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RESEARCH**

APPLICATION NUMBER:

761081Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date: March 14, 2018

From: Tiffany K. Ricks, PhD
Pharmacology/Toxicology Team Leader (acting)
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)

To: File for 351 (k) BLA 761081 for Trazimera (PF-05280014)

Re: Approvability for Pharmacology and Toxicology

The nonclinical data submitted to BLA 761081 were reviewed by Claudia P. Miller, PhD. The nonclinical findings are summarized in the “Executive Summary” section of the pharmacology/toxicology BLA review. Based on the determination of similarity of Trazimera to US-licensed Herceptin, the nonclinical sections of the labeling should be comparable to those in the labeling for US-licensed Herceptin.

I concur with Dr. Miller’s conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the safety and PK profiles of PF-05280014 to US-licensed Herceptin and EU-approved Herceptin in mice. I concur that the pharmacology and toxicology data support approval of BLA 761081 for Trazimera from the perspective of the pharmacology/toxicology discipline.

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/s/

TIFFANY RICKS
03/14/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 761081
Supporting document/s: 1
Applicant's letter date: June 22, 2017
CDER stamp date: June 22, 2017
Product: PF-05280014 (Trazimera)
Indication: Treatment of patients with HER2-
overexpressing breast cancer
Applicant: Pfizer Inc
235 E. 42nd Street
New York, NY 10017
Review Division: Division of Hematology Oncology Toxicology
(DHOT) for Division of Oncology Products 1
(DOP1)
Reviewer: Claudia P Miller, PhD
Team Leader: Tiffany Ricks, PhD (Acting)
Division Director: John K Leighton, PhD, DABT (DHOT)
Julia Beaver, MD (Acting; DOP1)
Project Manager: Clara J Lee, PharmD

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1 Executive Summary

1.1 Introduction

On June 22, 2017, Pfizer Inc (the Applicant) submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for PF-05280014 (Trazimera), a proposed biosimilar to US- licensed Herceptin (trastuzumab). The Applicant submitted animal pharmacokinetic and toxicology studies in mice in support of this BLA.

1.2 Brief Discussion of Nonclinical Findings

The Applicant submitted two nonclinical animal studies to support this BLA: (1) a single-dose comparative toxicokinetic study, including evaluation for anti-drug antibodies (ADA), with PF-05280014, US-licensed Herceptin and EU-approved Herceptin in male CD-1 mice and (2) a noncomparative, 2-week, repeat-dose toxicity study in male and female CD-1 mice with PF-05280014. Of note, the test-articles used in these studies are recombinant humanized IgG1 monoclonal antibodies directed against the human HER2 receptor and do not bind to the mouse *neu* receptor. The comparative toxicokinetic study was conducted to support the original IND, based on the Agency's recommendation that an in vivo single-dose PK/tolerability assessment with PF-05280014, US-licensed Herceptin and EU-approved Herceptin should be done to provide a scientific bridge between products in either monkeys or rodents. The Applicant selected the mouse species for evaluation because they rationalized that the distribution and clearance of all three versions of trastuzumab would not be affected by the interaction with the HER2/*neu* receptor, and a direct comparison of the PK profiles could be made. Overall results from the single-dose study demonstrated that tolerability, toxicokinetic profile and ADA responses to PF-05280014 were comparable to US-licensed Herceptin and EU-approved Herceptin. The Applicant conducted the repeat-dose study to test for toxicities with possible impurities. In the repeat-dose study, administration of PF-005280014 (twice weekly for 2-weeks, for a total of 5 doses) to mice did not reveal any toxicity findings compared to vehicle-treated mice.

The comparative animal study submitted in the current BLA provided a bridge between PF-05280014 and US-licensed Herceptin and EU-approved Herceptin. These results did not identify differences in the PK or toxicity profile (mortality, clinical signs and body weight) between PF-05280014 and US-licensed Herceptin and EU-approved Herceptin. From the perspective of the Pharmacology and Toxicology discipline, the results of these animal studies are adequate to demonstrate PK profiles and safety of PF-05280014 to US-licensed Herceptin in mice. No other issues were identified by the Pharmacology and Toxicology discipline that would preclude the determination of biosimilarity.

1.3 Recommendations

1.3.1 Approvability

Based on the nonclinical pharmacology and toxicology studies submitted in this BLA, the application is recommended for approval from the perspective of the Pharmacology and Toxicology discipline.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Refer to the final approved Prescribing Information for the final labeling. Based on the overall determination of similarity of Trazimera to US-licensed Herceptin, the nonclinical sections of the labeling were comparable to those in the label for US-licensed Herceptin.

2 Drug Information

2.1 Drug

Generic Name	Trastuzumab-qyyp
Code Name	PF-05280014 (Trazimera) or trastuzumab-Pfizer
Chemical Name	Immunoglobulin G, anti-human HER2/neu receptor monoclonal antibody (mAb)
Molecular Formula/Molecular Weight	185 kDa
Structure or Biochemical Description	a recombinant, humanized anti-HER2 IgG1 kappa mAb with two identical heavy chains and two identical light chains, covalently linked with four inter-chain disulfide bonds.
Pharmacologic Class	HER2/neu receptor antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 110427 for PF-05280014

2.3 Drug Formulation

PF-05280014 will be provided as a lyophilized powder at dosage strength of 440 mg. Lyophilized product will be reconstituted with 20 mL of either sterile water for injection (SWFI) or the supplied bacteriostatic water for injection (BWFI), which will make a solution containing 21 mg/mL of PF-05280014, pH ~6.

Table 1: Composition of PF-05280014 (440 mg) drug product

Name of Ingredients	Reference to Standard	Function	Unit Formula (mg/vial)
PF-05280014	In-house specification	Active ingredient	440
L-histidine	Ph. Eur., USP, JP		(b) (4)
L-histidine hydrochloride monohydrate	Ph. Eur., JP		
Polysorbate 20	Ph. Eur., NF, JPE		
Sucrose	Ph. Eur., NF, JP		

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

- Proposed clinical population: patients with HER-2 overexpressing breast cancer or HER-2 overexpressing gastric or gastroesophageal junction adenocarcinoma.
- Dosing regimen:
 - Adjuvant treatment of HER-2 overexpressing breast cancer
 - Initial dose of 4 mg/kg over 90 min IV infusion, then 2 mg/kg over 30 min IV infusion weekly for 52 weeks, or
 - Initial dose of 8 mg/kg over 90 min IV infusion, then 6 mg/kg over 30-90 min IV infusion every three weeks for 52 weeks.
 - Metastatic HER-2 overexpressing breast cancer
 - Initial dose of 4 mg/kg as a 90 min IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 min IV infusions.
 - Metastatic HER-2 overexpressing gastric cancer
 - Initial dose of 8 mg/kg over 90 min IV infusion, followed by 6 mg/kg over 30 min to 90 min IV infusion every 3 weeks.

2.7 Regulatory Background

FDA held a pre-IND meeting with the Applicant on April 13, 2011 and subsequently received the initial IND 110427 submission for PF-05280014 on April 24, 2012. On June 22, 2017, Pfizer Inc submitted this original 351(k) BLA for PF-05280014.

3 Studies Submitted

3.1 Studies Reviewed

Study No.	Study Title
8253552	Single-dose intravenous toxicokinetic study with Trastuzumab-PF (PF-05280014), Trastuzumab-US and Trastuzumab-EU in mice
13GR047	2-week intravenous bolus toxicity study of PF-05280014 in mice

3.2 Studies Not Reviewed

Study No.	Study Title
8254-560	Validation of an ELISA method for quantification of Trastuzumab in mouse serum
8254-565	Validation of an ECL method for quantification of anti-Trastuzumab (US formulation) antibody in mouse serum
8254-564	Validation of an ECL method for quantification of anti-Trastuzumab EU-antibody in mouse serum
8254-566	Validation of an ECL method for quantification of anti-Trastuzumab (PF formulation) in mouse serum

3.3 Previous Reviews Referenced

Nonclinical review for IND 110427 by Dr. Kimberly Ringgold.

4 Pharmacology

4.1 Primary Pharmacology

The Applicant did not submit any pharmacology studies in the primary pharmacology section of the BLA submission in support of this BLA.

4.2 Secondary Pharmacology

The Applicant did not submit any pharmacology studies in the secondary pharmacology section of the BLA submission in support of this BLA.

4.3 Safety Pharmacology

The Applicant did not submit any studies in the safety pharmacology section of the BLA submission in support of this BLA.

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: Single-dose intravenous toxicokinetic study with Trastuzumab-PF (PF-05280014), Trastuzumab-US, and Trastuzumab-EU in Mice

Study no.:	11GR302
Study report location:	eCTD Section 4.2.3.1.
Conducting laboratory and location:	[REDACTED] (b) (4) [REDACTED] [REDACTED]
Date of study initiation:	October 17, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PF-05280014, Trastuzumab-Pfizer Lot# 88200; Herceptin® (Trastuzumab-US) Lot # 931211; Herceptin® (Trastuzumab-EU) Lot # H0750B01

Key Study Findings

- No remarkable toxicity findings in mortality, clinical signs and body weight were noted in mice treated with PF-05280014, US-licensed Herceptin (Trastuzumab-US) or EU-approved Herceptin (Trastuzumab-EU).
- Based on C_{max} and AUC, the relative exposure of PF-05280014 to US-licensed Herceptin or EU-approved Herceptin was similar at all doses tested.
- The incidence of ADA was 11% (8/74) for PF-05280014, 8% (6/75) for US-licensed Herceptin, and 11% (8/75) for EU-approved Herceptin.

Methods

Doses: 0, 1, 10, 100 mg/kg
 Frequency of dosing: Single dose
 Route of administration: IV, bolus
 Dose volume: 5 mL/kg
 Formulation/Vehicle: Vehicle Control Article/Diluent 1: 4.9mM Histidine/His-HCl, 1.96% sucrose, 0.09% polysorbate 20, pH 6.0 in water
 Vehicle/Diluent 2: 4.2mM Histidine/His-HCl, 1.9% trehalose dihydrate, 0.08% polysorbate 20, pH 6.0 in water
 Species/Strain: Mouse/CD-1, Male
 Number/Group: 55/group
 Age: 6 to 7 weeks
 Weight: 25.5 to 43.4 g Males
 Satellite groups: None
 Unique study design: None
 Deviation from study protocol: None were considered to have a major impact on the validity and interpretation of study results.

Table 2: Study Design

Group	No. of Males ^a	Dose Level (mg/kg)	Dose Concentration ^b (mg/mL)
1 (Control) ^c	55	0	0
2 Trastuzumab-PF (Low)	55	1	0.2
3 Trastuzumab-PF (Mid)	55	10	2.0
4 Trastuzumab-PF (High)	55	100	20.0
5 Trastuzumab-US (Low)	55	1	0.2
6 Trastuzumab-US (Mid)	55	10	2.0
7 Trastuzumab-US (High)	55	100	20.0
8 Trastuzumab-EU (Low)	55	1	0.2
9 Trastuzumab-EU (Mid)	55	10	2.0
10 Trastuzumab-EU (High)	55	100	20.0

a Eleven animals/group were dosed on 31 October 2011 (Cohort 1), 22 animals/group were dosed on 02 November 2011 (Cohort 2), and 22 animals/group were dosed on 03 November 2011 (Cohort 3).

b The dose volume was 5 mL/kg.

c Group 1 received Vehicle Control Article/Diluent 1 only.

(Excerpted from Applicant's submission)

Observations and Results

No toxicity is expected in mice exposed to PF-05280014, as mouse *neu* receptor (the rodent homologue of human HER2) is not recognized by trastuzumab.

Mortality

All animals survived to necropsy.

Clinical Signs

Unremarkable

Body Weights

Unremarkable

Toxicokinetics**Table 3: Summary of toxicokinetics parameters for Trastuzumab-PF, US-licensed Herceptin (Trastuzumab-US), and EU-approved Herceptin (Trastuzumab-EU) following single dose administration in male mice**

Test Article	Dose Group	Dose Level (mg/kg)	C _{max} (µg/mL)	AUC ₀₋₂₈₈₀ (µg•hr/mL)	AUC _{0-∞} (µg•hr/mL)	AUC _{ext} (%)	t _{1/2} (hr)
Trastuzumab-PF	2	1	22.8	4200	4220	0.274	380
	3	10	318	51400	51800	0.724	440
	4	100	2520	285000	286000	0.157	309
Trastuzumab-US	5	1	26.3	4050	4080	0.780	416
	6	10	269	49800	50000	0.306	352
	7	100	2620	289000	289000	0.164	320
Trastuzumab-EU	8	1	18.6	4590	4650	1.28	536
	9	10	281	51500	51800	0.453	392
	10	100	2700	298000	298000	0.0810	280

(Excerpted from Applicant's submission)

Table 4: Dose proportionally ratios for Trastuzumab-PF, US-licensed Herceptin (Trastuzumab-US), and EU-approved Herceptin (Trastuzumab-EU) following single dose administration in male mice

Test Article	Dose Group	Dose Level (mg/kg)	Dose Ratio	C _{max} Ratio	AUC _{0-∞} Ratio
Trastuzumab-PF	2	1	1.0	1.0	1.0
	3	10	10 ^a	14	12
	4	100	10 ^b	7.9	5.5
Trastuzumab-US	5	1	1.0	1.0	1.0
	6	10	10 ^a	10	12
	7	100	10 ^b	9.7	5.8
Trastuzumab-EU	8	1	1.0	1.0	1.0
	9	10	10 ^a	15	11
	10	100	10 ^b	9.6	5.8

a Represents increase in dose level from 1 to 10 mg/kg.

b Represents increase in dose level from 10 to 100 mg/kg.

(Excerpted from Applicant's submission)

Table 5: Comparison of C_{max} and $AUC_{0-\infty}$ values for Trastuzumab-PF, US-licensed Herceptin (Trastuzumab-US), and EU-approved Herceptin (Trastuzumab-EU) following single dose administration in male mice

Dose Level (mg/kg)	C_{max} PF:US	C_{max} PF:EU	$AUC_{0-\infty}$ PF:US	$AUC_{0-\infty}$ PF:EU
1	0.867	1.23	1.03	0.908
10	1.18	1.13	1.04	1.00
100	0.962	0.933	0.990	0.960

PF:US = The ratio of trastuzumab-PF to trastuzumab-US.

PF:EU = The ratio of trastuzumab-PF to trastuzumab-EU.

(Excerpted from Applicant's submission)

Dosing Formulation Analysis

The 2.0 mg/mL dose formulation of trastuzumab-PF was 14 % higher than theoretical value, with a mean of 114.3%. All other dosing formulations tested were within specification, (b) (4) % from theoretical value, ranging from 102.3 to 105.0%. Per the sponsor, "this deviation was small (approximately 14% compared to the (b) (4) % acceptable range) and the dose-normalized toxicokinetic data showed that the interpretation of the exposure data did not appear to be impacted by the deviation, the nominal concentration (10 mg/kg) was utilized in this report for this group."

6.2 Repeat-Dose Toxicity

Study title: 2-week intravenous bolus toxicity study of PF-05280014 in mice

Study no.:	13GR047
Study report location:	eCTD Section 4.2.3.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 26, 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PF-05280014, Trastuzumab-Pfizer Lot# Z00515, 98%

Key Study Findings

- No remarkable test article-related toxicity findings were noted in mice treated with PF-05280014.

Methods

Doses: 0, 10, 100 mg/kg
 Frequency of dosing: Twice weekly (on Days 1, 4, 8, 11 and 14)
 Route of administration: Intravenous injection
 Dose volume: 5 mL/kg
 Formulation/Vehicle: 4.9mM Histidine/His-HCl, 1.96% sucrose, 0.009% polysorbate 20, pH 6.0 in water
 Species/Strain: Mouse/CD-1
 Number/Sex/Group: 10/sex/group
 Age: 11 weeks
 Weight: 30.8 to 42.8 g Males; 23.1 to 28.6 g Females
 Satellite groups: TK group; 5/sex/group
 Unique study design: None
 Deviation from study protocol: None reported

Table 6: Study Design

Group Number	Dose (mg/kg) ^a	Concentration (mg/mL)	Dose Volume (mL/kg) ^b	Animal Numbers			
				Main Study		Toxicokinetics (TK)	
				Males	Females	Males	Females
1	0	0	5	1-10	31-40	NA	NA
2	10	2	5	11-20	41-50	NA	NA
3	100	20	5	21-30	51-60	NA	NA
4	10	2	5	NA	NA	501-505	511-515
5	100	20	5	NA	NA	506-510	516-520

^a. All dose levels are expressed as mg of active drug per kg of body weight.

^b. The dose volume was based on the most recent individual body weight.

NA. Not applicable.

(Excerpted from Applicant's submission)

Observations and Results

No toxicity is expected in mice exposed to PF-05280014, as mouse *neu* receptor (the rodent homologue of human HER2) is not recognized by trastuzumab.

Mortality

All animals survived.

Clinical Signs

Unremarkable

Body Weights

Unremarkable

Feed Consumption

Unremarkable

Ophthalmoscopy

No test-article related changes were noted.

Hematology

No test-article related changes were noted.

Clinical Chemistry

No test-article related changes were noted.

Urinalysis

Not evaluated.

Gross Pathology

No remarkable changes were noted.

Organ Weights

A statistically significant decrease in prostate organ weight to body weight ratio was noted in treated males (-20% for 10 mg/kg; and -27% for 100 mg/kg) versus control. However, this decrease was not statistically significant in organ weight to brain weight ratio or in absolute organ weight.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Granuloma in the lung were noted in one control female and in one male and 3 females at 100 mg/kg/dose, some of which contained hair fragments. According to pathology report, the presence of granuloma in the lung is consistent with intravenous bolus injection procedure. One female at 100 mg/kg/dose had a focal area of inflammation caudal to the stifle joint. According to pathology report, this finding may have occurred as a result of handling trauma.

Toxicokinetics/Bioanalytical Report

The Applicant assessed the concentration of serum PF-05280014 by ELISA in samples collected 24 h after the last dose (5th dose) to confirm exposure in treated mice. The mean serum concentrations at this time point are shown in Table 7. Similar exposures were noted between sexes, and the mean concentration of 100 mg/kg was approximately 4x of the mean concentration of 10 mg/kg.

Table 7: Serum PF-05280014 concentration, 24 hours post-last dose of study

Dose	Gender n=5/sex/dose	Serum PF-05280014 µg/mL
10 mg/kg	Male	330
	Female	251
100 mg/kg	Male	1240
	Female	1030

Dosing Formulation Analysis

The dosing formulation for PF-05280014 ranged from 99 to 107%, which was within the acceptable criteria range of (b) (4) %.

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/s/

CLAUDIA P MILLER
03/08/2018

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