes are identified and justified with acceptable ranges (alert and termination limits). A production bioreactor culture is harvested and clarified by centrifugation and depth filtration to remove cells and debris. Inoculum culture from a seed bioreactor is added to production medium in the production bioreactor to a pre-defined target seed density.

After this harvest step, the product is purified by an affinity chromatography step, a virus inactivation step followed by ion exchange chromatography steps. The product is then processed through a virus retaining filter (VRF) followed by concentration and buffer exchange in an ultrafiltration/diafiltration (UF/DF) step. The excipients are added to the product to achieve the final formulation of active substance, followed by final filtration and freezing. For the purification process “process inputs” and “process controls” have been provided.

The process controls include a combination of critical process parameters (CPP), non-critical process parameters (non-CPP), critical material attributes (CMA), and in-process tests. Acceptable ranges for input process controls (CPP, non-CPP and CMA) have been stated. If the results of these controls are outside of the acceptable ranges or control limits, 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, labeled, frozen, and shipped frozen to the finished product manufacturing site.

Control of Materials

Sufficient information on the materials used in the manufacture of PF-05280014 active substance have been provided. The acceptance criteria for non-compendial raw materials used in the manufacture of PF-05280014 have been provided. The active substance manufacturing process uses a cell culture media which 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 characterised according to ICH requirements, e.g. Q5A (R1), Q5B and Q5D. The adventitious agents assays test results indicate that the cell bank is sterile and free of detectable mycoplasma and viruses. During routine production, cell culture age is controlled to less than the limit of in vitro cell age (LIVCA). The provided data support the proposed PF-05280014 LIVCA. This is supported by

several assays demonstrating phenotypic and genotypic stability. Data have been provided to indicate that the cell line is robust with respect to critical parameters MCB and WCB stability under the defined storage conditions will be monitored. All newly prepared WCBs will also be manufactured in accordance with a pre-specified protocol and cGMP guideline and qualified, complying with ICH Q5D and Q5A (R1).

Adequate process controls with their control limits for the upstream and downstream process have been provided.

Process Validation

The validation of the PF-05280014 active substance manufacturing process included three successful process performance qualification (PPQ) batches from three independent, consecutive thaws of the WCB. Process parameters (inputs) were maintained within pre-defined limits. The process validation was demonstrated by meeting pre-determined acceptance criteria for product quality and performance parameters. The PF-05280014 manufacturing process has been shown to effectively and consistently remove process-related impurities to levels which do not pose a safety risk to patients. The impurities include host cell proteins (HCP), DNA, trace elements and organic compounds that were derived from the host cells, medium, or purification process.

In-process pool hold times were validated to demonstrate biochemical stability of PF-05280014 over a defined period of time. The active substance is frozen and shipped for finished product manufacture. Testing results met the specified acceptance criteria and support shipments of frozen PF-05280014 active substance. The establishment of the resin lifetimes was performed at small scale for each of the chromatographic steps.

In general, the data provided support that the process is well established and robust enough as to yield a consistent product. Several other aspects have also been validated or evaluated, including impurity clearance (from commercial manufacturing process), in-process hold times and shipping validation.

Additional process evaluation studies have been carried out, including bioreactor data and impurity data for additional batches manufactured before the process validation campaign. The information presented is considered adequate.

Manufacturing process development

The PF-05280014 active substance manufacturing process was developed using the applicant's platform Chinese hamster ovary host cell line and cell culture and purification mAb processes. All batches executed during development were identified as representative of the intended commercial process. Product quality results (together with the relative potency) from batches defined as representative are comparable and acceptable, meeting the acceptance criteria in place at time of release and the commercial acceptance criteria.

The control strategy for PF-05280014 active substance is linked to finished product. Prior to finalisation of the control strategy, both active substance and finished product elements were considered in totality to ensure that final finished product quality through shelf life is met. The quality attributes (QAs) have been categorized as critical and non-critical, and the output of the criticality risk assessments together with the requirement to demonstrate similarity were considered when defining the control strategy applied to the individual attributes. The QAs within the control strategy were selected specifically to both monitor process consistency and to ensure that the PF-05280014 profile is maintained. For QAs that have been ranked as critical quality

attributes (CQAs), most are controlled through release and stability testing. The relationship between process parameters and each of the CQAs was assessed by cause and effect analysis to understand which parameters were likely to affect CQAs.

Risk assessment was performed by assessing the parameters for severity, detectability and occurrence based on the potential impact of each parameter on product quality. A final risk priority number (RPN) number was assigned to each process parameter evaluated based on multiplying the scores for severity, occurrence and detection (SEV x OCC x DET). Lower RPN scores are indicative of acceptable manufacturing ranges and that they are controlled with minimal risk to product quality and/or process performance. The production bioreactor unit operation was identified as the most important cell culture unit operation affecting product quality attributes. Multivariate design of experiments (DoE) studies were executed on the production bioreactor unit operation resulting in acceptable process parameters ranges and criticality classification.

Characterization

A range of state-of-the-art orthogonal methodologies was used in order to elucidate the primary and higher order structures, as well as the purity/impurity, charged variants and glycan structures. Multiple biological assays were employed addressing multiple putative mechanisms of action of trastuzumab, in order to assess the potency and binding affinity of 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.

Specification

Adequate active substance specifications have been provided. The list of test parameters for the active substance specification includes tests for appearance, identity, purity, adventitious agents, potency and general tests. The set of specifications proposed covers the characteristics of the molecule including post-translational modifications.

Analytical methods

A summary of each analytical procedure has been provided. Standard methods for biophysical and biochemical testing are used. The potency assay reflects one of the major mechanism of action (MoA). Compendial methods are performed in accordance with current pharmacopoeia. The validation and suitability of the analytical procedures was performed according to ICH Q2 (R1): Validation of Analytical Procedures: Text and Methodology. Both, compendial and in-house methods have been described in detail. Compendial analytical procedures were verified and confirmed suitable for its intended use. The validation of non-compendial methods has been conducted using pre-approved validation protocols in accordance with the principles of ICH Q2 (R1).

Batch analysis

Release results from several PF-05280014 active substance batches have been presented which demonstrate that manufacturing generates a consistent active substance, and all results were within the acceptance criteria.

Reference material

A two-tiered system for in-house PF-05280014 reference material has been implemented to support the commercial product. The existing primary reference material (PRM) and working reference material (WRM) have been suitably manufactured and characterised for their purpose. The acceptance criteria for the qualification of the future working reference material will be based on product specification at the time of manufacture. Characterization tests will also be performed on the future working reference material.

Container Closure

The active substance is filled in containers designed for freeze/thaw. Leachable studies were completed for the PF-05280014 active substance in the commercial container closure systems. The containers are designed and qualified to appropriately protect the active substance from the environment throughout storage. Biocompatibility tests have been performed by the vendor to demonstrate that all components used for manufacture are biocompatible and meet or exceed the current ISO 10993 requirements on “Biological Evaluation of Medical Devices”.

Stability

A suitable shelf life is proposed for active substance stored at the intended storage conditions. This shelf life claim is based on an ICH compliant stability programme, including long term and accelerated conditions and photostability. Based on the data presented, the proposed active substance shelf life is supported. The proposed stability protocol containing adequate stability-indicating test parameters is considered appropriate.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

PF-05280014 (Trazimera) is supplied as a lyophilized finished product in a dosage strength of 150 mg. The excipients present are L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20 and sucrose. The finished product is supplied in a 15 mL glass vial sealed with a stopper and an aluminium seal with flip-off plastic cap.

Prior to use, the lyophilized finished product is reconstituted with sterile water for injections (SWFI) to form a solution that is further diluted with sterile 0.9% sodium chloride for administration by intravenous infusion. Lyophilized finished product reconstituted with SWFI contains no preservative and is for single use only.

Pharmaceutical development

The composition of the final formulation is different from the reference product. The predominant 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.

The active substance is formulated in L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 20, and water for injections (WfI). Container closure integrity testing has been performed using a dye ingress test method and microbial ingress test method. All sealed vials remain free of dye ingress or microbial growth.

Manufacture of the product and process controls

The manufacturing process of the finished product is a standard aseptic process for lyophilised product. Initially the active substance is thawed using controlled thaw equipment. Thawed active substance is transferred to a manufacturing vessel to continue finished product manufacture. The bulk finished product is then sterile filtered and aseptically filled into vials. Vials are partially stoppered prior to lyophilisation. Upon completion of the lyophilisation cycle, the vials are fully stoppered and capped with a crimp seal. Following this capping operation, the vials are visually inspected. The different steps have been sufficiently described.

Critical process parameters (CPPs) are highlighted, and hold times have been defined. The reason for potential re-processing has been defined and accepted. Process controls with their control limits for the finished product manufacturing process have been provided and are acceptable.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Process controls with their control limits for the finished product manufacturing process have been provided and are acceptable.

All excipients present in the PF-05280014 active substance and finished product (L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 20) are well-established pharmaceutical excipients. Specifications and analytical procedures have been provided. No excipients of human or animal origin, as well as no novel excipients are used in the manufacture of the product.

Product specification

The list of test parameters for the finished product specification contains tests for appearance, residual moisture, reconstitution time, pH, osmolality, content uniformity, protein concentration, sub-visible particles, charge heterogeneity, identity, impurities, potency, endotoxins and, sterility. The acceptance criteria are applicable from lot release to end of shelf-life. The specification for the finished product release has been set in accordance with Ph. Eur. Requirements and ICH Q6B.

Analytical methods

Sufficiently detailed summary of the analytical procedures used to test the finished product have been provided. Validation summaries for analytical procedures used to test both the active substance and finished product have been provided. Analytical procedures were validated in accordance with the ICH Q2(R1) Guideline, Validation of Analytical Procedures: Text and Methodology.

Compendial methods were appropriately verified for their intended use. All lots met the acceptance criteria in place at the time of release.

Reference standard

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

Container closure

The PF-05280014 finished product, 150 mg is packaged in a 15 mL Type I clear glass vial with a butyl rubber stopper laminated with a fluoro-resin film. The glass vial and the stopper, which are in product contact, meet the requirements of the Ph. Eur. 3.2.1 and Ph. Eur. 3.2.9 respectively.

Stability of the product

The stability program followed the relevant ICH guidelines for stability of the finished product.

The shelf life claim is based on the long term stability programs with lots of 150 mg finished product stored at 5 ± 3 ºC through 48 months and thermal cycling stability programs. The accumulated data demonstrated that the quality attributes remain in conformance with the commercial acceptance criteria for the corresponding analytical procedures throughout the time points tested.

Results from an ICH photostability study demonstrate that the product is photolabile. Photostability testing resulting in the protoype commercial package was acceptable, therefore it should be stored in the original package in order to protect from light.

Based on the stability results provided the claimed shelf life for the finished product of 48 months when stored at the recommended temperature of 2 - 8 ºC is supported. After reconstitution with sterile water for injections the reconstituted solution is physically and chemically stable for 48 hours at 2°C – 8°C. Any remaining reconstituted solution should be discarded.

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.

From a microbiological point of view, the reconstituted solution and Trazimera infusion solution should be used immediately. The product is not intended to be stored after reconstitution and dilution unless this has taken place under controlled and validated aseptic conditions.

Biosimilarity

A 3-way comparability exercise was performed comparing PF-05280014 to US-licensed Herceptin (further listed as trastuzumab-US), PF-05280014 to EU-approved Herceptin (further listed as trastuzumab-EU), and

US-licensed Herceptin to EU-approved Herceptin. The primary focus is the comparison of PF-05280014 to EU-approved Herceptin taking the other as potentially supportive into account.

Data from a sufficient number of lots of trastuzumab-EU (150 mg presentation) and of trastuzumab-US (440 mg presentation) were purchased and included as licensed trastuzumab product in the similarity assessment. These licensed product lots represent nearly the full 48-month expiry period (stored at 2 to 8ºC) of the licensed trastuzumab product; and at the time of analysis, the individual lots had between 3 and 44 months remaining prior to expiry.

PF-05280014 active substance batches and finished product lots were included in the similarity assessment.

A shift in total afucosylation, terminal galactosylation and G0 species for both EU and US reference product manufactured with expiry beyond December 2016 was been observed. The impact of this on biosimilarity assessment has been considered.

The data set obtained on 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.

PF-05280014, trastuzumab-US, and trastuzumab-EU samples have been characterized, side-by-side, for the secondary structure by far-UV CD and FTIR spectroscopy, the tertiary structure by near-UV CD and intrinsic fluorescence emission spectroscopy, and the thermal stability of higher order structure by DSC. The data support the similarity between PF-05280014 and trastuzumab-EU. The SE-HPLC, CGE (reducing and non-reducing), and SDS-PAGE (reducing) purity profiles were similar for PF-05280014 and trastuzumab-EU. Similar levels of monomer and high molecular mass species (HMMS) (SE-HPLC) were observed as well as similar levels of HC + LC and fragments (CGE reducing). Lower level of intact IgG was observed for PF-05280014 in comparison to trastuzumab-EU and –US, which can be attributed to slightly higher levels of PF-05280014 fragments.

To assess the contribution of basic species containing C-terminal lysine on the H chain to the overall charge profile, PF-05280014 active substance batches were assessed after treatment with carboxypeptidase B.

In conclusion, the extensive similarity assessment of PF-05280014, trastuzumab-US, and trastuzumab-EU showed highly similar biological activity of both the fragment antigen-binding (Fab) and Fc-based functionality when pre-glycan shift batches were used for comparison. Any minor differences seen in structural assays had no impact on biological activity. Based on the biological activity similarity assessment, PF-05280014 is highly similar to trastuzumab-US and trastuzumab-EU, and trastuzumab-EU is highly similar to trastuzumab-US.

The similarity assessment of PF-05280014, trastuzumab-US, and trastuzumab-EU glycan structures was performed using orthogonal analytical methods. The profiles and the relative quantity of major and minor glycan species were evaluated by HILIC with fluorescence detection. The distribution of main glycoforms is considered similar across PF-05280014, trastuzumab-US, and trastuzumab-EU. The criteria for similarity were met.

Afucosylated and terminal galactosylated N-linked glycans are structural attributes linked to effector function of antibodies. The influence of varying levels of afucosylated Fc glycan content on ADCC activity and binding to FcγRIIIa was investigated. The levels of afucosylated and terminal galactosylated N-linked glycans were determined to be well within the originators range.

The MoA of trastuzumab involves both, the Fab antigen binding domain and the Fc domain with its effector functions. Binding to HER2 and inhibition of downstream signaling and cell proliferation was assessed by multiple functional and binding assays. Similar binding to HER2 target antigen on tumor cell surface was confirmed and similar HER2 signaling pathway was demonstrated. Comparable ADCC activity in primary NK cell ADCC assay was demonstrated and confirmed in an orthogonal PBMC ADCC assay. Binding to FcγRIIIa, both 158V and 158F, was demonstrated to be similar. Binding to FcγRIIa 131H and 131R was similar. It is acceptable to consider the binding to FcγRIIa as a surrogate for antibody-dependent cellular phagocytosis (ADCP) function. No differences were found between PF-05280014, trastuzumab-US, and trastuzumab-EU with regard to binding to FcγRI, FcγRIIb, FcγRIIIb, fragment crystallizable receptor neonatal (FcRn), and C1q protein. Absence of CDC activity was also demonstrated.

The applicant noted a shift in the N-linked glycan profile, beginning in early 2015, in trastuzumab-US and trastuzumab-EU lots. Given the correlation of afucosylated structures, FcγRIIIa binding and ADCC activity pre-glycan shift and post-glycan shift lots have distinct activity profiles. Despite the shift observed for the originator lots the overall similarity assessment of PF-05280014, trastuzumab-US, and trastuzumab-EU showed similar biological activity of both the Fab and Fc-based functions. No significant differences were detected. In addition it is noted that pre-glycan shift and post-glycan shift trastuzumab-EU lots were used in clinical Study B3271002. The clinical data in patients with HER 2 positive metastatic breast cancer demonstrated no clinically meaningful difference between PF-05280014 and trastuzumab-EU product.

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 outcome of the physicochemical and biological comparability exercise between Trazimera and Herceptin is summarised in the tables below.

Table 1 - Physicochemical Characterization of Heterogeneity and Degradation Profiles

Molecular Parameter	Attribute	Analytical Procedure	Key Findings
Primary Structure and Posttranslational Modifications	Amino acid sequence	LC/MS/MS – Peptide Mapping with specialized bioinformatics	Identical amino acid sequence
		Peptide Mapping/ Edman Degradation	
	Molecular mass and size	nanoElectrospray Ionization Mass Spectrometry	Similar molecular mass and size at the intact molecule level
	Posttranslational modifications	nanoElectrospray Ionization Mass Spectrometry	Identical primary structure and similar posttranslational modifications at the intact molecule level
		LC/MS – Subunit Analysis	
		LC/MS and LC/UV – Peptide Mapping (Trypsin)	
N-Linked Glycan Structure	Total afucosylation	HILIC with fluorescence detection	Similar ranges of total afucosylation

Table 1 - Physicochemical Characterization of Heterogeneity and Degradation Profiles

Molecular Parameter	Attribute	Analytical Procedure	Key Findings
	Terminal galactosylation	HILIC with fluorescence detection	Similar ranges of terminal galactosylation
	N-linked glycan distribution profile, structure, composition, and glycosidic linkages	HILIC/MS	Similar relative proportions of major level N-linked glycans
		Exoglycosidase Digestion/HILIC	Similar N-linked glycan structural assignments and glycosidic linkages
		Sialic Acid Assay	Same sialic acid forms
Charge Heterogeneity	Acidic and basic isoforms	CEX-HPLC	Similar levels of acidic species
			Different levels of basic species due to differences in levels of H chain C-terminal lysine which is not considered clinically relevant.
	Major and minor charge isoforms	iCE	Similar major and minor charge isoform species
		CEX-HPLC profile characterized by MS	Similar major and minor charge isoform species. Difference in H chain C-terminal lysine is not considered clinically relevant.
		Carboxypeptidase B/CEX-HPLC	Similar charge isoform profile after removal of H chain C-terminal lysine
Product Purity	Monomer	SE-HPLC	Similar, high levels of monomer
	HMMS	SE-HPLC	Low levels of HMMS
	HC + LC and fragments	CGE (reducing)	Similar levels of HC + LC and fragments
		SDS-PAGE (reducing) (Total protein staining and Western blotting)	Similar banding patterns
	Intact IgG	CGE (Non-reducing)	Similar levels of Intact IgG
Disulfide Bonds	State of cysteines and disulfide bonds	Sulfhydryl Analysis by UV/VIS Spectrophotometry and SE-HPLC	Similar trace level of unpaired protein sulfhydryl groups
		LC/MS – Non-reduced Peptide Mapping (Lys-C)	Identical disulfide bond connectivity
Higher Order Structure	Secondary structure	Far-UV Circular Dichroism (CD) Spectroscopy	Similar secondary structure
		Fourier Transform Infrared (FTIR) Spectroscopy	
	Tertiary structure	Near-UV CD Spectroscopy	Similar tertiary structure
		Intrinsic Fluorescence Spectroscopy	
	Thermal stability of higher order structure	Differential Scanning Calorimetry (DSC)	Similar thermal stability of higher order structure and T_ms

Table 2- Binding assays and *in-vitro* bioassays

Biological Activity	Attribute	Analytical Procedure	Key Findings
Binding to HER2 Target Antigen	Relative potency	Inhibition of Cell Growth Assay	Similar dose-response curves and relative potency
	Binding affinity and kinetics	Binding to HER2 Target Antigen by SPR	Similar binding affinity and kinetics
	Binding activity on cell surface	Binding to Cell Surface HER2 Target Antigen by Flow Cytometry	Similar dose response curves

Table 1 - Physicochemical Characterization of Heterogeneity and Degradation Profiles

Molecular Parameter	Attribute	Analytical Procedure	Key Findings
	Phosphorylation levels	HER2 and HER3 phosphorylation by Western Blot	Similar phosphorylation levels
ADCC Activity	ADCC response	Primary NK Cell ADCC Assay	Similar ADCC activity
		PBMC ADCC assay	
	Reporter gene activity	FcγRIIIa Reporter Gene Assay	Similar binding to FcγRIIIa and signal activation pathway
	Binding affinity and kinetics	Binding to FcγRIIIa 158V and 158F by SPR	Similar binding affinity and kinetics
ADCP	Binding affinity and kinetics	Binding to FcγRIIa 131H and 131R by SPR	Similar binding affinity and kinetics
Apoptosis	Induction of apoptosis	Apoptosis assay	Similar low-level induction of apoptosis
Other Fcγ Receptor Binding	Binding affinity and kinetics	Binding to FcγRI, FcγRIIb, and FcγRIIIb by SPR	Similar binding affinity and kinetics
FcRn Binding	Binding affinity and kinetics	Binding to FcRn by SPR	Similar binding affinity and kinetics
CDC Activity	CDC activity	CDC assay	No CDC activity observed
	Binding to C1q	C1q binding assay	Similar dose response curves

Adventitious agents

Compliance with the TSE Guideline (EMEA/410/01, current version) has been sufficiently demonstrated. 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 cells used for production of PF-05280014 have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB with the exception of intracytoplasmic A-type as well as C-type retroviral particles which are well known to be present in rodent cells. This is acceptable since there is sufficient capacity within the manufacturing process for reduction of this type of viral particles.

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

In summary, the virus safety of PF-05280014 has been sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Development, characterisation, manufacture and control of trastuzumab active substance and finished product have been adequately and sufficiently described.

The specifications established are appropriate and covers the relevant characteristics of monoclonal antibodies. Acceptance limits have been well justified and mostly reflect manufacturing experience. Appropriate studies were conducted to further support the quantitative composition of the finished product and the selected finished product manufacturing process. The commercial manufacture of Trazimera has

been sufficiently described, controlled and verified to ensure a consistent production of the finished product. Finished product stability studies were adequately performed and the results support the claimed shelf life for Trazimera.

Biosimilarity

An extensive analytical similarity study has been conducted. The comparative testing included analysis of primary structure and posttranslational modifications, biological activity, N-linked glycan structure, charge heterogeneity, purity, protein concentration, disulfide bonds and higher order structure, as well as comparative forced degradation at elevated temperature storage, light exposure, forced deamidation and forced oxidation.

The biosimilarity assessment is considered adequate displaying PF-05280014 a high degree of similarity to trastuzumab-EU and trastuzumab-US.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Biosimilarity to the reference product has been satisfactorily demonstrated at the quality level.

2.2.6. Recommendation for future quality development

In the context of the obligation of the Marketing Authorisation Holder (MAH) to take due account of technical and scientific progress, the CHMP recommended an additional following point for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

PF-05280014 has been developed as a biosimilar mAb to the trastuzumab products marketed globally as Herceptin.

2.3.2. Pharmacology

The nonclinical pharmacology of PF-05280014 was compared with trastuzumab-US and trastuzumab-EU in a number of in vitro functional and binding assays reflective of the MoA of trastuzumab.

The MoA of trastuzumab involves both the Fab antigen binding domain and the Fc domain with its effector functions. Binding to HER2 and inhibition of downstream signaling and cell proliferation was assessed by multiple functional and binding assays. Similar binding to HER2 target antigen on tumour cell surface was confirmed and similar HER2 signaling pathway was demonstrated.

Comparable ADCC activity in primary NK cell ADCC assay was demonstrated and confirmed in an orthogonal PBMC ADCC assay. Binding to FcγRIIIa, both 158V and 158F, was demonstrated to be similar. Binding to FcγRIIa 131H and 131R was similar. It is acceptable to consider the binding to FcγRIIa as a surrogate for ADCP function.

No differences were found between o PF-05280014, trastuzumab-US, and trastuzumab-EU with regard to binding to FcγRI, FcγRIIb, FcγRIIIb, FcRn, and C1q protein. A shift in the N-linked glycan profile, beginning in early 2015, was observed in trastuzumab-US and trastuzumab-EU (reference Herceptin) lots. Therefore data were presented as “All lots” as well as datasets excluding post-glycan shift lots. Despite the shift observed for the originator lots the overall similarity assessment of PF-05280014, trastuzumab-US, and trastuzumab-EU showed similar biological activity of both the Fab and Fc-based functions. No significant differences were detected. In addition it is noted that pre-glycan shift and post-glycan shift trastuzumab-EU lots were used in clinical Study B3271002. The clinical data in patients with HER 2 positive metastatic breast cancer demonstrated no clinically meaningful difference between PF-05280014 and trastuzumab-EU product.

2.3.3. Pharmacokinetics

The toxicokinetics (TK) and antidrug antibodies (ADA) of PF-05280014, trastuzumab-US, and trastuzumab-EU were evaluated in male CD-1 mice when administered as a single dose via bolus intravenous. The applicant provided a comparison of the Cmax and AUCinf values for trastuzumab-PF relative to trastuzumab-US and trastuzumab-EU expressed as a ratio of trastuzumab-PF to trastuzumab-US (PF:US) or trastuzumab-EU (PF:EU). Study 11GR301 was conducted to determine the toxicokinetics of three test articles, trastuzumab-PF (PF-05280014), trastuzumab-US, and trastuzumab-EU, when administered as a single dose via bolus intravenous injection to male mice. Systemic exposure of trastuzumab-PF, trastuzumab-US, and trastuzumab-EU increased with increasing dose from 1 to 100 mg/kg. Comparing AUCinfand Cmax no significant differences could be observed between PF-05280014, trastuzumab-US, and trastuzumab-EU.

2.3.4. Toxicology

The toxicology program with PF-05280014 and trastuzumab included a comparative 1-month TK study in male mice, a 2-week IV toxicity study in male and female CD-1 mice. In line with guidance on biosimilars single dose toxicity, genotoxicity, carcinogenicity, and developmental and reproductive toxicity studies are not warranted.

In the 2-week IV toxicity study, male and female CD-1 mice (10/sex/group) were administered PF-05280014 twice weekly at 10 or 100 mg/kg/dose (for a total of 5 doses). There was no test article-related mortality, clinical observations, effects on body weights or food consumption, ophthalmologic findings, or clinical laboratory measurements. There were no test article-related changes in organ weights, or gross or microscopic findings. Serum concentrations of PF-05280014 confirmed systemic exposure to the test article and increased with increasing dose in a less than dose proportional manner. Mean serum concentrations at 24 hours following the last dose were comparable.

Overall the toxicology data indicate that PF-05280014 and trastuzumab-EU and trastuzumab-US can be considered comparable.

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the CHMP guidance *EMEA/CHMP/SWP/4447/00* entitled, "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" published 01 June 2006, amino acids and proteins are exempted because they are unlikely to result in significant risk to the environment. PF-05280014 is a humanized IgG 1 monoclonal antibody consisting of naturally occurring amino acids, therefore, it is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

PF-05280014 has been developed as a similar biological medicinal product to the innovator product Herceptin (trastuzumab). The marketing authorisation of PF-05280014 is an abridged application for a biosimilar under the scope of the Article 10(4) of Directive 2001/83/EC. According to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, EMEA/CHMP/BMWP/42832/2005 Rev1, the applicant used a stepwise approach in order to demonstrate that PF-05280014 is comparable to Herceptin with respect to pharmacodynamics (PD)/pharmacokinetics (PK) and toxicity. Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity and on local tolerance are not required for non-clinical testing of biosimilars.

2.3.7. Conclusion on the non-clinical aspects

The overall data on PD/PK and toxicology indicate that PF-05280014 can be considered similar to the reference product Herceptin.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3 Summary of Clinical Studies

Study Number (Country)/Status	Study Design	Treatment	Study Population	Number of Subjects/Patients Randomized	Objectives
B3271001 (US)/completed	Double-blind (Sponsor unblinded), randomized (1:1:1), parallel-group, single-dose study	• A single dose of PF-05280014, trast-EU, or trast-US was administered at 6 mg/kg as a 90-minute IV infusion	Healthy male adults 18 to 55 years old	N = 105 PF 05280014 = 35 Trast-EU = 35 Trast-US = 35	Primary: • To demonstrate PK similarity of PF-05280014 to trast-EU, PF-05280014 to trast-US, and trast-EU to trast-US Secondary: • Evaluate safety and tolerability, and immunogenicity of PF-05280014 compared to trast-US and trast-EU • To demonstrate PK similarity of PF-05280014 to combined groups of trast-US and trast-EU
B3271006 (US)/completed	Double-blind (Sponsor unblinded), randomized (1:1), parallel-group, single-dose study	• PF-05280014 or trast-US was administered at a dose of 6 mg/kg as a 90-minute IV infusion	Healthy male adults 18 to 55 years old	N = 162 PF 05280014 = 81 Trast-US = 81	Primary: • To estimate the relative risk of an abnormal elevated body temperature compared to baseline following PF-05280014 or trast-US Secondary: • To evaluate the safety of PF-05280014 vs trast-US
B3271002 (WW)/ongoing	Double-blind, randomized clinical study	• PF-05280014 or trast-EU: Weekly regimen on Days 1, 8, 15 and 22 of each 28-day cycle. A loading dose of 4 mg/kg infused over 90 minutes on Day 1 (Cycle 1). Subsequent weekly infusions 2 mg/kg administered over 30 to 90 minutes depending on tolerability until Week 33, then dosage could be changed to 6 mg/kg once every 3 weeks • Paclitaxel: Administered on Days 1, 8 and 15 of each 28-day cycle. The starting dose of paclitaxel was 80 mg/m^2 by IV infusion over 60 minutes, and subsequent dose reduced as per protocol.	Female patients aged 18 years or older with confirmed diagnosis of breast cancer and presence of metastatic disease	N = 707 PF 05280014 = 352 Trast-EU = 355	Primary: • Compare the ORR in PF-05280014 to trast-EU in combination with paclitaxel. Secondary: • Evaluate the safety of PF-05280014 plus paclitaxel versus trast-EU plus paclitaxel; • Evaluate secondary measures of tumor control; • Evaluate the population PK of PF-05280014 and trast-EU; • Evaluate the immunogenicity of PF-05280014 and trast-EU.
B3271004 (WW)/completed	Double-blind, randomized clinical study	• PF-05280014 or trast-EU: A loading dose of 8 mg/kg infused over 90 minutes on Day 1, Cycle 1. Subsequent infusions every 3 weeks with a dose of 6 mg/kg administered over 30 to 90 minutes for a total of 6 cycles. • Docetaxel (75 mg/m^2) and carboplatin (AUC 6 IV) administered on Day 1 of each cycle for 6 cycles.	Female patients aged 18 years or older with confirmed HER2 overexpressing invasive breast cancer	N = 226 PF-05280014 = 114 Trast-EU = 112	Primary: • To compare the percentage of patients with steady state (Cycle 5) trough plasma concentration (C_{trough}) >20 µg/mL for PF-05280014 versus trast-EU Secondary: • To evaluate measures of tumor control for PF-05280014 versus trast-EU • To evaluate the safety of PF-05280014 versus trast-EU • To evaluate the immunogenicity of PF-05280014 versus trast-EU. • To evaluate the PK of PF-05280014 and trast-EU.

2.4.2. Pharmacokinetics

The PF-05280014 PK program consists of one pivotal comparative single-dose study carried out in healthy subjects (Study B3271001) and 2 supportive studies in patients with HER2-positive metastatic breast cancer in combination with Paclitaxel (Study B3271002) and in early breast cancer patients in combination with Carboplatin and Taxotere (Study B3271004).

The PK analytical method to quantify the concentration of trastuzumab in human plasma and in patients with HER2-positive Metastatic Breast Cancer consists of a capture enzyme-linked immunosorbent assay (ELISA) including an acid dissociation step. This step is expected to separate all possible complexes between drug and HER2 as well as between drug and ADAs present in serum samples (determination of total drug concentration). Validation results showed acceptable accuracy and precision for all three test compounds (PF-05280014, EU- and US-Herceptin) versus EU-Herceptin as calibrator.

PK comparability of PF-05280014 to each of the reference products (trastuzumab-EU or trastuzumab-US) was shown at the dose of 6 mg/kg body weight in healthy volunteers (Study B3271001), given that the 90% confidence intervals (CIs) for the test-to-reference ratios of Cmax, AUCt, and AUCinf were within the pre-specified equivalence margin of 80% to 125%. A similar result was obtained for the comparison of trastuzumab-EU to trastuzumab-US.

Geometric mean levels of AUCinf for PF-05280014 (36650 µg*h/mL) and EU-Herceptin (39770 µg*h/mL) were as expected from the mean levels obtained for Herceptin in similar studies after 6 mg/kg IV in healthy subjects (e.g. Wynne et al. 2013: 38640 µg*h/mL). The test-to-reference ratio for AUCinf between PF-05280014 and EU-Herceptin was 92.15% [90% CI: 86.03, 98.69].

PK results in patients with HER2-positive, metastatic breast cancer in the first-line metastatic treatment setting using the 4 mg/kg + 2 mg/kg qw dosing regimen (Study B3271002) comprised Ctrough values up to cycle 5 day 8, which is the day of administration of the 18th weekly dose of trastuzumab. Mean Ctrough values increased continuously from 27.6 µg/mL (pre-dose 2) to 60.3 µg/mL (pre-dose 18) in the PF-05280014 group, and from 28.8 to 62.3 µg/mL in the EU-Herceptin group. This is consistent with the expected time course (time to ss: 12 weeks) and steady state level of Ctrough for Herceptin in MBC after the weekly dosing regimen (Median trough minimum concentration (Cmin),ss: 63.1 µg/mL; Herceptin SmPC, 5.2, Table 15).

PK results in patients with operable HER2-positive, breast cancer in the neoadjuvant setting using the 8 mg/kg + 6 mg/kg q3w dosing regimen (Study B3271004) showed comparable geometric mean Ctrough values of 21.7, 30.5, 32.0, 34.6 ng/mL (PF-05280014) and 25.7, 34.9, 36.4, 34.6 ng/mL (EU-Herceptin) at the end of cycle 1, 3, 4, and 5, respectively.

2.4.3. Pharmacodynamics

Serum HER2 was evaluated as an exploratory biomarker of trastuzumab effect in Studies B3271002 and B3271004. A high interindividual variability (IIV) of baseline HER2 serum levels between the patients was observed in both studies (range from 6.0 to 6700 ng/mL, coefficient of variation [CV] 160 - 330%). Mean baseline values were 159.8 vs. 184.4 ng/mL in Study B3271002 and 24.7 vs. 20.4 ng/mL in Study B3271004 for PF-05280014 vs. EU-Herceptin, respectively.

The mean percent change from baseline at Cycle 8, Day 1 in Study B3271002 was -58.9% for PF-05280014 and (39.98) for trastuzumab-EU. The mean percent change from baseline at end of treatment (EOT) in Study B3271004 was -28.8% for PF-05280014 and -28.5% for trastuzumab-EU. This indicates a similar mean percentage change from baseline between the 2 treatments in both studies.

Immunogenicity profiles of PF-05280014 have been investigated in all 3 clinical studies, i.e. a single-dose study in healthy subjects (Study B3271001) and 2 multidose studies in patients with HER2-positive breast cancer (Study B3271002 and Study B3271004).

For screening of ADA independent drug-specific electrochemiluminescent (ECL) bridging immunoassays were used. Drug tolerance levels were different depending on the drug and the matrix (normal serum or patient serum).

Low to zero immunogenicity was found in healthy male volunteers after a single IV dose of 6 mg/kg EU-Herceptin or PF-05280014 (1/35 vs. 0/35).

In MBC patients receiving adjuvant treatment (Study B3271002) a high incidence of pre-existing antibodies (many of them neutralizing) was observed (8.6% and 4% in PF-05280014 and trastuzumab-EU, respectively), about 10% of these patients experienced IRRs. Of the 44 patients with baseline ADA, only 4 (3 in the PF-05280014 group and 1 in the trastuzumab-EU treatment group) had prior known exposure to trastuzumab. All except two patients were ADA negative post treatment. For both patients (one in each treatment group) the positive ADA result was observed at the end of the treatment visit in the final sample collected for the study. Final data (up to Week 53) on immunogenicity show an overall ADA incidence of 0.3% (1/336 and 1/338) in both arms.

None of 225 EBC patients receiving neoadjuvant treatment (Study B3271004) was tested positive for ADAs. Only 1 pre-treatment sample was positive (EU-Herceptin group). In comparison, a rate of 7.1% was observed in the IV arm of the HannaH trial for Herceptin (Jackisch et al. Future Oncology 2014; 8.1% reported in Herceptin SmPC).

2.4.4. Discussion on clinical pharmacology

In general, the Applicant´s development program to demonstrate the similarity between PF-05280014 and EU-Herceptin with respect to PK is considered adequate and was performed in general according to the guidance on biosimilars and the recommendations given in the Scientific Advices.

The acid dissociation step in the PK assay leading to measurement of total drug is not usual and might hinder comparison with PK data in historical studies with Herceptin. Sensitivity of the method was 0.5 µg/mL, which is acceptable. Validation of the method is considered sufficient.

PK similarity in healthy volunteers is considered as demonstrated between PF-05280014 and each of trastuzumab-EU and trastuzumab-US, and between trastuzumab-EU and trastuzumab-US.

PF-05280014 and trastuzumab levels in MBC patients after the weekly dosing regimen were as expected and comparable to EU-Herceptin supporting PK similarity of PF-05280014 in MBC patients. A population PK analysis using data from Study B3271002 was submitted to show that the population PK profiles of PF-05280014 versus trastuzumab-EU were not different in patients with HER2-positive MBC. The level of steady state trough concentrations of trastuzumab in the EBC neoadjuvant setting (3 weekly regimen) was also highly similar between the drugs. As expected, accumulation from cycle 1 to 5 is observed, however, median Ctrough levels after cycle 5 of 35.6 (PF-05280014) and 39.8 µg/mL (trastuzumab-EU) were lower than expected in this patient population (EBC neoadjuvant, 3 weekly regimen, population predicted median Cmin,ss: 53.8 µg/mL; Herceptin SmPC, 5.2, Table 15). This difference is suggested to be attributed to cross-study variability and to the fact that after cycle 5, steady state has not been fully reached.

Overall, the PK findings of similarity between PF-05280014 and trastuzumab-EU are consistent across all 3 studies.

Mean baseline values of serum HER2 were higher in Study B3271002 (159.8 vs. 184.4 ng/mL) than in Study B3271004 (24.7 vs. 20.4 ng/mL). This is considered as reflective of the higher tumour burden in metastatic

disease in Study B3271002, which is consistent with data in the literature. The comparable mean percentage change from baseline between the 2 treatments in both studies supports PD similarity. However, as no validated pharmacodynamics biomarker has been established for Herceptin so far, the results can be only considered as exploratory. They are not conclusive.

Low incidence of ADA in healthy volunteers is not unexpected, especially in view of the small number of subjects. Results on Day 43 and 71 were conclusive with respect to drug tolerance and support the conclusion that incidence of immunogenicity in healthy volunteers was low and comparable in the 3 treatment groups. The high number of MBC patients in Study B3271002 having pre-existing ADAs could partially be attributed to the low false-positive rate of 1%, to pre-existing antibodies caused by innate response or prior exposure to trastuzumab, or other biologics sharing the same immunogenicity-inducing epitopes. As only 4 patients had known prior exposure of trastuzumab, the impact of the inclusion of trastuzumab pre-treated patients on the evaluation of immunogenicity is considered negligible.

The discrepancy between ADA incidence expected in the EBC neoadjuvant setting (7-8%, HannaH study) and the very low incidence observed in Study B3271004 (1/224, 0 and 0.9%) might be partially attributed to assay methodology. More importantly, 98% (EU-Herceptin group) and 3.5% (PF-05280014 group) of the samples from Study B3271004 were inconclusive due to present drug concentrations > drug tolerance level (DTL) of the assay. Furthermore, in contrast to Study B3271004, in the HannaH study ADA samples were collected throughout the follow-up phase at 3, 6, and 12 months. Therefore, the lack of sampling time points in the follow-up period after end of treatment, i.e. in the absence of drug interference, might have contributed to an underestimation of ADAs in both groups of Study B3271004. However, at least the very low (0%) incidence of ADAs in the PF-05280014 group can be regarded as conclusive result.

2.4.5. Conclusions on clinical pharmacology

In conclusion, from a PK and PD perspective, the data provided support the biosimilarity of PF-05280014 and EU-Herceptin.

The totality of immunogenicity data in healthy volunteers and two patient populations also support comparability of immunogenicity between PF-05280014 and trastuzumab-EU reference product.

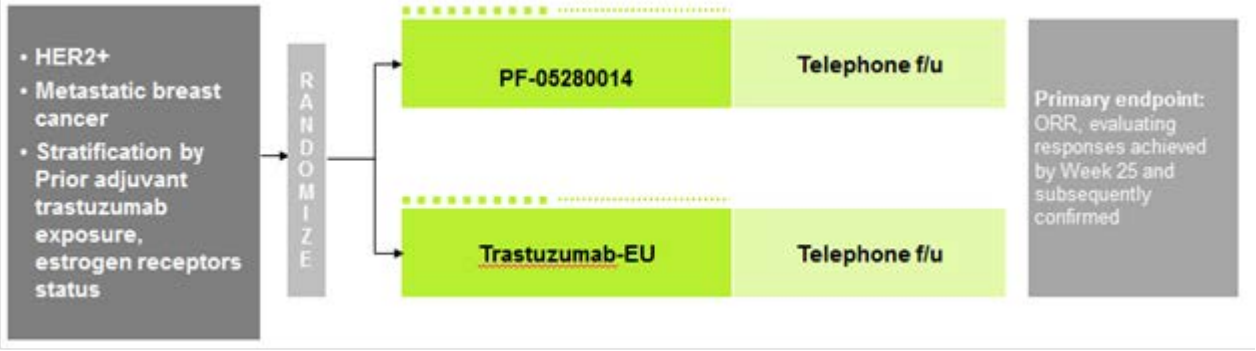
2.5. Clinical efficacy

Two clinical efficacy studies were conducted: Study B3271002 in patients with HER2-positive metastatic breast cancer (ongoing) and Study B3271004 in early breast cancer patients (completed). The cut-off date (24 August 2016) of the data included in this dossier was based on when all patients had either completed the Week 33 visit (to collect data for primary endpoint analysis) or discontinued study drug earlier than the Week 33 visit, and include data up to 378 days post randomization. Unless otherwise noted, the cutoff date (11 January 2017) of the data included in this dossier was based on when all patients had either completed at least 53 weeks of treatment or discontinued the study earlier. The primary efficacy analysis was based upon all available central radiology data as of the cutoff date of 24 August 2016, when all patients had either completed the Week 33 tumor assessment or discontinued study drug earlier than the Week 33 visit. All patients had data available for the primary analysis.

2.5.1. Main study

Study B3271002

The efficacy of PF-05280014 has been evaluated in Study B3271002 (primary comparative efficacy and safety study) in HER2-positive metastatic breast cancer patients. This study was a Phase III, randomized, double-blind, multicentre study evaluating the similarity of efficacy (as a primary endpoint), safety, PK, and immunogenicity of PF-05280014 versus trastuzumab-EU in combination with paclitaxel.



Methods

Study Participants

Key inclusion criteria

Eligible patients were required to meet the following and all other qualifying criteria:

Patient eligibility was required to be reviewed and documented by an appropriately qualified member of the investigator's study team before patients were included in the study.

1. Female patients aged 18 years or older. (Where required by regulations, consent from a legally acceptable representative was required for all patients who were 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 1 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 IHC categorized as IHC2+ with FISH, CISH, or DISH confirmation.

5. Available tumor tissue (ie, 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 estrogen receptor (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.

Key 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).
3. Prior systemic therapy for metastatic disease (except endocrine therapy)
4. Prior cumulative dose of doxorubicin of >400 mg/m2, epirubicin dose >800 mg/m2, or the equivalent dose for other anthracyclines or derivatives (e.g., 72 mg/m2 of mitoxantrone). If the patient has received more than one anthracycline, then the cumulative dose must not exceed the equivalent of 400 mg/m2 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 κ B (RANK) ligand inhibition therapy for pre-existing bone metastases or osteoporosis is allowed; prophylactic use to prevent bone metastasis is exclusionary.

Treatments

Paclitaxel (IV): “weekly” regimen on Days 1, 8 and 15 of each 28-day cycle (i.e., no paclitaxel was administered on Day 22 of each cycle) for at least 6 cycles or until maximal benefit of response was obtained. The starting dose of paclitaxel was 80 mg/m2 with an option for reduction to 70 mg/m2 and then 60 mg/m2 as needed.

PF-05280014/Trastuzumab (IV): in combination with paclitaxel until at least Week 33 of the study in a weekly regimen on Days 1, 8, 15 and 22 of each 28-day cycle. The first administration on Cycle 1, Day 1,

was a loading dose of 4 mg/kg. Subsequent 2 mg/kg q2w. After Week 33 the regimen could be changed at the discretion of the investigator to every 3 weeks at a dose of 6 mg/kg. Dose reductions for trastuzumab were not permitted.

Objectives

The primary objective was to compare the objective response rate (ORR) in patients with metastatic HER2-positive breast cancer who received PF-05280014 in combination with paclitaxel to those who received trastuzumab-EU in combination with paclitaxel.

Secondary objectives identified in the protocol included:

• To evaluate the safety of PF-05280014 plus paclitaxel versus trastuzumab-EU plus paclitaxel;

• To evaluate secondary measures of tumour control;

• To evaluate the population PK of PF-05280014 and trastuzumab-EU;

• To evaluate the immunogenicity of PF-05280014 and trastuzumab-EU.

Outcomes/endpoints

The primary efficacy endpoint 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 (Week 33 ± 14 days) in accordance with RECIST 1.1.

Secondary efficacy evaluations included:

• 1-year PFS rate, analyzed based on the time from date of randomization to first documentation of PD, or death due to any cause in the absence of documented PD;

• Duration of response (DOR, defined as the time from date of the first documentation of objective tumor response [CR or PR] to the first documentation of progressive disease [PD], or to death due to any cause in the absence of documented PD);

• 1-year survival rate where time to death was defined as the time from date of randomization to death due to any cause while the patient was on the study.

Sample size

The hypothesis to be tested in this study was that the risk ratio of ORR of PF-05280014 versus that of trastuzumab-EU by Week 25 was within a pre-specified margin of 0.80 to 1.25. A sample size of 630 patients (315 per treatment group) provided approximately 85% power for achieving equivalence under the specified margin with a 2.5% type I error rate assuming an ORR of 60% in both treatment groups. Considering a possible 10% attrition rate for patients reaching evaluation for ORR, a total sample size of approximately 690 patients (345 per treatment group) were planned to be randomized to achieve the target sample size of 630.

Randomisation

Patients were randomized (1:1) using an automated interactive web based response system (IWRS) to receive PF-05280014 plus paclitaxel or trastuzumab-EU plus paclitaxel.

Randomization was stratified by:

• Prior trastuzumab exposure (Yes/No) (protocol Amendment 2)

• ER status (ER positive versus ER negative).

Blinding (masking)

This study was double-blinded.

Statistical methods

The primary efficacy analyses were done for the intent-to-treat (ITT) population of all randomized patients. Sensitivity analyses were performed using the per-protocol (PP) population excluding patients with major protocol violations. The primary efficacy endpoint was the proportion of patients achieving ORR (according RECIST 1.1, central radiology assessment). Non-responder imputation was applied in case of missing endpoint information.

The estimated risk ratio in ORR between PF-05280014 and trastuzumab including the corresponding 95% CI was calculated. Equivalence was concluded in case the 95%-CI fell completely within the pre-defined biosimilar margin [0.80 to 1.25]. The margin derivation was based on a meta-analysis including 3 randomized studies of taxanes 7, 10, 12. 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. However, the traditional bioequivalence bounds of 0.80 to 1.25 were used to be more conservative. The primary analysis was repeated with the stratification variables used for randomisation (i.e. prior adjuvant trastuzumab exposure and/or ER status). As a sensitivity analysis the primary analysis was repeated using the PP population.

Secondary efficacy endpoints included DOR, 1-year PFS rate, and 1-year survival rate. For these time-to-event endpoints, a Cox proportional hazard model was used to assess covariates of interest. These analyses were primarily performed with the ITT population. As a confirmatory analysis, these analyses were repeated with the PP population.

Descriptive statistics (frequency and percentage) for CR, PR, and ORR were presented by treatment group. The 95% CI of these response rates was calculated. The estimated risk ratio in ORR between PF-05280014 and trastuzumab-EU was computed, and the asymptotic 95% CI of the ratio, as proposed by Miettinen and Nurminen (1985), was constructed.

The Kaplan-Meier (K-M) method was used to estimate the PFS rate at 1-year; the 2-sided 95% CI of the rate using Greenwood's formula was reported. A 1-sided stratified log-rank test was used to compare the PFS curve between the 2 treatment groups.

Results

Participant flow

Table 4 Patient Disposition

	PF-05280014	Trastuzumab-EU	Total
Number (%) of patients			
Randomized	352	355	707
Treated	349 (99.1)	353 (99.4)	702 (99.3)
Treated (trastuzumab) until objective progression or relapse	138 (39.2)	143 (40.3)	281 (39.7)
Treatment (trastuzumab) stopped before objective progression or relapse	43 (12.2)	47 (13.2)	90 (12.7)
Study			
Completed	20 (5.7)	12 (3.4)	32 (4.5)
Withdrawn after randomization but prior to treatment	3 (0.9)	2 (0.6)	5 (0.7)
Discontinued prior to long-term follow-up	18 (5.1)	24 (6.8)	42 (5.9)
Discontinued during long-term follow-up	43 (12.2)	49 (13.8)	92 (13.0)
Ongoing at date of cutoff	268 (76.1)	268 (75.5)	536 (75.8)
Actively being treated (trastuzumab)	171 (48.6)	165 (46.5)	336 (47.5)
No longer receiving treatment (trastuzumab) but remaining in long-term follow-up	97 (27.6)	103 (29.0)	200 (28.3)
Analyzed for efficacy:			
ITT population	352 (100.0)	355 (100.0)	707 (100.0)
PP Population	280 (79.5)	285 (80.3)	565 (79.9)
Analyzed for PK			
PK Population	349 (99.1)	353 (99.4)	702 (99.3)
Analyzed for safety:			
Adverse events	349 (99.1)	353 (99.4)	702 (99.3)
Laboratory data	348 (98.9)	351 (98.9)	699 (98.9)

Source Data: Table 14.1.1.1.
The number of randomized patients was used as the denominator for percentages.
Note: A patient was considered early discontinued from the study if they did not complete follow-up as per protocol. Completed patients at the time of the data cutoff included all follow-up as required by the protocol and as recorded on the End of Study page on the eCRF.
Abbreviations: eCRF=electronic Case Report Form; EU=European Union; ITT=intent-to-treat; PK=pharmacokinetic; PP=per protocol.

Recruitment

Study initiation date: 24 February 2014 (first subject, first visit)

Study completion date: 24 August 2016 (Week 33 Analysis)

Data cutoff date: 11 January 2017 (Week 53 Analysis)

Data Snapshot date: 17 February 2017 (Week 53 Analysis)

Final date of study report: 16 February 2017 (Week 33 Analysis)

Conduct of the study

The final protocol (dated 28 March 2013) had 4 amendments. Amendment 1 (29 July 2013) was implemented in response to recommendations made by regulatory agencies during reviews performed prior to Health Authority, IRB or EC submissions; no patients had been screened or randomized at the time of the amendment. Amendment 2 (dated 10 July 2014) was implemented due to feedback from a retrospective review by Parexel Informatics of randomized patients to determine if they had measurable disease (following investigator assessment), and subsequent to feedback from regulatory agencies. Amendment 3 (27 September 2016) was implemented to update the study design to end patient treatment after the completion of Week 53 visit assessments, following communication with regulatory agencies. Amendment 4 (dated 16 March 2017) was issued to address regulatory responses to protocol Amendment 3, and delineated 2 treatment periods (TP1 and TP 2). The amendment allowed for continued treatment beyond Week 53 (PF-05280014 or trastuzumab-EU monotherapy every 3 weeks at a dose of 6 mg/kg), but with limited protocol-required assessments. In total, 276 patients were screened under protocol Amendment 1, with the remainder (431 patients) screened under protocol Amendment 2. All data included in this report (using the data cutoff date of 11 January 2017) was from patients enrolled and managed prior to implementation of Amendment 3.

Approximately half (54.6%) of all patients had an important (as defined by the sponsor) protocol deviation, with a comparable number and category of protocol deviations reported across both treatment groups. The most frequently reported important deviations were those related to procedures/tests (215 [30.4%] patients) and informed consent (166 [23.5%] patients).

Baseline data

Overall, the demographic and baseline characteristics were relatively balanced between the treatment groups. About 67% of patients were white, 27% were Asian and 2% black.

Slightly more patients with longer prior disease duration were randomized to the PF-05280014 arm (median 6.7 vs 6.1 months), but this would rather be to a disadvantage. Otherwise baseline characteristics (age, Eastern Cooperative Oncology Group [ECOG], histopathologic disease, IHC results, left ventricular ejection fraction (LVEF) status, ER status, prior trastuzumab) appear balanced between the groups. There were slightly more liver metastases in the trastuzumab-EU arm (47% vs 42%) and slightly more lung metastases in the PF-05280014 arm (53% vs 52%).

Previous systemic therapy for breast cancer in the neoadjuvant/adjuvant setting reported in ≥5% of patients included cyclophosphamide (255 [36.1%] patients), doxorubicin (211 [29.8%] patients), fluorouracil (147 [20.8%] patients), docetaxel and trastuzumab (72 [10.2%] patients each), tamoxifen (69 [9.8%] patients), and paclitaxel (55 [7.8%] patients), with comparable proportions reported in both treatment groups. The incidence of prior radiation was comparable across treatment groups (115 [32.7%] patients in the PF-05280014 group and 117 [33.0%] patients in the trastuzumab-EU group).

Numbers analysed

Of the 707 patients randomized, 536 patients remained ongoing in the study at the data cutoff date: 171 and 165 patients still actively treated with PF-05280014 and trastuzumab-EU, respectively; 97 and 103

patients, respectively, no longer received study drug but remained in the long-term follow-up (LTFU) phase of the study.

A total of 32 patients completed the study at the time of the data cutoff (including all follow-up as required according to the protocol), 42 (5.9%) patients discontinued the study prior to the completion of LTFU and 92 (13.0%) patients discontinued during LTFU.

The ITT population (707 [100.0%] patients) was used for the efficacy analysis and the safety population was used for the analyses of adverse events (AEs) (702 [99.3%] patients) and laboratory data (699 [98.9%] patients). The PP population (565 [79.9%] patients) was used for sensitivity analyses of the primary and secondary efficacy and biomarker analyses.

Outcomes and estimation

The data provided in Marketing Authorization Application (MAA) **(13 July 2017) were based on the cutoff date 24 August 2016** when all patients had either completed the Week 33 visit (to collect data for primary endpoint analysis) or discontinued study drug earlier than the Week 33 visit.

Primary endpoint

Similarity between PF-05280014 and trastuzumab-EU was statistically demonstrated for the primary efficacy endpoint, ORR (defined as the percent of patients within each treatment group that achieved CR or PR by Week 25 [±14 days] and confirmed on a follow-up assessment).

The analysis of ORR derived from central radiology assessments showed a risk ratio of 0.940 (PF-05280014 over trastuzumab-EU), with a 95% CI of (0.842, 1.049), which fell entirely within the 0.80 to 1.25 equivalence margin.

Table 5 Analysis of Objective Response Rate Derived From Central Radiology Assessments - ITT Population

	PF-05280014 (N=352)	Trastuzumab-EU (N=355)	Risk Ratio[a] Estimate (95% CI)
Objective Response Rate			
n (%)	220 (62.5)	236 (66.5)	0.940
(95% CI)	(57.2, 67.6)	(61.3, 71.4)	(0.842, 1.049)

Source Data: Table 14.2.3.1.
Notes: Objective Response Rate was defined as the percentage of patients within each treatment group who achieved Complete Response or Partial Response by Week 25 of the study which was subsequently confirmed by Week 33 ± 14 days (or early discontinuation), in accordance with RECIST 1.1.
Abbreviations: CI=confidence interval; EU=European Union; ITT=intent-to-treat; n/N=number of patients with observation/total number of patients; RECIST=Response Evaluation Criteria in Solid Tumors.
a. Risk Ratio and associated 95% CI were based on the Miettinen and Nurminen method.

In the PF-05280014 treatment group, 220 patients (62.5%) had PR or CR, 76 patients (21.6%) had Stable Disease, and 18 patients (5.1%) had PD. In the trastuzumab-EU treatment group, the corresponding numbers (%) of patients were 236 (66.5%), 74 (20.8%), and 11 (3.1%). Overall, 72 patients (10.2%) had an Indeterminate response (38 [10.8%] and 34 [9.6%] in the PF-05280014 and trastuzumab-EU groups, respectively).

Table 6 Summary of Best Overall Response Derived from Central Radiology Assessments – ITT Population

Number (%) of Subjects Overall Response Category	PF-05280014 (N=352)	Trastuzumab-EU (N=355)	Risk Difference[a] Estimate (95% CI)
Complete Response (CR)	10 (2.8)	13 (3.7)	-0.821 (-3.659, 1.929)
Partial Response (PR)	210 (59.7)	223 (62.8)	-3.158 (-10.312, 4.025)
Objective Response Rate (ORR) (n (%), 95%-CI)	220 (62.5) (57.2, 67.6)	236 (66.5) (61.3, 71.4)	-3.979 (-11.005, 3.080)

The ORR was 62.5% and 66.5% in PF-05280014 and trastuzumab-EU treatment groups, respectively. The risk difference of the ORR between the 2 treatment groups was -3.979% (95% CI: -11.005%, 3.080%) (PF-05280014 minus trastuzumab-EU). The 95% CI was within the equivalence margin of -13% to 13% recommended by Scientific Advice.

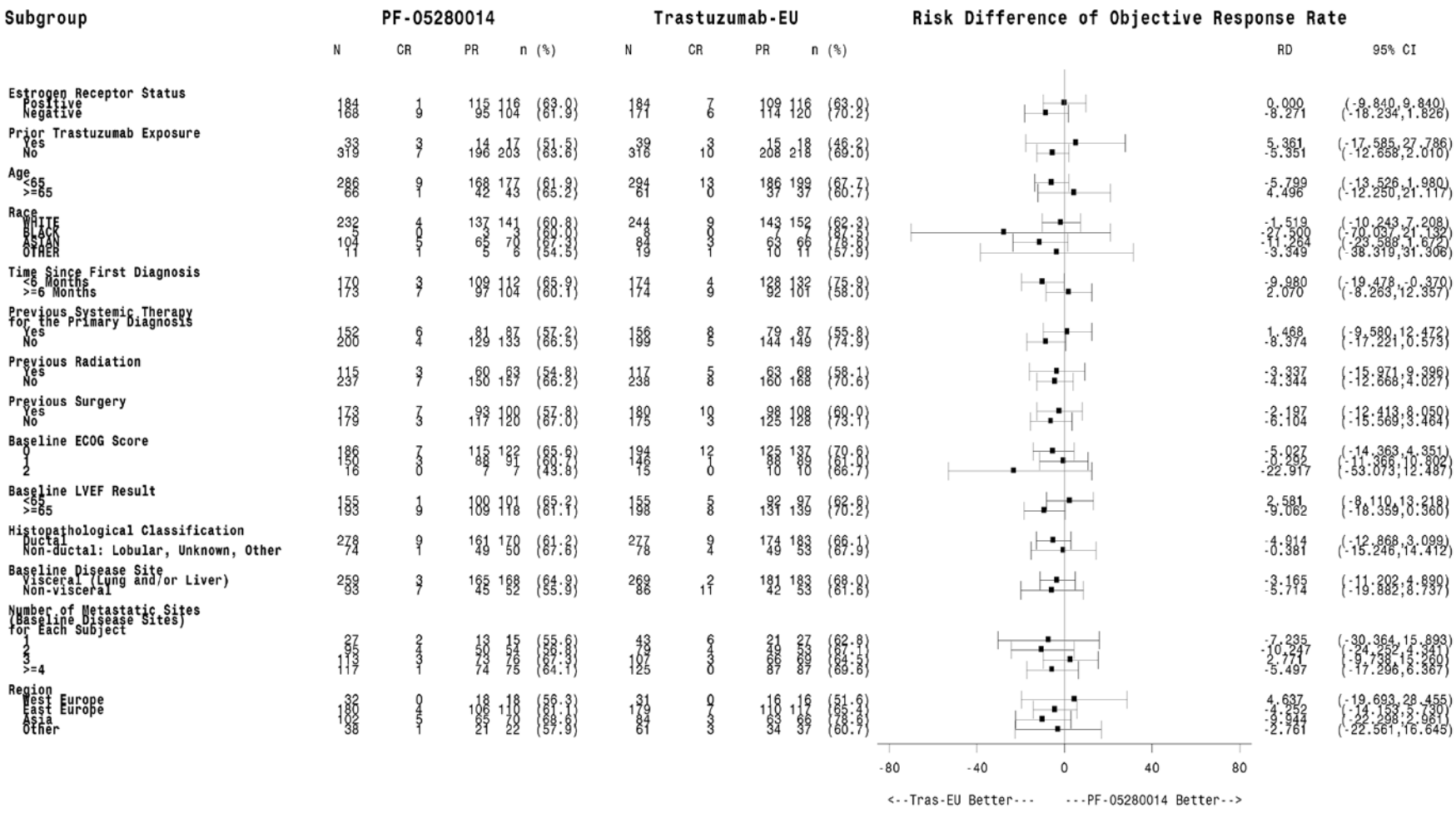
Sensitivity analyses

An additional analysis for equivalence of ORR adjusting for covariates (prior adjuvant trastuzumab exposure and/or ER status) indicated similarity between the 2 treatment groups; the risk ratio of ORR was 0.940 with a 95% CI of (0.839, 1.044), which also fell within the specified equivalence margins of 0.80 to 1.25.

The ORR Derived From Central Radiology Assessments – Per Protocol Population was 71.1% and 73.7% in PF-05280014 and trastuzumab-EU treatment groups, respectively. The risk difference of the ORR between the 2 treatment groups was -3.315% (95% CI: -10.656%, 4.039%) (PF-05280014 minus trastuzumab-EU). The 95% CI is within the recommended equivalence margin of -13% to 13%. These results are consistent with the analysis in the ITT population.

The ORR Derived From Investigator Assessments - ITT Population was 65.3% and 65.9% in PF-05280014 and in trastuzumab-EU treatment groups, respectively. The risk difference of the ORR between the 2 treatment groups was -0.570% (95% CI: -7.537%, 6.400%) (PF-05280014 minus trastuzumab-EU). The 95% CI is within the recommended equivalence margin of -13% to 13%.

In order to assess the homogeneity of treatment effects across relevant subgroups, a Forest Plot of Risk Difference of ORR Derived From Central Radiology Assessments (Risk Difference) - ITT Population by stratification factors, main demographic and disease characteristics was provided:



N: Total number; n: ORR number

Figure 1. Forest Plot of Subgroup Analyses of Objective Response Rate Based on Central Radiology Assessments (Risk Difference) - ITT Population

The Risk difference is different from 0 and/or the CIs are wide when only few patients are observed, as e.g. patients with ECOG 2, black race and patients from West Europe.

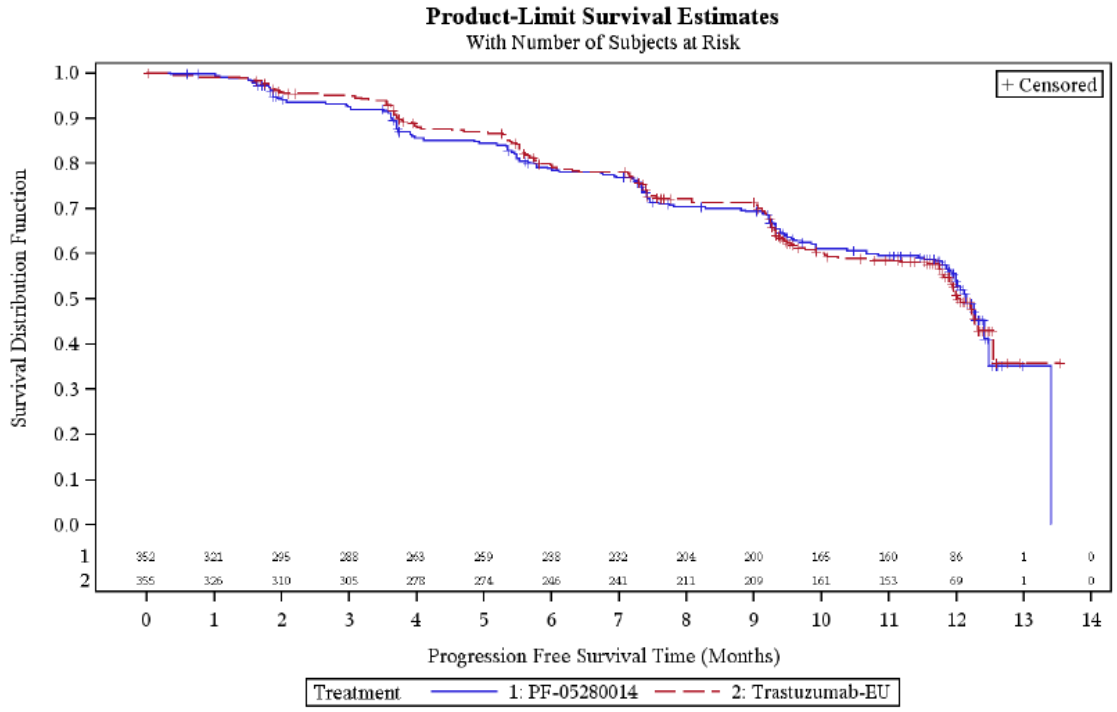
Otherwise the Forest plots of the ITT population (and PP population, data not shown) largely demonstrate homogeneity of treatment effects across relevant subgroups, i.e. stratification factors and main demographic and disease characteristics.

Secondary endpoints

Analyses for the secondary endpoints include all available radiology data up to Week 53 and all available data up to 378 days post-randomization.

1-Year Progression-Free Survival Rate

Using all available data in the data snapshot up to 1-year post randomization, 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 median time to PFS was 12.16 months in the PF-05280014 group and 12.06 months in the trastuzumab-EU group.



Source data: Figure 14.2.4.1.
Abbreviations: EU=European Union; ITT=intent-to-treat.

Figure 2 Kaplan-Meier Plot of Progression-Free Survival Based on Central Radiology Assessments – ITT Population

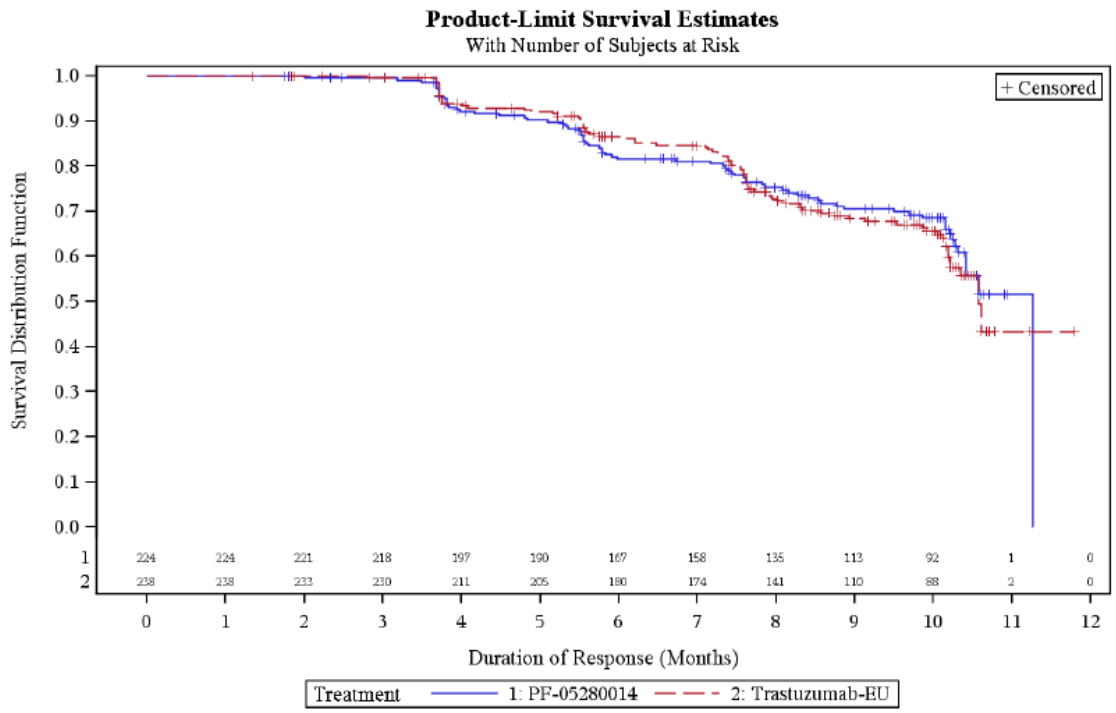
Table 7 Analysis of Progression-Free Survival Derived From Central Radiology Assessments – ITT Population

Number (%) of Patients	PF-05280014 (N=352)	Trastuzumab-EU (N=355)
Progressed or died	144 (40.9)	148 (41.7)
Censored	208 (59.1)	207 (58.3)
Kaplan-Meier estimate of PFS at 6-months (95% CI)	0.79 (0.74, 0.83)	0.80 (0.75, 0.84)
Kaplan-Meier estimate of PFS at 9-months (95% CI)	0.69 (0.64, 0.74)	0.71 (0.66, 0.76)
Kaplan-Meier estimate of PFS at 1-year (95% CI)	0.54 (0.48, 0.60)	0.51 (0.45, 0.57)
Kaplan-Meier estimates of PFS (months) quartiles (95% CI)[a]		
25%	7.33 (5.75, 8.28)	7.39 (5.98, 9.07)
50% (median)	12.16 (11.93, 12.48)	12.06 (11.79, -)
75%	13.40 (12.48, 13.40)	-
Stratified log-rank test[b]	0.505	
Hazard ratio[c]		
PF-05280014 vs trastuzumab-EU	1.00	
95% CI of hazard ratio	(0.80, 1.26)	

Source Data: Table 14.2.4.1.
Censored: Patients who did not progress or died were censored.
Note: Applicable clinical eCRF data including concomitant radiotherapy for target lesions, concomitant surgical resection of target lesions and follow-up anticancer therapy were implemented for censoring in the derived analysis of PFS based on central radiology assessments.
Abbreviations: CI=confidence interval; eCRF=electronic Case Report Form; ER=estrogen receptor; EU=European Union; ITT=intent-to-treat; N=total number of patients; PD=progressive disease; PFS=progression-free survival; vs=versus.
a. 95% CI based on the Brookmeyer and Crowley method.
b. 1-sided p-value from the log-rank test stratified by prior trastuzumab exposure (Yes/No) and ER status (ER positive vs. ER negative).
c. Hazard ratio from a Cox Proportional Hazards model with prior trastuzumab exposure (Yes/No) and ER status (ER positive vs. ER negative) as strata. A hazard ratio=1 indicated no difference in PD/death between PF-05280014 and trastuzumab-EU; >1 indicated an increase in PD/death in PF-05280014; <1 indicated an increase in PD/death in trastuzumab-EU.

Duration of Response

There were 224 (63.6%) and 238 (67.0%) patients who had confirmed response without subsequent progression or death in the PF-05280014 group and the trastuzumab-EU group, respectively. The median DOR was observed as 11.27 months for the PF-05280014 group and 10.58 months for the trastuzumab-EU group.

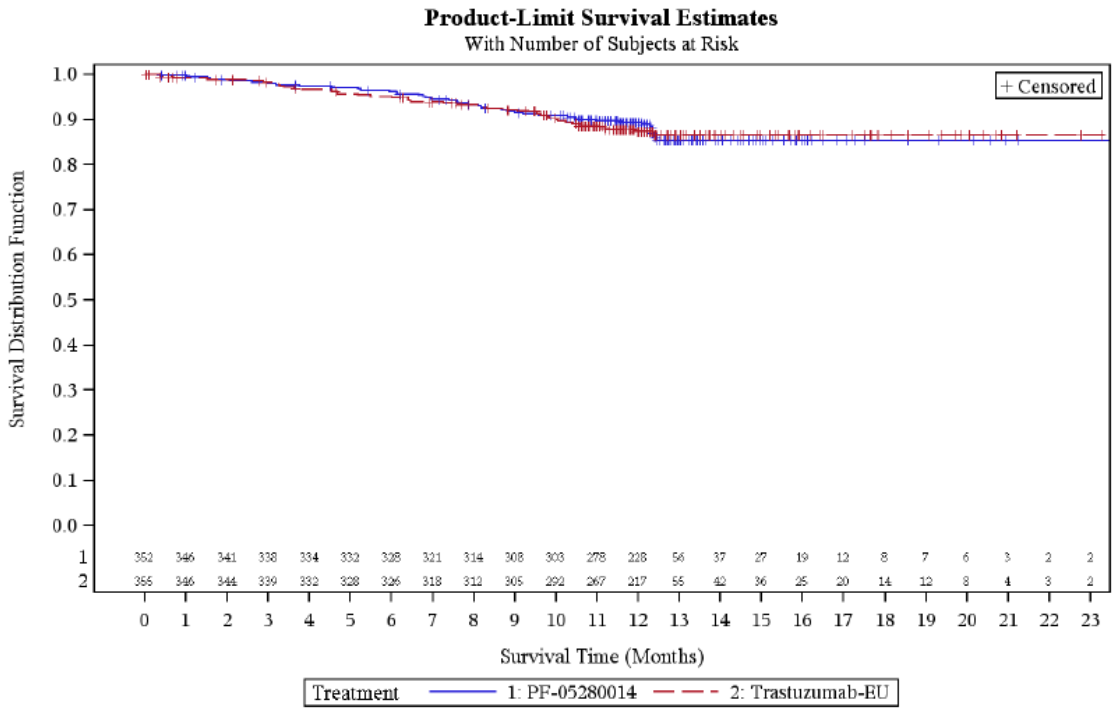


Source Data: Figure 14.2.6.1.
Abbreviations: EU=European Union; ITT=intent-to-treat.

Figure 3 Kaplan-Meier Plot of Duration of Response Based on Central Radiology Assessments – ITT Population

1-Year Overall Survival Rate

The median time to death could not be estimated in either treatment group due to the small proportion of deaths observed. The hazard ratio when comparing overall survival (OS) between PF-05280014 and trastuzumab-EU was 1.004, with 95% CI of (0.655, 1.539). The stratified log-rank test resulted in a 1-sided p-value of 0.507, indicating no statistically significant difference between the 2 treatment groups.



Source Data: Figure 14.2.5.1.
Abbreviations: EU=European Union; ITT=intent-to-treat.

Figure 4 Kaplan-Meier Plot of Overall Survival – ITT Population

Table 8 Analysis of Overall Survival – ITT Population

	PF-05280014 (N=352) n (%)	Trastuzumab-EU (N=355) n (%)
Number of deaths	42 (11.9)	43 (12.1)
Cause of death		
Disease under study	38 (10.8)	32 (9.0)
Study drug toxicity	0	3 (<1.0)
Other	4 (1.1)	9 (2.5)
Number censored	310 (88.1)	312 (87.9)
Reason for censorship		
Patient remains in Follow-up	276 (78.4)	266 (74.9)
Patient no longer being followed for survival	34 (9.7)	46 (13.0)
Number of patients with last contact date >1 year prior to data cutoff date	105 (29.8)	104 (29.3)
Survival probability at Month 6[a] (95% CI[b])	96.23 (93.59, 97.79)	95.09 (92.21, 96.92)
Survival probability at Month 9[a] (95% CI[b]	91.79 (88.33, 94.26)	92.12 (88.72, 94.53)
Survival probability at Month 12[a] (95% CI[b])	89.31 (85.48, 92.17)	87.36 (83.27, 90.51)
Kaplan-Meier estimates of time-to-event (month) Quartiles (95% CI)[c]		
25%	-	-
50% (median)	-	-
75%	-	-
Versus trastuzumab-EU		
Hazard ratio[d]	1.004	
95% CI of hazard ratio	(0.655, 1.539)	
P-value[e]	0.507	

Source Data: Table 14.2.5.1.
Abbreviations: CI=confidence interval; ER=estrogen receptor; EU=European Union; HR=hazard ratio; ITT=intent-to-treat; n/N=number of patients with observation/total number of patients.
a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley Method. The quartiles not presented were not calculable.
d. Based on the Cox Proportional Hazards model stratified by prior trastuzumab exposure (Yes/No) and ER status (positive versus negative). Assuming proportional hazards, a HR <1 indicates a reduction in hazard rate in favor of PF-05280014; a HR >1 indicates a reduction in favor of trastuzumab-EU.
e. 1-sided p-value from the log-rank test stratified by prior trastuzumab exposure (Yes/No) and ER status.

The updated 1-year efficacy data for all patients in the study are provided in the clinical study report (CSR) B3271002 Week 53 Analysis and are based on a cutoff date of 11 January 2017 when all patients had either completed the Week 53 tumor assessment or discontinued study drug earlier than the Week 53 visit.

Table 9 Analysis of Progression-Free Survival Derived From Central Radiology Assessments - ITT Population

Number (%) of Patients	PF-05280014 (N=352)	Trastuzumab-EU (N=355)
Progressed or died	144 (40.9)	148 (41.7)
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Kaplan-Meier estimate of PFS at 1-year (95% CI)	0.54 (0.48, 0.60)	0.51 (0.45, 0.57)
Kaplan-Meier estimates of PFS (months) quartiles (95% CI)[a]		
25%	7.33 (5.75, 8.28)	7.39 (5.98, 9.07)
50% (median)	12.16 (11.93, 12.48)	12.06 (11.79, -)
75%	13.40 (12.48, 13.40)	-
Stratified log-rank test[b]	0.505	
Hazard ratio[c]		
PF-05280014 vs trastuzumab-EU	1.00	
95% CI of hazard ratio	(0.80, 1.26)	

Source Data: Table 14.2.4.1.
Censored: Patients who did not progress or died were censored.

The median time to PFS and the percentage of patients who progressed/died or were censored were comparable between the 2 treatment groups. 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 (95% CI) survival rate was 89.31% (85.48%, 92.17%) compared with 87.36% (83.27%, 90.51%) for the PF-05280014 and trastuzumab-EU groups, respectively. The median time to death was not estimable due to too few deaths.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10 Summary of Efficacy for Trial B3271002

Title: A Phase 3 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					
Study identifier	B3271002				
Design	Parallel-group, active-controlled				
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 cycles (~ 6 month) not applicable not applicable		
Hypothesis	Equivalence				
Treatments groups	PF-05280014		IV 4 mg/kg bwt (loading dose), 2 mg/kg bwt (weekly until Week 33) N = 352		
	Trastuzumab-EU		IV 4 mg/kg bwt (loading dose), 2 mg/kg bwt (weekly until Week 33) N = 355		
Endpoints and definitions	Primary endpoint	ORR	CR or PR by Week 25 [±14 days] and confirmed on a follow-up assessment as assessed by RECIST 1.1 (local assessment)		
	Secondary endpoint	1 year PFS rate	Based on time from date of randomization to first PD or death due to any cause in the absence of documented PD.		
		DOR	Time from date of the first documented objective tumour response (CR or PR) to the first documented progression of disease (PD) or to death due to any cause in the absence of documented PD		
		1 year OS rate	Based on time from date of randomization to death due to any cause.		
Database lock	17/02/2017				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	ITT population, Week 33				
Descriptive statistics and estimate variability	Treatment group	PF-05280014	Trastuzumab-EU		
	Number of subject	352	355		
	ORR	220 (62.5%)	236 (66.5%)		
	95%-CI	(57.2%, 67.6%)	(61.3%, 71.4%)		
Effect estimate per comparison	ORR	Comparison groups	PF-05280014 vs. Trastuzumab-EU		
		Risk ratio	0.94		
		95%-CI	(0.842, 1.049)		
		Equivalence margin	(0.8, 1.25)		
Notes	Sensitivity analyses (i.e. stratified analysis), analysis based on the PP population, as well as analyses using investigator-rated ORR support the results of the primary endpoint analysis concluding similarity. The approach chosen by the Applicant				
Analysis description	**Secondary analyses**				
Analysis population and time point description	ITT population, Week 53				
Descriptive statistics and estimate variability	Treatment group	PF-05280014	Trastuzumab-EU		
	Number of subject	208	207		
	1 year PFS rate	54%	51%		
	95%-CI	(48%, 60%)	(45%, 57%)		

	DOR median (months)	12.16	12.06	
	95% CI	(11.93, 12.48)	(11.79, -)	
	Survival probability at 1 year	89.31%	87.36%	
	95% CI	(85.48%, 92.17%)	(83.27%, 90.51%)	
Effect estimate per comparison		Comparison groups	PF-05280014 vs. Trastuzumab-EU	
	PFS	HR	1.00	
		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)	
Notes	The results for the secondary parameter do not indicate any treatment difference			

Supportive study

Study B3271004

This was an international, double-blind, randomized, Phase 3 clinical trial evaluating the PK, efficacy, safety, and immunogenicity of PF-05280014. Patients were randomized (1:1) 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 by investigator report (ER positive versus ER negative) and by progesterone receptor status (progesterone receptor positive versus progesterone receptor negative).

- *Study participants*

Inclusion criteria (excerpt)

1. Female patients aged 18 years or older.

2. Evidence of a personally signed and dated ICD indicating that the patient (or a legal representative) had been informed of all pertinent aspects of the study

3. Histologically confirmed HER2-overexpressing invasive breast cancer.

4. Plan for definitive surgical resection of breast tumor (ie, lumpectomy or mastectomy, and SN biopsy or ALND).

5. Plan for neoadjuvant chemotherapy.

6. Documentation of HER2 gene amplification or overexpression

Exclusion Criteria (excerpt)

1. Patients who were 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 were Pfizer employees directly involved in the conduct of the trial.

2. Bilateral breast cancer.

3. Inflammatory breast cancer.

4. Presence of known distant metastases (determined by Principal Investigator).

5. Received prior treatment, including chemotherapy, endocrine therapy, biologic therapy, radiation or surgery with the exception of diagnostic biopsy for primary breast cancer.

6. Other concomitant active malignancy or history of malignancy in the past 5 years except treated basal cell carcinoma of the skin or carcinoma in-situ of the cervix.

7. Pre-existing clinically significant (≥Grade 2) peripheral neuropathy.

8. Any history of documented or current congestive heart failure, current high-risk uncontrolled arrhythmias, current angina pectoris requiring a medicinal product, current clinically significant valvular disease, current evidence of transmural infarction on electrocardiogram (ECG), or current poorly controlled hypertension.

- *Treatments*

PF-05280014/trastuzumab-EU (IV): first administration on Day 1, Cycle 1 was a loading dose of 8 mg/kg; subsequent infusions followed with a dose of 6 mg/kg q3w for 6 cycles

Taxotere (IV): 75 mg/m2 on Day 1 of each Cycle

Carboplatin (IV): AUC 6, IV on Day 1 of each Cycle.

Patients were to undergo a definitive surgical resection of their primary tumor, as part of their standard of care 3 to 7 weeks after completion of the last dose at Cycle 6.

Statistics

The hypothesis to be tested in this study is the percentage of patients with steady state Cycle 5 Ctrough (Cycle 6 pre-dose) >20 µg/mL of trastuzumab-Pfizer is similar to EU-approved trastuzumab, using a lower limit of -12.5%.

To test for non-inferiority of PF-05280014 to trastuzumab-EU, the null hypothesis will be tested with α=0.025 (one-sided). A 95% confidence interval for the difference (PF-05280014 minus trastuzumab-EU) between the two treatment groups will be calculated. If the lower limit of the confidence interval is greater than -12.5%, the null hypothesis is rejected and PF-05280014 is considered non-inferior to trastuzumab-EU.

Efficacy endpoints were analyzed using 2 populations:

- The PP population was the primary analysis set. The PP population was defined as all patients who:

  1. Had HER2-positive breast cancer and randomized into the study;
  2. Received 6 cycles of PF-05280014 or trastuzumab-EU treatment;
  3. Had no temporary delays of PF-05280014 or trastuzumab-EU treatment lasting more than 1 week;
  4. Had no other significant protocol deviations.

- The ITT population was defined as all patients who were randomized to study drug assignment designated according to initial randomization. The ITT population was used as sensitivity analyses of the efficacy endpoints.

  - The percentage of patients in each treatment group who have pathologic complete response (pCR) as well as ORR was determined, using the denominator as the number of patients in the analysis population for each treatment group, excluding patients who were never going to receive surgery. The difference in percentage of patients between the 2 treatment groups was estimated, along with a

95% CI, using the normal approximation to the binomial distribution, adjusting for the randomization strata. These analyses were performed in the PP population, with a sensitivity analysis being performed in the ITT population using the same methods.

- *Randomization*

Patients were randomized (1:1) 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), as per investigator report.

- *Participant flow*

There were 226 patients randomized to the double-blind treatment (Table 11); 1 patient was randomized but did not receive study drug. Of the 225 patients treated, 215 patients (109 patients in the PF-05280014 group and 106 patients in the trastuzumab-EU group) completed the study.

All randomized patients (n=226) were included in the ITT population. Of these, 190 patients (101 patients in the PF-05280014 group and 89 patients in the trastuzumab-EU group) met the requirements for the PP population, which was used for the primary endpoint analysis. For the safety population, 225 patients (113 patients in the PF-05280014 group and 112 patients in the trastuzumab-EU group) were included.

Table 11 Patient Evaluation Groups

	PF-05280014	Trastuzumab-EU	Total
Number (%) of Patients			
Screened			279
Assigned to Study Treatment	114	112	226
Treated	113 (99.1)	112 (100.0)	225 (99.6)
Completed	109 (95.6)	106 (94.6)	215 (95.1)
Discontinued[a]	4 (3.5)	6 (5.4)	10 (4.4)
Analyzed for Efficacy:			
ITT Population	114 (100.0)	112 (100.0)	226 (100.0)
PP Population	101 (88.6)	89 (79.5)	190 (84.1)
Analyzed for Safety:			
AEs	113 (99.1)	112 (100.0)	225 (99.6)
Laboratory data	111 (97.4)	112 (100.0)	223 (98.7)

Source: Table 14.1.1.1
Note: Patient 10011010 was randomized but not treated; this patient was included in the ITT population, but not in the safety population.
Abbreviations: AE=adverse event; EU=European Union; ITT=intent-to-treat; PP=per protocol.
a. Discontinuations from study.

- *Outcomes/endpoints*

The primary endpoint was the percentage of patients with steady state (Cycle 5) Ctrough (Cycle 6 pre-dose) >20 µg/mL between PF-05280014 versus trastuzumab-EU.

Secondary endpoints included pCR, ORR, safety, immunogenicity, and selected trough drug concentrations.

Results

Numbers analyzed

There were 226 patients randomized to the double-blind treatment who were included in the ITT population. Of these, 190 patients met the requirements for the PP population, which was used for the primary endpoint analysis.

Baseline data

Demographic characteristics were comparable across treatment groups). All patients were female and over 18 years of age, in accordance with the protocol requirements. Over half of all patients were 45 to 64 years of age (54.4%) and 97.8% had the reported race of White.

Table 12 Demographic Characteristics – ITT Population

	PF-05280014 (N=114)	Trastuzumab-EU (N=112)	Total (N=226)
Number (%) of Patients	**n (%)**	**n (%)**	**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)

Source: Table 14.1.2.1
Note: Baseline was defined as the value recorded at Cycle 1 Day 1. If this value was missing, the value recorded at Screening was used.
Body Mass Index was defined as weight/(height × 0.01)^2
Abbreviations: EU=European Union; ITT=intent-to-treat; n/N=number of patients; SD=standard deviation.

Further, there were 112 patients (58 patients [50.9%] in the PF-05280014 group and 54 patients [48.2%] in the trastuzumab-EU group) with positive ER status and 81 patients (41 patients [36.0%] in the PF-05280014 group and 40 patients [35.7%] in the trastuzumab-EU group) with positive progesterone receptor status.

Investigator-reported medical history (other than the primary diagnosis) was reported for 91 (79.8%) patients in the PF-05280014 group and 78 (69.6%) patients in the trastuzumab-EU group. The most commonly reported conditions were pancreatitis chronic, cholecystitis chronic, obesity, uterine leiomyoma and hypertension.

Outcomes and estimation

pCR

Pathological response assessments in the PP population revealed that the pCR for PF-05280014 and trastuzumab-EU was 47.0% (95% CI: 36.9% to 57.2%) and 50.0% (95% CI: 39.0% to 61.0%), respectively. The estimated stratified difference between PF-05280014 and trastuzumab-EU was -2.81%

(95% CI: -16.58% to 10.96%). Analysis of patients with pCR in the ITT population (pCR for PF-05280014 and trastuzumab-EU was 45.4% [95% CI: 35.8% to 55.2%] and 49.1% [95% CI: 39.2% to 59.0%]). Data on tumor stage of patients (i.e. disease stage [I-IV], T-stage, N-stage) and also breast conservation surgery are presented and are comparable. The results of pathological response assessments are summarized in Table 13 for the PP population. In the PF-05280014 treatment group, 47 patients (46.5%; 95% CI: 36.9% to 57.2%) 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, as the patient completed the study but did not have surgery. In the trastuzumab-EU treatment group, 43 patients (48.3%; 95% CI: 39.0% to 61.0%) 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; 1 patient completed the study but did not have surgery, and 2 patients completed treatment but were lost-to-follow-up prior to surgery.

Table 13 Summary Results of Pathological Response Assessments – PP Population

	PF-05280014 (N=101)	Trastuzumab-EU (N=89)
Response Category, n (%)		
Pathological Complete Response	47 (46.5)	43 (48.3)
Pathological Partial Response	51 (50.5)	40 (44.9)
No Pathological Response	2 (2.0)	3 (3.4)
Not Done[a]	1 (1.0)	3 (3.4)

Source: Table 14.2.3.1
Note: Where responses have been provided for both breast and axilla locations, the response for breast location has been used as the pathological response.
Abbreviations: EU=European Union; N=number of patients; PP=per protocol.
a. PF-05280014: 1 patient completed study but had no surgery therefore pathology data not recorded or response assessed. Trastuzumab-EU: 2 patients completed treatment but were lost-to-follow-up prior to surgery and 1 patient completed study but had no surgery therefore pathology data not recorded or response assessed

Table 14 Analysis of Number (%) of Patients With pCR – PP Population

	PF-05280014 (N=101)	Trastuzumab-EU (N=89)
Patients who have had surgery	100 (99.0)	86 (96.6)
Number (%) with Complete Pathological Response	47 (47.0)	43 (50.0)
Approximate 95% CI	[36.9, 57.2]	[39.0, 61.0]
Estimated difference between PF-05280014 and Trastuzumab-EU (unstratified)	-3.00	
Standard error for the difference	7.35	
Approximate 95% CI (unstratified) for the difference	[-17.40, 11.40]	
Estimated difference between PF-05280014 and Trastuzumab-EU (stratified)	-2.81	
Standard error for the difference	7.03	
Approximate 95% CI (stratified) for the difference	[-16.58, 10.96]	

Source: 14.2.3.2
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).
The denominator for percentages included only patients who have had surgery.
Abbreviations: CI=confidence interval; pCR= pathologic complete response; EU=European Union; ER=estrogen receptor; N=number of patients; PP=per protocol.

ORR

A summary of overall tumor response based on central radiology assessments at Cycle 6/EOT is provided in Table 15 for the PP population. 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. Across both arms there were 3 patients that had missing images for assessment at Cycle 6/EOT, 1 patient was not assessed as the images did not include the needed field of view and 2 patients had no scans assessed as all scanning was performed by mammography or ultrasound.

Table 15 Summary Results of Overall Tumor Response Based on Central Radiology Assessments at Cycle 6/End of Treatment – PP Population

	PF-05280014 (N=101)	Trastuzumab-EU (N=89)
Response Category, n (%)		
Complete Response	3 (3.0)	0 (0.0)
Partial Response	86 (85.1)	73 (82.0)
Stable Disease	7 (6.9)	4 (4.5)
Progressive Disease	2 (2.0)	1 (1.1)
Non-Evaluable	1 (1.0)	6 (6.7)
Non-Complete Response/ Non-Progressive Disease	1 (1.0)	3 (3.4)
Missing	1 (1.0)	2 (2.2)

Source: Table 14.2.4.1
Abbreviations: EU=European Union; N=number of patients; PP=per protocol.

Table 16 Analysis of Objective Response Rate Based on Central Radiology Assessments – PP Population

	PF-05280014 (N=101)	Trastuzumab-EU (N=89)
Overall Response Category by Cycle 6/EOT		
Complete Response	3 (3.0)	0
Partial Response	86 (85.1)	73 (82.0)
Objective Response Rate		
n (%)	89 (88.1)	73 (82.0)
95% CI	[80.2, 93.7]	[72.5, 89.4]
Estimated difference between PF-05280014 and Trastuzumab-EU (unstratified)	6.10	
Standard error for the difference	5.19	
Approximate 95% CI (unstratified) for the difference	[-4.08, 16.27]	
Estimated difference between PF-05280014 and Trastuzumab-EU (stratified)	5.96	
Standard error for the difference	5.09	
Approximate 95% CI (stratified) for the difference	[-4.01, 15.94]	

Source: Table 14.2.4.2
Note: ORR was defined as the percentage of patients within each treatment group who achieved complete response or partial response by Cycle 6/EOT, in accordance with RECIST 1.1.
Stratified analysis was based on the normal approximation to the binomial distribution, adjusting for the randomization strata of primary tumor size (<5cm, or ≥5cm), ER status (ER positive versus ER negative) and by progesterone receptor status (progesterone receptor positive versus progesterone receptor negative).
Abbreviations: CI=confidence interval; EOT=end of treatment; ER=estrogen receptor; EU=European Union; N=number of patients; ORR=objective response rate; PP=per protocol; RECIST=Response Evaluation Criteria in Solid Tumors.

Concordance analysis of overall tumor response of central radiology review versus investigator assessment at Cycle 6/EOT has been conducted. The disagreement rate was 19.3% for PF-05280014 and 17.6% for trastuzumab-EU; the difference between PF-05280014 and trastuzumab-EU was 1.67%. These analyses are presented for the ITT population.

2.5.2. Discussion on clinical efficacy

The efficacy similarity evaluation in the framework of the current application for marketing authorization for the PF-05280014 trastuzumab biosimilar of Herceptin in the indications of metastatic breast cancer, early breast cancer and metastatic gastric cancer was conducted based on two trials. The Applicant aims to show similarity only for IV administration; SC administration is not applied for.

Design and conduct of clinical studies

Study B3271002

The pivotal trial, B3271002 was a multicentre, double-blind, randomized, parallel-group, study to compare the efficacy and safety of PF-05280014 plus paclitaxel versus Herceptin plus paclitaxel in patients with HER2-positive MBC with continuation of single-agent PF-05280014 or combination treatment versus Herceptin or combination treatment for patients who had at least stable disease (SD) in order to evaluate continued safety and immunogenicity. After discontinuation of treatment, patient survival status was and further will be collected by telephone contact every 2 months (±14 days) until death or 1 year from patient randomization and at least 6 months following receipt of last study drug, whichever is longer.

The trial itself was split in two parts, with the D80 data package containing only data from the first part as only 2% of patients have actually completed the study and 79% of patients are still being followed. Treatment in Part 1 was foreseen for 25 weeks during which PF-05280014 plus a taxane or Herceptin plus a taxane was administered for a minimum of 6 treatment cycles of 4 weeks each. The hypothesis to be tested in this study was that the risk ratio of ORR of PF-05280014 versus that of trastuzumab-EU by Week 25 (and subsequently confirmed by Week 33) was within a pre-specified margin of 0.80 to 1.25. Tumour assessments were conducted Weeks 9, 17, 25, 33, 41 and 53 and then every 12 weeks.

Concomitant chemotherapy

Only paclitaxel was allowed as taxane treatment which supports homogeneity of patient population. However, the chemotherapy regimen used in this pivotal trial was 80 mg/m2 paclitaxel and not as in the label paclitaxel (175 mg/m2 over 3 hours every 21 days for at least six cycles), however, dosage was aligned with Gasparini et al..

Dosing

Dosing of the treatments was based on the dosing of the reference product as prescribed in the product's SmPC. Taxanes were dosed as per Gasparini et al.

Eligibility criteria

The patients that were deemed eligible for enrollment had to have histologically confirmed diagnosis of breast cancer with at least 1 metastatic targetable lesion, and not having received prior systemic therapy in the metastatic disease setting. Particularly observance of maximum anthracycline doses is appreciated and adequate. HER2 assays had to be either approved by the FDA or be a Sponsor-provided central laboratory; OR HER2 local testing using both an IHC and an in-situ hybridization analytical test which ensured proper identification of biomarker positive patients.

The choice for MBC as target in a biosimilarity exercise could be considered as not being the most optimal in terms of homogeneity or sensitivity. A setting in neoadjuvant early breast cancer evaluating the pCR might

be more appropriate in regards to those aspects, the choice of MBC is not wrong per se as long as effort is made to control and minimise heterogeneity.

Sample size & randomization

A sample size of 630 patients (315 per treatment group) would provide approximately 85% power for achieving equivalence for the risk ratio of ORR of PF-05280014 versus that of trastuzumab-EU by Week 25 with a 2.5% type I error rate (1-sided) and an equivalence margin of [0.8, 1.25] assuming an ORR of 60% in both treatment groups. The equivalence margin was based on a meta-analysis of the 3 randomized studies of taxanes vs. taxanes plus trastuzumab.

The ITT population (707 [100.0%] patients) was used for the efficacy analysis and the safety population was used for the analyses of AEs (702 [99.3%] patients) and laboratory data (699 [98.9%] patients).

The PP population (565 [79.9%] patients) was used for sensitivity analyses of the primary and secondary efficacy and biomarker analyses.

Randomization was stratified according to two covariates; ER status and prior trastuzumab therapy. This is considered too restricted and additional factors should have been included.

Overall, the demographic and baseline characteristics were relatively balanced between the treatment groups. About 67% of patients were white, 26% were Asian and 2% black, largely balanced between treatmentgroups.

Slightly more patients with longer disease duration were randomized to the PF-05280014 arm (median 6.7 vs 6.1 months), but this would rather be to a disadvantage.

Otherwise baseline characteristics (age, ECOG, histopathologic disease, IHC results, LVEF status, ER status, prior trastuzumab) appear balanced between the groups.

There were slightly more liver metastases in the trastuzumab-EU arm (47% vs 42%) and slightly more lung metastases in the PF-05280014 arm (53% vs 52%).

A summary of previous systemic therapy for breast cancer in the neoadjuvant/adjuvant setting and also prior radiation therapy for the primary diagnosis was provided and is similar at baseline.

Efficacy data and additional analyses

Primary endpoint

Similarity between PF-05280014 and trastuzumab-EU was statistically demonstrated for the primary efficacy endpoint as specified for this trial, ORR derived from central radiology assessments, and showed a risk ratio of 0.940 (PF-05280014 over trastuzumab-EU), with a 95% CI of (0.842, 1.049), which fell entirely within the 0.80 to 1.25 equivalence margin.

However, the primary biosimilar assessment only relates to the risk ratio. The ORR derived from central radiology assessments for the ITT population was 62.5% and 66.5% in PF-05280014 and trastuzumab-EU treatment groups, respectively. The risk difference of the ORR between the 2 treatment groups was -3.979% (95% CI: -11.005%, 3.080%) (PF-05280014 minus trastuzumab-EU). The 95% CI was within the recommended equivalence margin of -13% to 13%.

The results from primary analysis are supported by the results of several sensitivity analyses.

Secondary endpoints

Using all available data in the data snapshot up to 1-year post randomization, 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 median time to PFS was 12.16 months in the PF-05280014 group and 12.06 months in the trastuzumab-EU group and the KM curves overlap which confirms similarity of the two products.

There were 224 (63.6%) and 238 (67.0%) patients who had confirmed response without subsequent progression or death in the PF-05280014 group and the trastuzumab-EU group, respectively. The median DOR was observed as 11.27 months for the PF-05280014 group and 10.58 months for the trastuzumab-EU group. The percentage of all patients who achieved confirmed response (CR or PR, with or without subsequent progression or death) was comparable between the 2 treatment groups and the KM curves overlap further supporting similarity.

The percentage of patients who died was comparable across the 2 treatment groups. 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) and the KM curves are largely superimposable thus further supporting similarity.

In summary, all analyses done in this regard fell within the predefined primary endpoint margins, thus supporting that the primary analysis findings are robust.

Supportive Study B3271004

The supportive study, Study B3271004, was an international, double-blind, randomized, Phase 3 clinical trial in patients with operable HER2-positive breast cancer in the neoadjuvant setting.

The primary endpoint was a PK endpoint, i.e. the percentage of patients with steady state (Cycle 5) Ctrough (Cycle 6 pre-dose) >20 µg/mL between PF-05280014 versus trastuzumab-EU in patients with operable HER2-positive breast cancer who received therapy together with Taxotere and carboplatin in the neoadjuvant setting. A central bioanalytical laboratory conducted the PK sampling required for analysis of the primary endpoint.

Secondary endpoints were not statistically powered to evaluate similarity in efficacy between PF-05280014 and the reference product and included pCR, ORR, safety, immunogenicity, and selected trough drug concentrations. The most frequently published definition of pCR (absence of invasive neoplastic cells in the breast and lymph nodes following neoadjuvant therapy= tpCR) was used in this study consistent with previous studies in this setting and is acceptable.

All randomized patients (n=226) were included in the ITT population. Of these, 190 patients (101 patients in the PF-05280014 group and 89 patients in the trastuzumab-EU group) met the requirements for the PP population, which was used for the primary endpoint analysis. For the safety population, 225 patients (113 patients in the PF-05280014 group and 112 patients in the trastuzumab-EU group) were included.

Analyses of activity of both trastuzumab products in patients regarding the secondary endpoint pCR appear similar in the PP and ITT population and these results support clinical comparability. Pathological response assessments in the PP population revealed that the pCR for PF-05280014 and trastuzumab-EU was 47.0% (95% CI: 36.9% to 57.2%) and 50.0% (95% CI: 39.0% to 61.0%), respectively. The estimated stratified difference between PF-05280014 and trastuzumab-EU was -2.81% (95% CI: -16.58% to 10.96%), thus

supporting similarity. Results obtained for secondary endpoint ORR, also compared by type of response (CR, PR, SD, PD), central versus investigator review and also percentage of patients with breast conservation surgery (PF-05280014 vs trastuzumab-EU being 13.2% vs 17.0%, respectively) also appear similar. The difference in terms of the secondary endpoint of ORR for PP was 5.96 (PF-05280014 minus trastuzumab-EU) with a 95% CI of (-4.01 to 15.94).

2.5.3. Conclusions on the clinical efficacy

In the confirmatory Study B3271002, the similarity in terms of ORR at Week 25 (and subsequently confirmed by Week 33) has been shown for risk ratio within the a priori defined margins of similarity (0.80 and 1.25), even for the risk difference falling within EMA recommended margins (-13%, 13%).

In this pivotal trial, equivalence with regards to efficacy has also been confirmed both with regard to risk ratio and risk difference and when accounting for stratification factors. These results were confirmed by way of sensitivity analyses and secondary endpoints. PFS, TTP and OS have been fully confirmed by an analysis with data cut off January 2017.

The supportive B3271004 trial was not powered to investigate similarity in efficacy and had a different design and endpoints. Nonetheless, on sufficiently broad level its findings were in line with those of the pivotal trial.

Though the similarity investigation was done in metastatic breast cancer patients, the confirmed similarity in efficacy, as well as the non-clinical, pharmacodynamic and -kinetic similarity between PF-05280014 and Herceptin support extrapolation towards all other indications currently approved for the latter.

2.6. Clinical safety

The safety of PF-05280014 was evaluated in 2 single-dose studies (healthy subjects, Studies B3271001 and B3271006) and 2 multidose studies (patients with HER2-positive metastatic breast cancer, Study B3271002, and patients with operable HER2-positive, early breast cancer, Study B3271004).

Study B3271006 was initiated to estimate the relative risk of pyrexia due to the observation of a higher incidence of pyrexia in Study B3271001.

In studies B3271002 and B3271004 safety was evaluated as part of the secondary objectives. Patients who received at least 1 dose of study drug were included in the safety evaluation. 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.

Patient exposure

A total of 1194 patients/subjects received at least 1 dose of study drug in the 4 studies (PF-05280014 [n=578], trastuzumab-US [n=116], and trastuzumab-EU [n=500]). Of the 1194 patients/subjects, 906 received 2 or more infusions of the study drug (PF-05280014 [n=452] and trastuzumab-EU [n=454]).

Study B3271002 (MBC)

702/707 patients received at least 1 dose of study drug.

The mean (SD) duration of treatment for patients receiving either PF-05280014 or trastuzumab-EU treatment was 41.1 (16.51) weeks and 41.2 (15.83) weeks, respectively. The mean (SD) relative dose was 96.3% [8.08] in the PF-05280014 group and 96.2% [8.40] in the trastuzumab-EU group. The mean duration of paclitaxel treatment was 29.5 (12.28) weeks and 30.8 (12.59) weeks, respectively.

There were 204 patients in the PF-05280014 group and 194 patients in the trastuzumab-EU group who had their treatment regimen switched to 3-weekly trastuzumab monotherapy. There were 9 (2.6%) patients in the PF-05280014 group and 3 (0.8%) patients in the trastuzumab-EU group who were switched to a 3-weekly regimen prior to Cycle 9, Day 1.

Study B3271004 (EBC)

225/226 patients received at least 1 dose of the study drug. Of these, 215 (95.1%) completed the study. A total of 10 (4.4%) patients discontinued from study treatment and 11 (4.9%) patients discontinued from the study.

109 patients in each group received 6 treatment cycles (PF-05280014: 96.5%; trastuzumab-EU: 97.3%) and a mean (SD) relative dose of 100.1% [0.73] in the PF-05280014 group and 100.2% [0.91] in the trastuzumab-EU group, respectively.

Studies B3271001 and B3271006 (HV)

In both studies all subjects received the assigned study drug.

Demographic characteristics

In studies B3271001 and B3271006, patients presented similar demographic characteristics in all arms. In both studies, the majority of subjects were Black, followed by White.

In studies B3271002 and B3271004, baseline characteristics were similar in both treatmentgroups. Although patients treated with PF-05280014 in Study B3271004 were older than patients treated with trastuzumab. The proportion of patients aged 45-64 was 57.5% and 51.8% and patients aged ≥65 was 22.1% and 15.2% in the PF-05280014 group and trastuzumab-EU group, respectively. In Study B3271002, the proportion of Asian patients was higher in the PF-05280014 group (29.5%) than in the trastuzumab-EU arm (23.5%).

Adverse events

Study B3271002 (MBC)

The overall incidence of treatment-emergent adverse events was comparable between the treatment groups (337 (96.6%) patients in the PF-05280014 and 339 (96.0%) patients in the trastuzumab-EU group, respectively) with some slight imbalances in favour of PF-05280014 regarding treatment-related Grade ≥3 events (N=74 [21.2%] vs. N=88 [24.9%]) and in favour of trastuzumab-EU regarding serious and related treatment-emergent adverse events (TEAEs) resulting in treatment discontinuation (N=10 [2.9%] vs. N=6 [1.7%] and N=5 [1.4] vs. N=3 [0.8%], respectively).

Table 17 Treatment-Emergent Adverse Events, All Causalities - Safety Population (Study B3271002) (cutoff date of 11 Jan 2017)

Number(%) of Patients	PF-05280014 (N=349)	Trastuzumab-EU (N=353)	Total (N=702)
Number of TEAEs	2336	2436	4772
Number (%) of patients with			
Any TEAEs	337 (96.6)	339 (96.0)	676 (96.3)
Grade 3 or higher TEAEs	120 (34.4)	129 (36.5)	249 (35.5)
Treatment-related TEAEs	315 (90.3)	314 (89.0)	629 (89.6)
Trastuzumab-related TEAEs	104 (29.8)	101 (28.6)	205 (29.2)
Paclitaxel-related TEAEs	283 (81.1)	281 (79.6)	564 (80.3)
Treatment-related Grade 3 or higher TEAEs	74 (21.2)	88 (24.9)	162 (23.1)
Trastuzumab-related TEAEs	9 (2.6)	11 (3.1)	20 (2.8)
Paclitaxel-related TEAEs	60 (17.2)	60 (17.0)	120 (17.1)
TEAEs resulting in treatment discontinuation	46 (13.2)	41 (11.6)	87 (12.4)
Trastuzumab discontinuation	16 (4.6)	12 (3.4)	28 (4.0)
Paclitaxel discontinuation	39 (11.2)	34 (9.6)	73 (10.4)
Treatment-related TEAEs resulting in treatment discontinuation	40 (11.5)	38 (10.8)	78 (11.1)
Trastuzumab discontinuation	9 (2.6)	8 (2.3)	17 (2.4)
Paclitaxel discontinuation	26 (7.4)	24 (6.8)	50 (7.1)
Serious TEAEs	53 (15.2)	56 (15.9)	109 (15.5)
Treatment-related serious TEAEs	17 (4.9)	16 (4.5)	33 (4.7)
Trastuzumab-related serious TEAEs	5 (1.4)	5 (1.4)	10 (1.4)
Paclitaxel-related serious TEAEs	11 (3.2)	6 (1.7)	17 (2.4)
Serious TEAEs resulting in treatment discontinuation	10 (2.9)	6 (1.7)	16 (2.3)
Trastuzumab discontinuation	6 (1.7)	5 (1.4)	11 (1.6)
Paclitaxel discontinuation	8 (2.3)	4 (1.1)	12 (1.7)
Treatment-related serious TEAEs resulting in treatment discontinuation	5 (1.4)	3 (0.8)	8 (1.1)
Trastuzumab discontinuation	1 (0.3)	2 (0.6)	3 (0.4)
Paclitaxel discontinuation	4 (1.1)	0	4 (0.6)
TEAEs resulting in treatment being temporarily stopped	138 (39.5)	144 (40.8)	282 (40.2)
Trastuzumab temporarily stopped	96 (27.5)	98 (27.8)	194 (27.6)
Paclitaxel temporarily stopped	123 (35.2)	124 (35.1)	247 (35.2)
TEAEs resulting in paclitaxel dose reduction	47 (13.5)	47 (13.3)	94 (13.4)
TEAEs resulting in trastuzumab infusion rate reduced	2 (0.6)	3 (0.8)	5 (0.7)

Source Data: Table 14.3.1.2.1.1.
Serious TEAE=serious TEAE (according to investigator's assessment of serious).
Patients discontinued due to adverse events implied those patients that permanently discontinued the study drug.
TEAE was defined as any event that occurred on or after the first dose of study drug administration or any pre-existing event, which worsened in severity after dosing.
TEAE was defined through last dose of trastuzumab + 70 days.
Treatment-related: related to trastuzumab and/or paclitaxel.
Trastuzumab-related: related only to trastuzumab; paclitaxel-related: related only to paclitaxel.
Note: For number of TEAEs, the event of 'infusion related reaction' was counted, however the number of associated signs and symptoms of infusion related reactions were counted in a separate table (Table 14.3.1.2.1.2).
Abbreviations: EU=European Union; N=total number of patients; TEAE=treatment-emergent adverse event.

The most frequently reported TEAEs (≥20% in either treatment group) were alopecia (189 [54.2%] patients in the PF-05280014 group and 185 [52.4%] patients in the trastuzumab-EU group), anaemia (120 [34.4%] patients in the PF-05280014 group and 131 [37.1%] patients in the trastuzumab-EU group), neutropenia (99

[28.4%] patients in the PF-05280014 group and 91 [25.8%] patients in the trastuzumab-EU group), and peripheral sensory neuropathy (93 [26.6%] patients in the PF-05280014 group and 83 [23.5%] patients in the trastuzumab-EU group).

A total of 120 (34.4%) patients in the PF-05280014 group and 129 (36.5%) patients in the trastuzumab-EU group reported a TEAE of Grade 3 or higher. The most frequently reported Grade 3 or higher TEAE was neutropenia in both the PF-05280014 group (35 [10.0%] patients) and in the trastuzumab-EU group (28 [7.9%] patients). TEAEs of Grade 3 or higher were comparable across the 2 treatment groups.

Treatment-related TEAEs were AEs considered by the investigator as related to trastuzumab or paclitaxel or both. A total of 315 (90.3%) patients in the PF-05280014 group and 314 (89.0%) patients in the trastuzumab-EU group experienced at least 1 treatment-related TEAE. The most frequently reported (>20% in either treatment group) treatment-related TEAEs were alopecia (185 [53.0%] patients in the PF-05280014 group and 184 [52.1%] patients in the trastuzumab-EU group), anaemia (98 [28.1%] patients in the PF-05280014 group and 112 [31.7%] patients in the trastuzumab-EU group), neutropenia (97 [27.8%] patients in the PF-05280014 group and 89 [25.2%] patients in the trastuzumab-EU group), and peripheral sensory neuropathy (91 [26.1%] patients in the PF-05280014 group and 81 [22.9%] patients in the trastuzumab-EU group).

Treatment-related TEAEs ≥ Grade 3 occurred less often in the PF-05280014 group (74 [21.2%] vs. 88 [24.9%]) with anaemia and neutropenia as the leading PTS. Trastuzumab-related TEAEs were considered by the investigator as related to trastuzumab only. Trastuzumab-related TEAEs were observed in 104 (29.8%) patients in the PF-05280014 group and in 101 (28.6%) patients the trastuzumab-EU group. The most frequent trastuzumab-related TEAEs were ejection fraction decreased, IRR, cardiac failure, and rash; with no notable differences in severity, seriousness or reason for treatment discontinuation/ interruption. The rate of Grade ≥3 trastuzumab-related TEAEs were 2.6% and 3.1% in the PF-05280014 and trastuzumab-EU arms, respectively. The most frequent Grade ≥3 trastuzumab-related TEAEs were ejection fraction decreased and cardiac failure with similar incidence between treatmentgroups.

Study B3271004 (EBC)

109 (96.5%) and 106 (94.6%) patients in Study B3271004 experienced at least 1 TEAE in the PF-05280014 group and the trastuzumab-EU group, respectively. The greatest differences between the treatment groups were observed for patients with Grade 3 or 4 AEs (N=43 [38.1%] vs. N=51 [45.5%]) and patients with AEs leading to reduction of dose or temporary discontinuation of treatment (N=37 [32.7%] vs. N=30 [26.8%]).

Table 18 Treatment-Emergent Adverse Events, All Causalities – Safety Population (Study B3271004)

	PF-05280014	Trastuzumab-EU
Patients Evaluable for AEs	**113**	**112**
Number of AEs	569	511
Number (%) of Patients:		
Patients with AEs	109 (96.5)	106 (94.6)
Patients with SAEs	7 (6.2)	6 (5.4)
Patients with Grade 3 or 4 AEs	43 (38.1)	51 (45.5)
Patients with Grade 5 AEs	1 (0.9)	0
Patients Discontinued Due to AEs	1 (0.9)	3 (2.7)
Patients Withdrawn from Treatment Due to AEs	4 (3.5)	3 (2.7)
Patients with Dose Reduced or Temporary Discontinuation Due to AEs	37 (32.7)	30 (26.8)

Source: Module 5.3.3.2 B3271004 Table 14.3.1.2.1.1.

The most frequently reported TEAEs in both treatment groups were alopecia (72 [63.7%] patients in the PF-05280014 group and 69 [61.6%] patients in the trastuzumab- EU group), anaemia (56 [49.6%] patients in the PF-05280014 group and 51 [45.5%] patients in the trastuzumab-EU group), neutropenia (38 [33.6%] patients in the PF-05280014 group and 41 [36.6%] patients in the trastuzumab-EU group), and nausea (38 [33.6%] patients in the PF-05280014 group and 34 [30.4%] patients in the trastuzumab-EU group).

A total of 44 (38.9%) patients in the PF-05280014 group and 51 (45.5%) patients in the trastuzumab-EU group experienced a TEAE of Grade 3 or higher. The most frequently reported Grade 3 or higher TEAE was neutropenia in both the PF-05280014 group (29 [25.7%] patients) and in the trastuzumab-EU group (34 [30.4%] patients). The rate of Grade ≥3 TEAE was comparable in both arms for all the categories, except for alopecia that was slightly higher in the PF-05280014 arm (6.2%) compared to the trastuzumab-EU arm (2.7%). The overall number of patients with Grade ≥3 alopecia was low: 7 (6.2%) patients in the PF-05280014 group and 3 (2.7%) patients in the trastuzumab-EU group.

The overall number of patients with pre-existing medical conditions of musculoskeletal and connective tissue disorders was comparable between the treatment groups despite a slightly higher number of patients with osteoarthritis and osteochondrosis at enrollment. It is understood that arthralgia and myalgia are associated with taxane-based chemotherapy. However, as taxanes were likewise administered in the trastuzumab group a similar incidence should be expected.

When looking at the data from the larger pivotal efficacy trial these differences are not as apparent between the treatment groups although still slightly increased in the PF-05280014 group. However, these events were mainly Grade 1 or 2 and did not result in permanent discontinuation of the study drug.

Treatment-related TEAEs were AEs considered by the investigator as related to trastuzumab, docetaxel, or carboplatin, either individually or in combination. A total of 108 (95.6%) patients in the PF-05280014 group and 106 (94.6%) patients in the trastuzumab-EU group experienced at least 1 treatment-related TEAE. The most frequently reported treatment-related TEAEs were alopecia (72 [63.7%] patients in the PF-05280014 group and 69 [61.6%] patients in the trastuzumab-EU group), anaemia (55 [48.7%] patients in the PF-05280014 group and 48 [42.9%] patients in the trastuzumab-EU group), neutropenia (38 [33.6%] patients in the PF-05280014 group and 41 [36.6%] patients in the trastuzumab-EU group), and nausea (37 [32.7%] patients in the PF-05280014 group and 33 [29.5%] patients in the trastuzumab-EU group).

A total of 41 (36.3%) patients in the PF-05280014 group and 49 (43.8%) patients in the trastuzumab-EU group experienced at least 1 treatment-related TEAE of Common Toxicity Criteria for Adverse Events (CTCAE) Grade 3 or higher with neutropenia and leukopenia as the most frequent PTs. Only few TEAEs were considered related to trastuzumab (4 [3.5%] in the PF-05280014 group and 3 [2.7%] in the trastuzumab-EU group).

Studies B3271001 and B3271006 (HV)

The majority of subjects in Study B3271001 experienced a TEAE: 28 (80.0%) subjects in the PF-05280014 group, 29 (82.9%) subjects in the trastuzumab-EU group, and 29 (82.9%) subjects in the trastuzumab-US group. Most of the TEAEs were Grade 1 or 2 in severity. Five patients experienced Grade ≥3 TEAEs in studies B3271001 (trastuzumab-EU arm: 2) and B3271006 (PF-05280014 arm: 3 [3.7%], trastuzumab-US arm: 1 [1.2%]). There were no AEs of Grade 4 or higher in any treatment group. The incidence of pyrexia was higher in the PF-05280014 group (n=10, 28.6%) than in the trastuzumab-EU group (n=3, 8.6%) and in the trastuzumab-US group (n=2, 5.7%). In order to investigate this higher incidence Study B3271006 was carried out.

The rate of palpitations was 8.6%, 2.9%, and 0%; the rate of abdominal pain was 8.6%, 2.9%, and 2.9%; and the rate of dyspepsia was 5.7%, 0%, and 0%; for the PF-05280014, trastuzumab-EU and trastuzumab-US groups, respectively.

The rate of eye disorders was 22.9% (8 subjects), 2.9% (1 subject), and 14.3% (5 subjects) for the PF-05280014, trastuzumab-EU and trastuzumab-US groups, respectively. In 4 of the 8 subjects in the PF-05280014 group and in 1 of 5 subjects in the trastuzumab-US group , the observed eye disorders were symptoms of IRRs occurring at Day 1. All of the observed eye disorders were Grade 1 and resolved.

Study B3271006 was conducted to estimate the relative risk of pyrexia for PF-05280014 compared to trastuzumab-US. In contrast to Study B3271001 no increased rate of pyrexia was observed for PF-05280014 (5 patients [6.2%] vs. 11 patients [13.6%] in the trastuzumab-US group).

Adverse events of Special Interest (AESIs)

TEAEs of IRRs

In Study B3271002 (MBC) signs and symptoms of infusion-related reactions were observed in 33 (9.5%) and 30 (8.5%) of patients in the PF-05280014 and the trastuzumab-EU groups, respectively. Most of the IRR events were Grade 1-2 in severity. Only 1 patient in the PF-05280014 and 3 patients in the trastuzumab-EU arm experienced Grade ≥3 IRR events.

In Study B3271004 (EBC) no patients experienced IRR events in the PF-05280014 arm compared to 2 patients (1.8%) who did experienced IRR events in the trastuzumab-EU arm.

A slightly higher rate of some IRR events was observed in Study B3271001 in patients treated with PF-05280014 (37.1%) compared to patients treated with trastuzumab-EU (28.6%), and to those treated with trastuzumab-US (20.0%). The rates of pyrexia were 28.6%, 8.6%, and 5.7% for the PF-05280014, trastuzumab-EU, and trastuzumab-US groups, respectively.

Given the high rate of pyrexia found in Study B3271001, a double-blind (Sponsor unblinded), randomized (1:1), single-dose study was performed to compare pyrexia (body temperature ≥38.0°C) between PF-05280014 and trastuzumab-US as the primary objective (Study B3271006). The rate of IRR events in

Study B3271006 were balanced between treatmentgroups. This study, did not find differences in pyrexia between the treatmentgroups. However, tachycardia AEs which were determined by the investigator as treatment related and IRRs were also slightly higher in the PF-05280014 arm (11.1%) compared to the trastuzumab-EU arm (7.4%).

Hypersensitivity and Anaphylactic Reactions

In Study B3271002 the incidence of drug hypersensitivity was comparable between the treatment groups: 3 (0.9%) patients in the PF-05280014 group and 5 (1.4%) patients in the trastuzumab-EU group. Of these, 2 (0.6%) patients in the PF-05280014 group and 1 (0.3%) patient in the trastuzumab-EU group had Grade 3 drug hypersensitivity events. All were considered related to paclitaxel; an event in 1 patient in the trastuzumab-EU group was considered related to both paclitaxel and trastuzumab.

There were 10 (1.4%) patients with a TEAE of (non-drug) hypersensitivity (4 [1.1%] and 6 [1.7%] patients in the PF-05280014 and trastuzumab-EU groups, respectively. All were Grade 1 or 2 in severity.

In Study B3271004 small differences were seen in Study B3271004 with higher rates of hypersensitivity events (3.5% vs. 1.8%) and anaphylactic reactions (0.9% vs. 0%) in the PF-05280014 and trastuzumab-EU arms, respectively; but all of them were Grade 1 or Grade 2.

No hypersensitivity or anaphylactic reactions were reported in studies B3271001 and B3271006.

TEAEs of cardiac toxicity

Studies B3271002 and B3271004 showed comparable rates cardiac disorders between the two treatmentgroups, including cardiac failure, left ventricular dysfunction, and ejection fraction decreased. The most frequently reported cardiac disorders were cardiac failure, tachycardia, and palpitations in Study B3271002 and sinus tachycardia and palpitations in Study B3271004. The rate of Grade ≥3 cardiac disorders was also comparable between treatmentgroups.

The assessment of cardiac disorders and ejection fraction decreased revealed higher rates of palpitations (8.6% vs. 2.9%) and tachycardia (11.1% vs. 7.4%) in patients treated with PF-05280014 in studies B3271001 and B3271006, respectively.

Serious adverse event / deaths / other significant events

Study B3271002 (MBC)

The overall incidence of serious adverse events was comparable between the treatment groups (70 [20.1%] patients in the PF-05280014 group and 73 [20.7%] patients in the trastuzumab-EU group) with a slightly higher incidence of disease progression (32 [9.2%] vs. 27 [7.6%]). The system organ class (SOC) Respiratory, Thoracic and Mediastinal Disorders occurred in 3.2% of patients in the PF-05280014 arm compared to 1.4% in the trastuzumab-EU arm.

73 (10.4%) patients (34 [9.7%] patients in the PF-05280014 group and 39 [11.0%] patients in the trastuzumab-EU group) died during the study or within 183 days (6 months) of discontinuing study drug. In addition, 12 (1.7%) patients (8 [2.3%] patients in the PF-05280014 group and 4 [1.1%] patients in the trastuzumab-EU group) died more than 183 days (6 months) after discontinuing study drug. The most frequent reason for death was disease progression. 3 patients in the trastuzumab-EU arm died due to cardiac toxicity caused to study treatment toxicity. In the Week 33 CSR it is stated that one (0.3%) patient in the

PF-05280014 arm died from a septic shock due to study treatment toxicity. This however was assessed not to be attributed to PF-05280014. Thirteen additional patients (1.9%) died due to other reasons.

With the responses to the D120 LoQ the applicant provided tables comparing demographic and baseline characteristics between the two treatment groups for all patients who died during the study. Overall, there are some slight differences (e.g. age, metastatic sites, prior radiation). In the PF-05280014 group fewer patients received prior radiation therapy and surgery and had more liver metastases. These factors might have contributed to a less favourable disease profile resulting in more disease progression. However, due to the small numbers no final conclusion can be drawn. It is however reassuring that the difference decreased with the updated safety dataset.

Study B3271004 (EBC)

There were 7 (6.2%) patients in the PF-05280014 group who experienced 7 SAEs and 6 (5.4%) patients in the trastuzumab-EU who experienced 10 SAEs (Febrile neutropenia was experienced by 1 (0.9%) patient in the PF-05280014 group and 2 (1.8%) patients in the trastuzumab-EU group. All other SAEs were reported by no more than 1 patient in each group. All SAEs were considered by the sponsor as unrelated to study treatment except for the Grade 5 pancytopenia experienced by 1 (0.9%) patient in the PF-05280014 group.

This patient, a 37-year old woman with right breast infiltrative ductal carcinoma, experienced pancytopenia on study day 6 after only 1 infusion cycle of trastuzumab (8 mg/kg, taxotere (75 mg/m2) and carboplatin 6 AUC on 27 Nov 2014 (study Day 1). The case of pancytopenia was attributed to both PF-05280014 and chemotherapy (docetaxel and carboplatin).

Studies B3271001 and B3271006 (HV)

One subject in Study B3271006 experienced 2 SAEs (bipolar disorder and psychotic behaviour) 7 days after PF-05280014 administration. The SAEs were Grade 4 in severity and were considered not related to study treatment. No deaths were reported in the single dose studies (B3271001 and B3271006).

Laboratory findings

Study B3271002 (MBC)

No notable differences in haematology and chemistry results were observed between the treatment groups. One patient in the PF-05280014 arm of Study B3271004 died due to pancytopenia.

Study B3271004 (EBC)

Haematology results were overall comparable in both treatment groups (beside the above described Grade 5 pancytopenia). Grade 4 chemistry abnormalities only occurred in the PF-05280014 group. Some differences were found for renal function and electrolytes parameters. The proportion of patients with urea > 1.3 x ULN was higher in the PF-05280014 arm (23.8%) compared to the trastuzumab-EU arm (15.4%), as well as the proportion of patients with creatinine > 1.3 x ULN (5.4% vs. 3.6%). Moreover, the proportion of patients with sodium levels > 1.05 x ULN (2.7 vs. 0.9) and calcium levels < 0.9 x LLN (6.3 vs. 2.7) were higher in the PF-05280014 arm, and Grade 4 clinical chemistry abnormalities of hypocalcemia (7 [6.3%] patients), hypercalcemia (1 [0.9%] patient), and hypokalemia (1[0.9%] patient) were reported in the PF-05280014 arm compared to no Grade 4 events in the trastuzumab-EU arm. Of the 7 patients with hypocalcemia at Cycle 1 in the PF-05280014 group only 1 patient had a decreased calcium value compared to the screening

value. All other patients either remained at their (low) calcium level or increased. One event of each Grade 4 hypercalcemia and Grade 4 hypokalemia was observed in the PF-05280014 group.

Studies B3271001 and B3271006 (HV)

There were no notable differences in laboratory parameters between PF-05280014 and trastuzumab-EU in healthy volunteers.

Immunological events

Immunogenicity of the study drug was evaluated in 3 studies: B3271001, B3271002, and B3271004.

Study B3271002 (MBC)

30 and 14 patients in the PF-05280014 group and the trastuzumab-EU group, respectively, had baseline ADA (predose). Of the 44 patients with a positive ADA result at Baseline 41 had post-treatment ADA tested. For the remaining 3 patients no samples were collected. Of the 41 patients with post-treatment ADA data, 1 patient in the PF-05280014 group had a positive post-treatment ADA test at the EOT visit. None of these 44 patients experienced anaphylactic or allergic reactions to trastuzumab in this study.

Of the patients who tested positive for ADA at Baseline, 66.7% (20/30) also tested positive for neutralizing antibodies (NAb) in the PF-05280014 group and 64.3% (9/14) also tested positive for NAb in the trastuzumab-EU group. Of the 26 patients who had post-treatment NAb samples collected, none were reported as NAb positive.

Of the 30 patients randomized in the PF-05280014 group with a positive ADA result at Baseline, 4 patients experienced an AE of IRR. All of the AEs of IRR in patients with positive ADA findings at Baseline were Grade 1 or 2 in severity with the exception of Patient 11961003 in the PF-05280014 group who had a Grade 3 IRR (signs and symptoms of Grade 2 chills and dyspnea) that resolved in 1.4 hours. All 6 of these patients with pre-dose ADA positive samples and an IRR continued to receive further treatment, with no further reported ADA and IRRs.

Following initiation of study drug, all patients with the exception of 2 (each in one treatment group) tested negative for ADA (titer <1.00) from Cycle 1, Day 1 post-treatment through 378 days post-randomization. For both patients, the positive ADA result was observed at the EOT visit in the final sample collected for the study; no events of IRR or anaphylactic reaction were reported.

Study B3271004 (EBC)

Of the 225 treated patients, none tested positive for ADA during the study.

Studies B3271001 and B3271006 (HV)

Of the 105 subjects, only 1 subject (in the trastuzumab-EU group) tested positive for ADA with low titer at a single time point post dosing. This subject tested negative for NAb. There were no unexpected AEs or SAEs reported for the one ADA-positive patient.

Discontinuation due to adverse events

Study B3271002 (MBC)

16 (4.6%) patients in the PF-05280014 group and 12 (3.4%) patients in the trastuzumab-EU group permanently discontinued from trastuzumab treatment due to AEs during the study. Of these patients, there

were 8 (2.3%) patients from PF-05280014 and 4 (1.1%) patients from trastuzumab-EU who were permanently discontinued from both trastuzumab and paclitaxel due to AEs. The most frequent reason for discontinuing trastuzumab treatment was ejection fraction decreased (6 [1.7%] and 4 [1.1%] patients in the PF-05280014 and trastuzumab-EU groups, respectively). There were no apparent differences in the number of patients with temporary discontinuation from trastuzumab due to TEAEs and IRRs as well as reduction of infusion rate due to IRR.

Study B3271004 (EBC)

In Study B3271004, 1 patient in the PF-05280014 group and 3 patients in the trastuzumab-EU group discontinued the study due to AEs: 1 patient in the PF-05280014 group was discontinued from the study due to a Grade 5 (fatal) SAE of pancytopenia. In the trastuzumab-EU group, 1 patient discontinued due to a Grade 3 SAE of hypokalemia, 1 patient discontinued due to a Grade 2 non-serious AE of erythema, and 1 patient discontinued due to Grade 3 anaemia. All AEs leading to discontinuation in the trastuzumab-EU group resolved. There were 4 (3.5%) patients in the PF-05280014 group and 3 (2.7%) patients in the trastuzumab-EU group who were permanently discontinued from any treatment due to AEs during the double-blind treatment period of Study B3271004.

Studies B3271001 and B3271006 (HV)

In both studies 2 subjects each permanently stopped study treatment due to AEs (3 due to Grade 2 IRR and 1 due to Grade 3 back pain determined as IRR).

2.6.1. Discussion on clinical safety

Safety data for PF-05280014 are derived from 4 clinical trials conducted in patients with metastatic and early breast cancer (multidose studies B3271002 and B3271004, respectively) as well as in healthy male subjects (single dose studies B3271001 and B3271006, respectively). 3 of the 4 studies have been completed. At the time of initial submission, 558 (78.9%) patients (279 patients each in the PF-05280014 group and the trastuzumab-EU group) were still ongoing in Study B3271002 at the time of data cutoff (24 August 2016). The applicant provided updated safety and immunogenicity data with cutoff 11 January 2017.

Breast Cancer Patients

Study B3271002 (MBC)

707 patients were randomized of which a total of 702 (349 in the PF-05280014 group and 353 in the trastuzumab-EU group) received at least 1 dose of the study drug. The mean (SD) duration of treatment for patients receiving either PF-05280014 or trastuzumab-EU treatment was comparable between the treatmentgroups.

337 (96.6%) patients in the PF-05280014 group and 339 (96.0%) patients in the trastuzumab-EU group experienced at least 1 treatment-emergent adverse event.

The most frequently affected SOCs were skin and subcutaneous tissue disorders and nervous system disorders. The most commonly observed AEs by preferred term were alopecia, anemia, neutropenia and peripheral sensory neuropathy with similar incidences among the treatment groups. TEAEs ≥ Grade 3 were noted for 120 (34.4%) patients in the PF-05280014 group and 129 (36.5%) patients in the trastuzumab-EU group.

Treatment-related TEAEs (ie. either trastuzumab or paclitaxel related) occurred in 315 (90.3%) and 314 (89.0%) patients of the PF-05280014 and trastuzumab-EU groups, respectively. The SOCs with the greatest difference between the treatment groups were investigations and nervous system disorders. For the latter the leading preferred term was peripheral sensory neuropathy of which none was related to PF-05280014/trastuzumab-EU. Trastuzumab-related TEAEs were observed equally in both treatment groups with no notable differences in severity, seriousness or reason for treatment discontinuation/interruption.

The number of patients who experienced serious adverse events was comparable between the treatment groups with a slightly higher incidence of disease progression in the PF-05280014 treatment group (32 [9.2%] vs. 27 [7.6%]).

A similar number of deaths was reported for both treatment groups. The observed difference with more patients in the PF-05280014 group dying from disease under study decreased with the updated safety dataset. In the Week 33 CSR it is stated that one (0.3%) patient in the PF-05280014 arm died from a septic shock due to study treatment toxicity. This, however, was assessed not to be attributed to PF-05280014.

No notable differences in laboratory findings were observed between the treatment groups.

The overall rate of patients discontinuing trastuzumab treatment was comparable between the treatment groups. There were also no major differences in the number of patients with temporary discontinuation from trastuzumab due to TEAEs and IRRs as well as reduction of infusion rate due to IRR.

TEAEs of special interest (ie. IRR, cardiac disorders, drug hypersensitivity) were reported with comparable incidences between the PF-05280014 and trastuzumab-EU treatment groups.

Study B3271004 (EBC)

109 patients in each group received 6 treatment cycles with similar mean relative doses.

109 (96.5%) and 106 (94.6%) patients in Study B3271004 experienced at least 1 TEAE in the PF-05280014 group and the trastuzumab-EU group, respectively.

The most frequently affected SOCs were blood and lymphatic system disorders and skin and subcutaneous tissue disorders. SOCs with a difference >5% between the treatment groups were mainly Grade 1 and 2 and not considered related to PF-05280014. The most commonly observed AEs by preferred term were alopecia, anemia, neutropenia and nausea.

The proportion of treatment-related TEAEs and trastuzumab-related TEAEs was similar between the treatment groups. The SOCs with the greatest difference between the treatment groups were general disorders and administration site conditions with asthenia as the most frequent PT and nervous system disorders. More ≥ Grade 3 treatment-related TEAEs were observed in the PF-05280014 group (N=41 [36.3%]) compared to the trastuzumab-EU group (N=49 [43.8%]) with neutropenia and leukopenia as the most frequent PTs.

There was no notable difference for patients experiencing SAEs in both treatmentgroups. 1 SAE Grade 5 was reported. This single death occurred in a 37-year old woman with right breast infiltrative ductal carcinoma who experienced pancytopenia on study day 6 after only 1 infusion cycle of trastuzumab (8 mg/kg, taxotere (75 mg/m2) and carboplatin 6 AUC on 27 Nov 2014 (Study Day 1). The case of pancytopenia was attributed to both PF-05280014 and chemotherapy (docetaxel and carboplatin).

Overall, laboratory findings were comparable between the treatment groups.

1 patient in the PF-05280014 group (Grade 5 SAE of pancytopenia) and 3 patients in the trastuzumab-EU group (Grade 3 SAE of hypokalemia, Grade 2 non-serious AE of erythema, Grade 3 anemia) discontinued the study due to AEs.

10.7% (N=12 patients) and 5.4% (N=6 patients) experienced TEAEs of special interest in the PF-05280014 group and the trastuzumab-EU group, respectively. This difference is however not driven by a specific PT. No IRRs were observed in the PF-05280014 group. The incidence of cardiac SOCs was overall comparable between the treatment groups. 1 patient in the PF-05280014 group experienced an anaphylactic reaction.

The provided narrative of this event indicated that the event of anaphylactic reaction occurred on Day 1 during the Docetaxel infusion. The event was Grade 2, resolved the same day and did not preclude the subsequent Carboplatin administration. Docetaxel was never re-administered and the patient did not experience another anaphylactic reaction.

The narrative gives no cause for concern. However, the assessor was not able to locate the mentioned patient ID number (10641001) in any of the submitted documents.

Immunogenicity

In Study B3271002 30 and 14 patients in the PF-05280014 group and the trastuzumab-EU group, respectively, had baseline ADA (predose). None of the ADA positive patients experienced anaphylactic or allergic reactions to trastuzumab in this study. 20 and 9 patients in the PF-05280014 group and the trastuzumab-EU group, respectively, tested positive for NAb, none of which were post-treatment positive.

Of the 30 patients randomized in the PF-05280014 group with a positive ADA result at Baseline, 4 patients experienced an AE of IRR. All of the AEs of IRR in patients with positive ADA findings at Baseline were Grade 1 or 2 in severity with the exception of one patient in the PF-05280014 group who had a Grade 3 IRR (signs and symptoms of Grade 2 chills and dyspnea) that resolved in 1.4 hours. No events of IRR or anaphylactic reaction were reported for the 2 patients (one in each group) who tested ADA positive at EOT visit.

Healthy Volunteers

In both studies the incidence of TEAEs, SAEs and AEs leading to treatment discontinuation/interruption was comparable between the treatment groups. No deaths were reported in both single dose studies. There were no notable differences in laboratory parameters between PF-05280014 and trastuzumab-EU in healthy volunteers.

In Study B3271001 28 patients (80.0%) in the PF-05280014 group and 29 (82.9%) patients each in the trastuzumab-EU and trastuzumab-US groups reported TEAEs. The increased rate of pyrexia in the PF-05280014 group (10 patients [28.6%]) compared to the trastuzumab-EU group (3 patients [8.6%]) and the trastuzumab-US group (2 patients [5.7%]) led to the conduct of Study B3271006. The observed increased incidence of pyrexia in the PF-05280014 arm in Study B3271001 was not confirmed in Study B3271006.

2.6.2. Conclusions on the clinical safety

Overall, the safety profiles of PF-05280014 and trastuzumab-EU appear to be comparable among all four clinical studies. The available safety data support biosimilarity between Trazimera and Herceptin and extrapolation to other indications of the reference product is acceptable.

2.7. Risk Management Plan

The Marketing authorisation holder submitted RMP Version 1.2, dated 19 April 2018.

Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 19: **Summary of the Safety Concerns**

Summary of safety concerns	
Important identified risks	• Cardiac dysfunction • Administration-related reactions • Oligohydramnios
Important potential risks	None
Missing information	None

Pharmacovigilance plan and risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Cardiac dysfunction	Routine risk minimisation measures: This risk is communicated through the label (Sections 4.2 and 4.4 of the proposed SmPC). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Administration-Related Reaction	Routine risk minimisation measures: This risk is communicated through the label (Sections 4.2 and 4.4 of the proposed SmPC). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Oligohydramnios	Routine risk minimisation measures: This risk is communicated through the label (Sections 4.6 and 4.8 of the proposed SmPC). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Routine pharmacovigilance activities as well as routine risk minimisations measures are sufficient to identify, characterize and address the risks of the product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Trazimera (trastuzumab) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

In the development of a biosimilar product, there is no requirement to demonstrate benefit to the patient per se as this has been shown for the reference product. The benefits and risks are inferred from the similarity of

the test product to the reference product in terms of the totality of evidence collected from the quality, non-clinical and clinical data.

3.1. Therapeutic Context

3.1.1. Disease or condition

Trazimera (PF-05280014) has been developed by Pfizer Europe MA EEIG, as a similar biological medicinal product to Herceptin for IV use which was approved in the EU in August 2000 (EMEA/H/C/000278).

The therapeutic indications, dosage and route of administration proposed for Trazimera are identical to those approved for Herceptin for IV use in HER2-positive metastatic breast cancer, early breast cancer and metastatic gastric cancer.

3.1.2. Main clinical studies

Overall, the clinical development program for PF-05280014 includes 2 completed Phase 1 clinical studies in healthy subjects (Studies B3271001 and B3271006), 1 completed Phase 3 trial in patients with EBC (Study B3271004) and 1 ongoing Phase 3 study in patients with MBC (Study B3271002) and safety data is reported for all four studies.

Study B3271001 was designed to demonstrate the similarity between CT-P6 and Herceptin with respect to the PK profile but also in terms of comparative safety and tolerability. Study B3271006 was initiated to estimate the relative risk of pyrexia due to the observation of a higher incidence of pyrexia in Study B3271001.

Study B3271002 was designed to characterize and detect clinically meaningful differences in the efficacy and safety of PF-05280014 and trastuzumab-EU in patients with HER2-positive metastatic breast cancer (with ORR as primary endpoint) and to collect other comparative efficacy, PK/PD, safety and immunogenicity data for both treatment groups.

Study B3271004 was conducted based on a request from medical oncologists' feedback to generate data with PF-05280014 in early breast cancer patients.

All studies, with the exception of Study B3271002, had been completed at the time of initial submission. Study B3271002 was ongoing at that time. The cutoff date (24 August 2016) of the data included in the dossier was based on when all patients had either completed the Week 33 visit (to collect data for primary endpoint analysis) or discontinued study drug earlier than the Week 33 visit, and include data up to 378 days post randomization.

With the responses to the D120 LoQ the applicant provided an updated safety and immunogenicity dataset up to 1 year (Week 53 CSR).

3.2. Favourable effects

Quality

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. The primary focus was the comparison of PF-05280014 to EU-approved Herceptin taking the other as potentially supportive into account. The similarity assessment was performed using orthogonal analytical methods. The overall similarity assessment of PF-05280014, trastuzumab-US, and trastuzumab-EU showed similar biophysical, biochemical characteristics and biological activity. No significant differences were detected.

Non-Clinical

The overall data on PD/PK and toxicology indicate that Trazimera can be considered similar to the reference product Herceptin.

Clinical

Study B3271002

The primary endpoint was met:

- ORR was observed in 220 (62.5%) patients in the PF-05280014 group and in 236 (66.5%) patients in the trastuzumab-EU group and within the ±13% interval (difference calculated by the assessor: -0.033 [PF-05280014 minus trastuzumab-EU] with a 95% CI of [-0.106,0.040]).
- The risk ratio was 0.940 (PF-05280014 over trastuzumab-EU), with a 95% CI of (0.842, 1.049), which fell entirely within the 0.80 to 1.25 equivalence margin.

Sensitivity analyses support the results of the primary analysis.

The median PFS (12.16 months in the PF-05280014 group and 12.06 months in the trastuzumab-EU group) and the percentage of patients who progressed/died or were censored (144 [40.9%] and 148 [41.7%] patients in the PF-05280014 and trastuzumab-EU group, respectively) were comparable between the 2 treatment groups.

The percentage of all patients who achieved confirmed response (CR or PR, with or without subsequent progression or death) and duration of response was comparable between the 2 treatment groups.

The percentage of patients who died was comparable across the 2 treatment groups (42 [11.9%] and 43 [12.1%] patients in the PF-05280014 group and the trastuzumab-EU group, respectively [up to 378 days post-randomization]).

PF-05280014 levels in MBC patients after the weekly dosing regimen were as expected and comparable to EU-Herceptin supporting PK similarity of PF-05280014 in MBC patients.

- Mean Ctrough values increased continuously from 27.6 µg/mL (pre-dose 2) to 60.3 µg/mL (pre-dose 18) in the PF-05280014 group, and from 28.8 to 62.3 µg/mL in the EU-Herceptin group.

Study B3271004

Comparable pCR results (secondary endpoint) for PF-05280014 and trastuzumab-EU was 47.0% (95% CI: 36.9% to 57.2%) and 50.0% (95% CI: 39.0% to 61.0%), respectively.

Comparable ORR results (secondary endpoint) by type of response (CR, PR, SD, PD), central versus investigator review and also percentage of patients with breast conservation surgery (PF-05280014 vs trastuzumab-EU being 13.2% vs 17.0%, respectively) support robustness of clinical similarity data.

- ORR: 88.1% (95% CI: 80.2% to 93.7%) and 82.0% (95% CI: 72.5% to 89.4%) for PF-05280014 and trastuzumab-EU, respectively.

PK results showed comparable geometric mean Ctrough values of 21.7, 30.5, 32.0, 34.6 ng/mL (PF-05280014) and 25.7, 34.9, 36.4, 34.6 ng/mL (EU-Herceptin) at the end of cycle 1, 3, 4, and 5, respectively.

Study B3271001 and Study B3271006

Study B3271001: For PK similarity comparisons of PF-05280014 to each of the reference products (trastuzumab-EU or trastuzumab-US), the 90% CIs for the test-to-reference ratios of Cmax, AUCt, and AUCinf were within the equivalence margin of 80% to 125%. It seems as if the variability has been calculated from all three treatments combined. The mean values of Cmax, AUCt, and AUCinf for the trastuzumab-EU group were slightly higher (approximately 6% to 9%) in comparison to the PF-05280014 and trastuzumab-US groups. This could be explained by the higher dose administered to this group due to their higher body weight. Consequently, the mean values of Cl and Vss were both slightly lower for the trastuzumab-EU group, while half-life (t1/2) values were numerically higher, although no statistical analysis has been performed for these parameters.

As supportive data in patients, in Study B3271004, the mean trough concentration at each study cycle in PF-05280014 group was comparable to the respective mean trough concentration in trastuzumab-EU group.

PD findings do not contradict the available data for the overall comparability exercise.

Immunogenicity was overall low and comparable between PF-05280014 and Herceptin across clinical trials.

3.3. Uncertainties and limitations about favourable effects

There are no important uncertainties.

3.4. Unfavourable effects

Study B3271002

The safety data set (including immunogenicity) is complete with data up to 1 year (Week 53 CSR).

Overall, the safety profile of PF-05280014 is comparable to trastuzumab-EU. There were no major differences between the PF-05280014 and trastuzumab-EU group with regards to TEAEs (337 [96.6%] and 339 [96.0%] patients), treatment-related TEAEs (315 [90.3%] and 314 [89.0%] patients), patients discontinuing due to AEs (16 [4.6%] and 12 [3.4%] patients) and TEAEs of special interest.

73 (10.4%) patients (34 [9.7%] patients in the PF-05280014 group and 39 [11.0%] patients in the trastuzumab-EU group) died during the study or within 183 days (6 months) of discontinuing study drug. The most frequent reason for death was disease progression.

Study B3271004

The safety findings were overall comparable between the treatment groups. There were no major differences between the PF-05280014 and trastuzumab-EU group with regards to TEAEs (109 [96.5%] and 106 [94.6%] patients), treatment-related TEAEs (108 [95.6%] and 106 [94.6%] patients), patients discontinuing due to AEs (1 vs. 3 patients) and TEAEs of special interest. One patient died in the PF-05280014 arm due to pancytopenia attributed by the investigator to both PF-05280014 arm and chemotherapy.

Study B3271001 and Study B3271006

In both studies the incidence of TEAEs, SAEs and AEs leading to treatment discontinuation/interruption was comparable between the treatment groups.

3.5. Uncertainties and limitations about unfavourable effects

There are no important uncertainties.

3.6. Effects Table

Not needed for biosimilars.

3.7. Benefit-risk assessment and discussion

3.7.1. Balance of benefits and risks

Quality

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. The primary focus was the comparison of PF-05280014 to EU-approved Herceptin taking the other as potentially supportive into account. The similarity assessment was performed using orthogonal analytical methods. The overall similarity assessment of PF-05280014, trastuzumab-US, and trastuzumab-EU showed similar biophysical, biochemical characteristics and biological activity. No significant differences were detected.

Non-Clinical

The overall data on PD/PK and toxicology indicate that PF-05280014 can be considered similar to the reference product Herceptin.

Clinical

Efficacy and safety data indicate overall similarity between PF-05280014 and Herceptin. In Study B3271002 (MBC) the primary endpoint was met and is supported by results from sensitivity and secondary analyses.

In Study B3271004 (EBC) comparable pCR and ORR results were observed. However, no statistical assumptions for pCR have been defined and the sample size is not sufficient for formal equivalence testing. Therefore, this study may only be viewed as supportive. In addition, the steady state trough concentration at cycle 5 for both treatment groups is lower than expected.

In Study B3271001 (HV) PK data overall support similarity between PF-05280014 and trastuzumab-EU.

The safety profile was overall comparable between the treatment groups in all studies. The safety dataset (including immunogenicity data) up to 1 year has been provided with the responses to the D120 LoQ.

3.8. Conclusions

Trazimera is considered biosimilar to Herceptin and the overall B/R of Trazimera is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Trazimera is favourable in the following indication:

Metastatic breast cancer

Trazimera is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with 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 MBC, not previously treated with trastuzumab.

Early breast cancer

Trazimera is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).
- 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 Trazimera therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Trazimera should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see

sections 4.4 and 5.1).

Metastatic gastric cancer

Trazimera in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Trazimera should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.