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APPLICATION NUMBER:

761072Orig1s000

NON-CLINICAL REVIEW(S)

Pharmacology and Toxicology Secondary Review for BLA 761072

TO: BLA 761072 (PF-06438179 as a biosimilar to US-licensed Remicade® [infliximab])

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DATE: November 20, 2017

BLA 761072 was submitted by Pfizer, Inc. on February 13, 2017 under section 351(k) of the Public Health Service Act (PHS Act) to support licensure of PF-06438179 as a biosimilar to US-licensed Remicade® (infliximab). US-licensed Remicade is an intravenously administered product, originally developed by Centocor, Inc. (BLA 103772, August 24, 1998), indicated for the treatment of Crohn's disease, Pediatric Crohn's disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Rheumatoid Arthritis (in combination with MTX), Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis. Pfizer intends to use dosing regimens for PF-06438179 that are identical to US-licensed REMICADE, and is requesting approval for all currently approved REMICADE indications.¹

Dr. Matthew Whittaker's review dated October 20, 2017 focused on two *in vivo* nonclinical studies submitted in support of a demonstration of biosimilarity of PF-06438179 to US-licensed Remicade: (1) a single dose intravenous bolus toxicokinetic and tolerability study of PF-06438179 and EU-approved Remicade in male Sprague-Dawley rats, and (2) a 2-week intravenous bolus toxicity study of PF-06438179 in male and female Sprague-Dawley rats.

In a Pre-IND meeting written response dated January 28, 2013, it was stated in response to the Sponsor's nonclinical question as follows: "given that there is no pharmacologically relevant species available for toxicology studies, the proposed single-dose, TK/tolerability study in male rats has limited value. Instead, we recommend an *in vivo* study in the Tg197 transgenic mouse to aid in assessing pharmacodynamic and pharmacokinetic similarity between PF-06438179 and [EU-approved Remicade]." The Sponsor decided not to conduct the Tg197 mouse study in support of their initial IND submission. The Sponsor's analytical assessment of PF-06438179 (including physicochemical characterization as well as *in vitro* functional evaluation), submitted at the time that the initial IND was opened (IND 114828, March 28, 2013), was judged to be sufficient to allow for a limited *in vivo* nonclinical assessment of this molecule.

¹ Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at <http://www.accessdata.fda.gov/scripts/opdlisting/opa/index.cfm>. Accordingly, FDA will not be able to license PF-06438179 for this indication until the orphan exclusivity expires.

The clinical PF-06438179 formulation uses a succinate buffer. This formulation differs from the reference product which uses a phosphate buffer formulation. There is sufficient data for the safety qualification of succinic acid administered by the IV route with particular reference to potential systemic toxicity.

In a single-dose toxicokinetic study with male Sprague-Dawley rats, toxicokinetic parameters (T_{max} , C_{max} , and AUC_{0-1344}), following single IV doses of 10 or 50 mg/kg, were determined to be comparable between PF-06438179 and EU-approved Remicade. A 2-week repeat dose GLP toxicology study conducted with IV doses of 10 or 50 mg/kg PF-06438179 administered once per week (no reference product comparator) did not identify any novel toxicities that were judged to be clinically relevant.

Overall, the toxicology and toxicokinetic data submitted in BLA 761072 demonstrate the similarity of PF-06438179 and US-licensed REMICADE from the nonclinical pharmacology and toxicology perspective and support a demonstration that PF-06438179 is biosimilar to US-licensed Remicade.

I concur with Dr. Whittaker's review dated October 20, 2017 that recommends approval of PF-06438179 from the nonclinical Pharmacology and Toxicology perspective. Dr. Whittaker's recommended changes to the sponsor's proposed labeling were made to allow consistency with the labeling for the approved biosimilar product, RENFLEXIS (infliximab-abda) (BLA 761054, Samsung Bioepis, approved April 21, 2017). The labeling format complies with the Pregnancy and Lactation Labeling Rule (PLLR). It is noted that the reference product label has not yet undergone PLLR conversion.

Recommendation: From the nonclinical perspective, approval of the application is recommended.

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/s/

TIMOTHY W ROBISON
11/20/2017

**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: BLA 761072
Supporting document/s: Supporting document 1
Supporting document 8
Applicant's letter date: February 13, 2017
May 17, 2017
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May 17, 2017
Product: PF-06438179
Indication: Crohn's Disease, Pediatric Crohn's Disease,
Ulcerative Colitis, Rheumatoid Arthritis,
Ankylosing Spondylitis, Psoriatic Arthritis,
Plaque Psoriasis
Applicant: Pfizer
Review Division: Division of Pulmonary, Allergy & Rheumatology
Products (DPARP)
Reviewer: Matthew Whittaker, Ph.D.
Supervisor/Team Leader: Timothy Robison, Ph.D.
Division Director: Badrul Chowdhury, MD, Ph.D.
Project Manager: Sadaf Nabavian

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1 Executive Summary

1.1 Introduction

BLA 761072 was submitted by Pfizer, Inc. on February 13, 2017 under section 351(k) of the Public Health Service Act (PHS Act) to support registration of PF-06438179 as a biosimilar to US-licensed REMICADE (infliximab). REMICADE is an intravenously administered product, originally developed by Centocor, Inc. (BLA 103772, 8/24/1998), indicated for the treatment of Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, Rheumatoid Arthritis (RA) in combination with methotrexate (MTX), ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. Infliximab is a chimeric human-murine monoclonal IgG1 antibody directed against both soluble and membrane-bound human tumor necrosis factor α (TNF α). It is designed to inhibit TNF receptor mediated functions including cell proliferation, cytokine production, inflammatory cell recruitment and other inflammatory processes.

Pfizer intends to use dosing regimens for PF-06438179 that are identical to US-licensed REMICADE, and to obtain approval for all currently approved REMICADE indications with the exception of Pediatric Ulcerative Colitis (protected by orphan drug exclusivity expiring on September 23, 2018).

1.2 Brief Discussion of Nonclinical Findings

The analytical assessment of PF-06438179 (including physicochemical characterization as well as in vitro functional evaluation) was judged to be sufficient to allow for a limited in vivo nonclinical assessment of this molecule. Infliximab cross-reacts with TNF α from human and chimpanzee only. Therefore, there are no available pharmacologically relevant nonclinical species to conduct general toxicology evaluations of infliximab products such as PF-06438179.

Pfizer conducted a single-dose toxicokinetic study in male Sprague-Dawley rats to support clinical dosing of PF-06438179. After a single IV dose at 10 or 50 mg/kg, pharmacokinetic parameters (T_{max} , C_{max} , and AUC_{0-1344}) were comparable between PF-06438179 and EU-approved infliximab. An additional 2 week, repeated dose (once weekly) GLP toxicology study conducted with 10 or 50 mg/kg PF-06438179 (no reference product comparator) did not identify any novel toxicities that were judged to be clinically relevant.

Overall, the data submitted to the BLA demonstrate sufficient similarity between PF-06438179 and REMICADE from a nonclinical toxicology perspective.

1.3 Recommendations

1.3.1 Approvability

PF-06438179 is recommended for approval from the nonclinical toxicology perspective. Recommended labeling is discussed below.

1.3.2 Additional Nonclinical Recommendations

None. There are no outstanding nonclinical issues.

1.3.3 Labeling

Table 1 provides a side-by-side comparison of the language in the nonclinical sections of the labeling for (1) the reference product REMICADE, (2) Pfizer’s proposed labeling for PF-06438179 (submitted 5/17/17), and (3) the Division’s recommended labeling. All of the Division’s recommended changes to the sponsor’s proposed labeling were made to allow consistency with the labeling for the approved infliximab biosimilar product, RENFLEXIS (BLA 761054, Samsung Bioepis, approved April 21, 2017). The labeling format complies with the Pregnancy and Lactation Labeling Rule (PLLR). It is noted that the reference product label has not yet undergone PLLR conversion.

Table 1. Side-by-side comparison of nonclinical sections of labeling for the reference product, Pfizer’s proposed labeling, and DPARP-recommended labeling.

REMICADE (reference product) labeling ^a	Pfizer proposed PF-06438179 labeling ^b	DPARP recommended PF-06438179 labeling
Section 8. USE IN SPECIFIC POPULATIONS		
<p>8.1 Pregnancy</p> <p>Pregnancy Category B. It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed. Because infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF</p>	<p>8.1 Pregnancy</p> <p>(b) (4)</p>	<p>8.1 Pregnancy</p> <p>Risk Summary Available data from published literature on the use of infliximab products during pregnancy have not reported a clear association with infliximab products and adverse pregnancy outcomes. Infliximab products cross the placenta and infants exposed <i>in utero</i> should not be administered live vaccines for at least 6 months after birth (<i>see Clinical Considerations</i>). In a development study conducted in mice using an analogous antibody, no evidence of maternal toxicity, embryotoxicity or teratogenicity was observed (<i>see Data</i>). All pregnancies have a background risk of birth defect,</p>

REMICADE (reference product) labeling ^a	Pfizer proposed PF-06438179 labeling ^b	DPARP recommended PF-06438179 labeling
<p>analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.</p> <p>As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a six month waiting period following birth is recommended before the administration of live vaccines (e.g., BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants [see Warnings and Precautions (5.14)].</p>	<p>(b) (4)</p>	<p>loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.</p> <p><u>Clinical Considerations</u></p> <p><i>Fetal/neonatal adverse reactions</i></p> <p>Infliximab products cross the placenta, and have been detected in the serum of infants up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a six month waiting period following birth is recommended before the administration of live vaccines (e.g., BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants [see Warnings and Precautions (5.14)].</p> <p><u>Data</u></p> <p><i>Animal Data</i></p> <p>Because infliximab products do not cross-react with TNFα in species other than humans</p>

REMICADE (reference product) labeling ^a	Pfizer proposed PF-06438179 labeling ^b	DPARP recommended PF-06438179 labeling
	(b) (4)	<p>and chimpanzees, animal reproduction studies have not been conducted with infliximab products. An embryofetal development study was conducted in pregnant mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. This antibody, administered during the period of organogenesis on gestation day 6 and 12 at IV doses up to 40 mg/kg produced no evidence of maternal toxicity, embryotoxicity, or teratogenicity. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness.</p>
<p>8.3 Nursing Mothers</p> <p>It is not known whether REMICADE is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from REMICADE, women should not breast-feed their infants while taking REMICADE. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.</p>		<p>8.2 Lactation</p> <p>Risk Summary Available information is insufficient to inform the amount of infliximab products present in human milk, and the effects on the breastfed infant. There are no data on the effects of infliximab products on milk production.</p> <p>The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for an infliximab product and any potential adverse effects on the breastfed infant from infliximab products or from the underlying maternal condition.</p>

REMICADE (reference product) labeling ^a	Pfizer proposed PF-06438179 labeling ^b	DPARP recommended PF-06438179 labeling
	(b) (4)	
		<p><u>Reviewer's comment:</u> Section 8.3 was removed to be consistent with the labeling for the approved infliximab biosimilar product, RENFLEXIS.</p>
Section 12. CLINICAL PHARMACOLOGY		
<p>12.1 Mechanism of Action</p> <p>Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial</p>	(b) (4)	<p>12.1 Mechanism of Action</p> <p>Infliximab products neutralize the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibit binding of TNFα with its receptors. Infliximab products do not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and</p>

REMICADE (reference product) labeling ^a	Pfizer proposed PF-06438179 labeling ^b	DPARP recommended PF-06438179 labeling
<p>layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed <i>in vitro</i> or <i>in vivo</i>. Infliximab inhibits the functional activity of TNFα in a wide variety of <i>in vitro</i> bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which REMICADE exerts its clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.</p>	<p>(b) (4)</p>	<p>6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab products can be lysed <i>in vitro</i> or <i>in vivo</i>. Infliximab products inhibit the functional activity of TNFα in a wide variety of <i>in vitro</i> bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which infliximab products exert their clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab products prevent disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allow eroded joints to heal.</p>
<p>Section 13. NONCLINICAL TOXICOLOGY</p>		
<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to</p>	<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>(b) (4)</p>	<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given</p>

REMICADE (reference product) labeling ^a	Pfizer proposed PF-06438179 labeling ^b	DPARP recommended PF-06438179 labeling
<p>evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the <i>in vivo</i> mouse micronucleus test or the <i>Salmonella-Escherichia coli</i> (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.</p>	<p>(b) (4)</p>	<p>cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the <i>in vivo</i> mouse micronucleus test or the <i>Salmonella-Escherichia coli</i> (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.</p>
<p>^a Current Remicade label as of 6/19/17 (http://fdalabel.fda.gov) ^b Pfizer's proposed labeling was submitted on 5/17/17</p>		

2 Drug Information

2.1 Drug

CAS Registry Number: 170277-31-3

Code Name: PF-06438179

Molecular Formula/Molecular Weight

Pfizer's amino acid sequence for PF-06438179 is presented below. Connecting lines indicate predicted intra- and inter-chain disulfide bonds. Putative complementarity determining regions are underlined. N-linked glycosylation sequence is in bold italics.

Light (L) Chain

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1  DILLTQSPAILSVSSPGERVSFSCRASQFVGSSIHWYQQRTNGSPRLLIKYASEMSGIPS 60
                                     |
61  RFSGSGSGTDFTLSINTVESEDIADYYCQQSHSWPFTFGSGTNLEVKRTVAAPSVFIFPP 120
                                     |
121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 180
                                     |
181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
                                     |
                                     → H Chain
    
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Heavy (H) Chain

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1  EVKLEESGGGLVQPGGSMKLSCVASGFIFSNHWMNWVRQSPEKGLEWVAEIRSKSINSAT 60
                                     |
61  HYAESVKGRFTISRDDSKSAVYLQMTDLRTEDTGVYYCSRNYYGSTYDYWGQGTTLTVSS 120
                                     |
121 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS 180
                                     |
181 GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG 240
                                     |
                                     ← L Chain
                                     |
                                     → H Chain
241 PSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN 300
                                     |
301 STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE 360
                                     |
361 LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSGDSFFLYSKLTVDKSRW 420
                                     |
421 QQGNVFSCSVMHEALHNHYTQKSLSLSPG (K) 450
    
```

Pfizer's theoretical molecular mass values for the major N-linked glycoforms of PF-06438179 are listed in the table below:

N-linked Glycoform	Theoretical Mass (Da)
G0F/G0F	148513.4
G0F/G1F	148675.5
G1F/G1F	148837.7

Biochemical Description

Infliximab is a chimeric human-murine antibody against human tumor necrosis factor α (TNF α), with a molecular weight of approximately 149 kDa. The molecule contains an approximately (b) (4) murine variable region amino acid sequence (antigen-binding region to human TNF α). (b) (4) a human IgG1 heavy chain constant region and a human kappa light chain constant region (IgG1 κ). Pfizer reports that the amino acid sequence of PF-06438179 is identical to that of REMICADE (infliximab), based on published literature.

PF-06438179 drug substance (DS) is produced in a (b) (4) cell line (b) (4). This cell line differs from the (b) (4) cell line used for production of licensed infliximab. Pfizer developed their biosimilar product using this cell line based on their knowledge and experience in cell culture and purification processes using this platform. The Sponsor acknowledges that the use of a different cell line for production of their product is likely to result in differences in post-translational modification of the protein.

Pharmacologic Class

Tumor necrosis factor (TNF) blocker

2.2 Relevant INDs, NDAs, BLAs and DMFs

Application	Sponsor	Relationship to current BLA
IND 114828	Pfizer	Nonclinical and clinical development of PF-06438179 were conducted under this IND
BLA 125544	Celltrion	<ul style="list-style-type: none"> ▪ INFLECTRA is the first approved infliximab biosimilar product in the United States (April 5, 2016) ▪ INFLECTRA labeling was not required to conform to PLLR guidelines (initial 351(k) BLA application was pending as of the effective date of the PLLR, 6/30/15)
BLA 761054	Samsung Bioepis	<ul style="list-style-type: none"> ▪ RENFLEXIS is the second approved infliximab biosimilar product in the United States (April 21, 2017) ▪ Drug product labeling for PF-06438179 is to be identical to RENFLEXIS

2.3 Drug Formulation

PF-06438179 is supplied as a lyophilized concentrate to be reconstituted with 10 ml of Sterile Water for Injection to a final infliximab concentration of 10 mg/ml. The reconstituted solution is further diluted with sterile 0.9% sodium chloride for administration by intravenous infusion. The instructions for preparation and administration of PF-06438179 are consistent with REMICADE.

Table 2. Composition of PF-06438179 & REMICADE drug product formulations.

PF-06438179 (Biosimilar)			REMICADE (Reference product)		
Component	Amount (mg/mL)	Amount (mg/vial)	Component	Amount (mg/mL)	Amount (mg/vial)
PF-06438179	10	100	Infliximab	10	100
Disodium succinate hexahydrate	1.21	12.1	Dibasic sodium phosphate dihydrate	0.61	6.1
Succinic acid	0.06	0.6	Monobasic sodium phosphate monohydrate	0.22	2.2
Sucrose	25	250	Sucrose	50	500
Polysorbate 80	0.05	0.5	Polysorbate 80	0.05	0.5
pH 6.0			pH 7.2		

2.4 Comments on Novel Excipients

The PF-06438179 drug product is presented in a succinate (b) (4) while the reference product is presented in a phosphate (b) (4). The PF-06438179 total succinic acid dose can range from approximately 22.9 to 76.2 mg/dose (based upon infliximab doses ranging from 3 to 10 mg/kg). The use of succinic acid as an excipient in the biosimilar DP represents a potential toxicologic concern. However, the nonclinical development program for PF-06438179 provides some support for the safety of this formulation. In particular, there was no evidence of relevant systemic toxicity in a 2 week (3 x once weekly doses) rat study with the clinical PF-06438179 formulation.

Furthermore there are multiple FDA-approved succinic acid-containing, intravenously administered drug products. KADCYLA (ado-trastuzumab emtansine) is an antibody-drug conjugate approved for repeated intravenous administration once every three weeks. This product includes sodium succinate at a concentration of (b) (4) mg/ml. At the maximum recommended human dose of 3.6 mg/kg, the succinic acid exposure is (b) (4) mg/dose. PARSABIV is another approved IV product (three times weekly dosing) that contains succinic acid in its formulation. The succinic acid exposure at the maximum recommended human dose of 15 mg PARSABIV is (b) (4) mg/dose.

There are minimal concerns related to the systemic toxicity of succinic acid given that it occurs widely as a natural constituent of plants and animals consumed as food by humans. It is considered Generally Recognized as Safe (GRAS) as a flavor enhancer and pH control agent for use in foods¹.

¹ GRAS Notice No. 552: Succinic Acid. May 13, 2015.

The approved dosing schedule for REMICADE (and the proposed dosing schedule for PF-06438179) includes at least 2 weeks (6 to 8 weeks in the maintenance phase) between each repeated dose. This low dosing frequency further minimizes the toxicologic concern for repeat dosing with succinic acid.

All other excipients in the PF-06438179 drug product are within the range of previously approved intravenous products. There are no nonclinical safety concerns related to the formulation differences between the biosimilar and reference products.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population and dosing regimen for PF-06438179 are identical to those of the reference product. Pfizer is seeking approval for PF-06438179 in all indications for which REMICADE is currently approved, with the exception of pediatric ulcerative colitis (protected by orphan drug exclusivity expiring on September 23, 2018).

The REMICADE dosage recommendation for RA is 3 mg/kg at 0, 2, and 6 weeks then every 8 weeks. The dose can be increased up to 10 mg/kg or treatment can be given as often as every 4 weeks. For Ankylosing Spondylitis, the treatment regimen is 5 mg/kg at 0, 2, and 6 weeks, then every 6 weeks. For all other indications the dosage is 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks with the provision that in adult Crohn's disease patients, the dose may be increased to 10 mg/kg if patients initially respond but later lose their response.

2.7 Regulatory Background

- January 28, 2013: DPARP provided responses to Pfizer's pre-IND questions. The nonclinical question and response are excerpted below:

Sponsor Question 2: *Assuming that the quality evaluation demonstrates similarity of infliximab-Pfizer to infliximab-US and EU-approved infliximab as outlined in briefing document, does the Agency agree that the proposed comparative single-dose, GLP-compliant, TK/tolerability study in male rats with EU-approved infliximab and infliximab-Pfizer is sufficient to support opening the IND and the subsequent FIH study in healthy volunteers?*

FDA Response: We do not agree. Given that there is no pharmacologically relevant species available for toxicology studies, the proposed single-dose, TK/tolerability study in male rats has limited value. Instead, we recommend an *in vivo* study in the Tg197 transgenic mouse to aid in assessing pharmacodynamic and pharmacokinetic similarity between PF-06438179 and EU-approved infliximab. We recommend that you include a range of 3 doses that will allow a dose-response assessment (e.g. 1, 3, and 10 mg/kg) below target saturation. This study should include appropriate PK parameters (i.e.,

AUC, C_{max} , T_{max}), an assessment of anti-drug antibody (ADA) formation, and a histopathological assessment of arthritic disease progression. Evaluation of parameters in this study will be used in addition to your *in vitro* analytical data to compare your proposed product to EU approved infliximab. Refer to FDA's response to Question 4 regarding use of a non-US-licensed comparator in nonclinical studies.

Additional Comment:

...FDA supports a risk-based approach to determining the necessity of animal studies to support opening an IND for a biosimilar development program. The lack of analytical similarity data at the time you are requesting FDA advice on your proposed nonclinical program to support opening an IND and the lack of information regarding the intended amount of analytical similarity data to be submitted at the time of IND opening precludes us from assessing risk. **If analytical similarity data was provided, a different assessment of risk may be made leading to revision of the advice regarding your nonclinical program intended to support opening your IND.**

- March 28, 2013. Pfizer submitted the opening IND materials for IND 114828 to support development of PF-06438179 in the United States
- April 10, 2013: A nonclinical information request was sent to Pfizer. The content of the IR is shown below:
 1. The Division provided a written response to your Nonclinical pre-IND meeting question (1/28/2013) recommending that you conduct an *in vivo* study in Tg197 transgenic mice (which express human TNF α) to assess pharmacodynamic and pharmacokinetic similarity between infliximab-Pfizer and the reference product. Pharmacodynamic and pharmacokinetic similarity cannot be assessed in the rat, as it is not a pharmacologically relevant species in which to test this molecule. Further, an *in vivo* study with Tg197 mice would provide safety information, which cannot be provided by a study in rats. Provide justification for your decision to not conduct an *in vivo* study with Tg197 mice.
 2. You are proposing a clinical dose of 10 mg/kg for your Phase 1 single dose study in healthy volunteers. This dose exceeds the approved clinical dose for infliximab. At this high dose, it is likely that systemic exposure will be saturated and differences between infliximab-Pfizer and the reference product will be obscured. Further, as noted above, an *in vivo* study with Tg197 mice was not conducted. Thus, assessments of pharmacodynamic and pharmacokinetic similarity as well as safety are not available to provide support for the use of your product at the approved clinical dose for infliximab. Provide justification for using the clinical dose of 10 mg/kg in your Phase 1 study.
- April 15, 2013: Pfizer provided their responses to the Division's questions. The main points put forth by Pfizer in support of their nonclinical development program are summarized as follows:

1. 10 mg/kg Remicade is an approved dose that “can be used in chronic therapy in some patients with rheumatoid arthritis and Crohn’s disease”.
 - As stated in their IND package: Use of a higher infliximab dose would result in decreased ADA formation and therefore decreased PK variability.
 2. The CMC data shows that infliximab-Pfizer is sufficiently similar to Reference Infliximab that it supports reduced *in vivo* nonclinical studies and evaluation.
 3. The Tg197 mouse model is an efficacy model. Detecting differences in toxicity in animals experiencing systemic inflammation and joint swelling would be difficult.
 4. The objective of the first in human study is to determine PK similarity, not pharmacodynamic similarity
 - Clinical PK of infliximab is linear over a wide range of doses – saturation is not expected at 10 mg/kg dose [Note: this statement was verified by the Clinical Pharmacology reviewer Liang Zhao on 4/16/13].
 5. Their single dose rat study provides data on non-target mediated toxicity of infliximab-Pfizer relative to reference infliximab
 6. There is clinical experience with infliximab in healthy volunteers at doses up to 10 mg/kg
 - Preliminary data from a Pfizer sponsored pilot study in 20 healthy subjects treated with a single 10 mg/kg IV infliximab dose (EU Remicade). No data was included in the submission (data is stated to be on file at Pfizer).
- April 28, 2013: The nonclinical review team concluded that Pfizer’s proposed clinical investigation of PF-06438179 at a dose of 10 mg/kg was safe to proceed:
 1. The physico-chemical characterization data and in vitro functional data provided evidence that PF- 06483179 was provisionally highly similar to the reference product according to Product Quality reviewers from the Office of Biologic Products.
 2. Clinical Pharmacology reviewer Liang Zhou confirmed that systemic exposure of infliximab is linear at doses between 3 – 20 mg/kg. There is clinical experience with the 10 mg/kg infliximab dose in healthy volunteers in studies carried out by the Innovator as well as by Pfizer.
 3. DPARP, in consultation with Pharmacology/Toxicology Associate Directors David Jacobson-Kram and Paul Brown, judged that the

requirement for an additional toxicology study in Tg197 mice would not be necessary prior to initiation of a single dose clinical study in healthy volunteers.

3 Studies Submitted

3.1 Studies Reviewed

Study	Description	Test articles used
12GR295	Single dose TK study in male rats	PF-06438179 EU-approved infliximab
14GR168	Repeat dose (2 week) TK/toxicology study in male & female rats	PF-06438179

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study 12GR295: Single dose intravenous bolus toxicokinetic and tolerability study of PF-06438197 and EU-approved infliximab in male rats

Study Rationale

Pfizer chose not to follow the Division's recommendation to carry out an *in vivo* comparative efficacy study in Tg197 mice (See Section 2.7). Pfizer provided several reasons to support their use of rats rather than Tg197 mice in this study. These include:

- (1) The innovator (Centocor) carried out studies in rats to examine non-target mediated effects of infliximab.
- (2) Rat FcRn binds to the Fc region of human IgG. Therefore the rat provides information on non-target related clearance/antibody recycling of human IgGs.
- (3) The use of the rat allowed for serial blood sampling for PK assessment.
- (4) The Tg197 mouse model is primarily an efficacy model for RA therapies. Tg197 mice experience systemic inflammation, weight loss and joint swelling. From the sponsor's perspective, the objective of the *in vivo* nonclinical studies in development of their biosimilar product is to identify differences in PK parameters and toxicity between PF-06438179 and EU-approved infliximab. It would be challenging to quantify differences in treatment-induced toxicity in an RA disease model. Therefore, the rat represents a better model for evaluating differences in treatment-induced toxicity.

Key Study Findings

- After a single IV dose at 10 or 50 mg/kg, pharmacokinetic parameters (C_{max} , T_{max} , AUC_{0-1344}) were comparable between PF-06481379 and EU-approved infliximab.
- The significance of the results from this study is uncertain due to the fact that the rat is not a pharmacologically relevant species for infliximab products (no binding to rat TNF- α).

Methods

The design for Study 12GR295 is summarized below:

Group Number	Test or Control Article or Vehicle Control	Dose (mg/kg) ^a	Concentration (mg/mL)	Dose Volume (mL/kg) ^b	Main Study Animal Numbers Males
1	Vehicle Control ^c	0	0	5	1-5
2	Infliximab-Pfizer	10	2	5	6-10
3	Infliximab-Pfizer	50	10	5	11-15
4	Vehicle Control ^d	0	0	5	16-20
5	Infliximab-EU	10	2	5	21-25
6	Infliximab-EU	50	10	5	26-30

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

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

c. Vehicle Control Article/Diluent 1.

d. Vehicle Control Article/Diluent 2.

Test articles used

- PF-06438179 (Lot 94200)
- EU-approved infliximab (Lot 2RMA63702)

Animals

Male Rats ($n=5$ /group, 9-10 weeks, 338 – 393 g) were administered a single intravenous bolus dose of 0, 10, or 50 mg/kg infliximab. The rationale for using male rats only is explained by reference to an absence of sex-related differences in infliximab PK in the non-clinical setting based on data from the Innovator.

There were two control groups: one for PF-06438179 vehicle and one for EU-approved infliximab vehicle. The clinical formulations for both PF-06438179 and EU-approved infliximab were used in this study.

Experimental Methods

Rats were retained for 8 weeks after the infliximab dose for observation and toxicokinetic sampling. Clinical signs were observed twice daily on non-dosing days. On the day of dosing, clinical signs were recorded pre-dose, 1 and 4 hours post dose and at the end of the work day. Body weights were measured twice during the pretreatment period, prior to dosing on Day 1, and weekly thereafter for 8 weeks. Food consumption was measured weekly for 8 weeks after infliximab administration.

Blood samples were taken for TK analysis at 0.5, 4, 8, 24, 48, 96, 168(1 wk), 336 (2 wk), 672 (4 wk), 1008 (6 wk), and 1344 (8 wk) hours post dose. Samples from all dose groups from pretreatment, day 1, 6 weeks, and 8 weeks post dose were evaluated for anti-drug antibodies (ADA).

Serum infliximab concentrations were determined using a validated ELISA. Wells were coated with human TNF α . Separate standard curves were prepared using PF-06438179 and EU-approved infliximab. The lower limit of quantitation was listed as 100 ng/ml.

The ADA assay also used an ELISA platform. Serum samples were incubated with biotinylated drug substance (PF-06438179 or EU-approved infliximab) and sulfo-tagged ruthenium labeled drug substance. The resulting mixture was added to streptavidin coated ELISA plates. ADAs were detected via electrochemiluminescence (ECL). The positive control was rabbit anti-EU-approved infliximab and the negative control was pooled normal rat serum. Sensitivity was listed as 21.4 ng/ml.

Results

There were no deaths, and no treatment related effects on clinical signs, body weight, or food consumption. There was no histopathology assessment conducted. Plots of mean serum infliximab concentration over time are shown in Figure 1. PF-06438179 and EU-approved infliximab show similar serum concentrations over time at both the 10 mg/kg and 50 mg/kg dose levels.

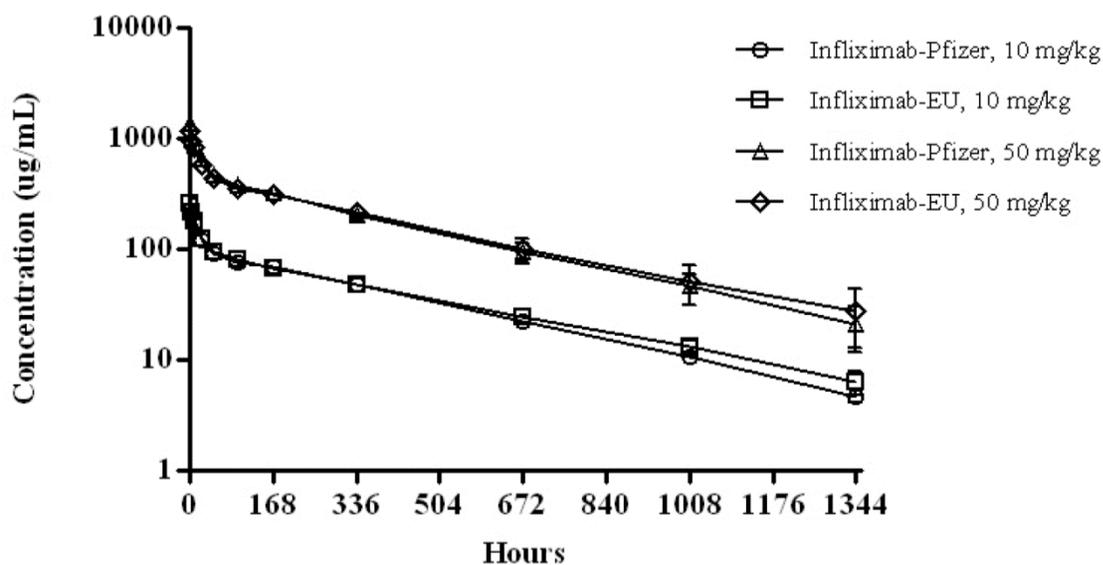


Figure 1. Serum concentration of PF-06438179 or EU-approved infliximab in male rats after a single intravenous dose of 10 mg/kg or 50 mg/kg (Sponsor's figure).

Pharmacokinetic parameters are summarized in Table 3. C_{max} is comparable between PF-06438179 and EU-approved infliximab at both the 10 mg/kg and 50 mg/kg doses. Systemic exposure over 8 weeks after infliximab administration is also comparable between the biosimilar and reference products at both the 10 mg/kg and 50 mg/kg doses. Both C_{max} and $AUC_{0-1344 h}$ increase approximately proportionally with dose for PF-06438179 and EU-approved infliximab. Furthermore T_{max} (0.5 -1.2 h) and $T_{1/2}$ (300 – 350 h [12-14 d], not shown) are comparable between PF-06438179 and EU-approved infliximab at both dose levels.

Table 3. Sponsor's summary table of toxicokinetic data from single dose (IV) administration of infliximab-Pfizer or EU-approved infliximab to male rats (Study 12GR295).

Dose (mg/kg)	C _{max} (µg/mL)			C _{max} Ratio ^a	T _{max} (Hours)			AUC ₁₃₄₄ (µg•Hours/mL)			AUC ₁₃₄₄ Ratio ^a
	Mean	SD	n		Mean	SD	n	Mean	SD	n	
10 Infliximab-Pfizer	225	53.3	5	0.88	1.2	1.6	5	45000	2000	5	0.96
10 Infliximab-EU	256	19.4	5		0.50	0.0	5	47100	2700	5	
50 Infliximab-Pfizer	1340	113	5	1.16	0.50	0.0	5	206000	23700	5	0.99
50 Infliximab-EU	1160	30.3	5		0.50	0.0	5	209000	31700	5	

Anti-drug antibodies were not detected in treated rats in this study. The presence of high levels of drug in serum samples may have interfered with ADA detection. There were no unusual declines of drug exposure that might have been suggestive of the presence of ADA.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: 2-week intravenous bolus toxicity study of PF-06438179 in Sprague-Dawley rats

Study no.:	14GR168
Study report location:	BLA 761072 Module 4.2.3.2
Conducting laboratory and location:	Pfizer Worldwide Research & Development Groton, CT USA
Date of study initiation:	May 8, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PF-06438179 Lot #A03038 97.3% intact IgG

Key Study Findings

- There was no Reference Product comparator group included in this study. Direct comparison of the potential toxicity of PF-06438179 relative to the reference product was not possible.
- In a published paper, Pfizer states that the conduct of this study was required by another “country/region” before clinical trials could proceed²
- The study was evaluated in the current review to assess whether repeated intravenous administration of PF-06438179 induced overt and/or unexpected toxicity in rats. The study data contributes to the assessment of safety of the succinic acid-containing drug product formulation administered by the IV route.
- Injection site findings were consistent with expected findings with intravenously administered products (inflammation, hemorrhage/necrosis) and were of minimal severity
- Liver sinusoidal cell hyperplasia was observed in 9/10 HD males and 9/10 HD females vs. 0/10 in control or LD males and females

² Derzi, M. et al. (2016) Nonclinical evaluation of PF-06438179: A potential biosimilar to Remicade® (Infliximab). *Advances in Therapy*. 33, 1964-1982.

- PF-06438179 exposure increased approximately proportionally with dose
 - There was no evidence for decreased exposure in individual rats that could be attributable to anti-drug antibodies

Methods

Doses: 0 mg/kg (clinical vehicle formulation)
10 mg/kg
50 mg/kg

Frequency of dosing: Once weekly

Route of administration: Intravenous

Dose volume: 5 ml/kg

Formulation/Vehicle: Disodium succinate hexahydrate (1.2 g/L)
Succinic acid (0.06 g/L)
Sucrose (25 g/L)
Polysorbate 80 (0.06 g/L)

Species/Strain: Sprague Dawley rat

Number/Sex/Group: Main study: 10
TK: 3

Age: 9 weeks

Weight: Males: 289 – 342 g
Females: 204 – 252 g

Satellite groups: TK animals were included

Study Design

Group Number	Dose (mg/kg) ^a	Concentration (mg/mL)	Dose Volume (mL/kg) ^b	Main Study <u>Animal Numbers</u>		Toxicokinetic (TK) Study <u>Animal Numbers</u>	
				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	50	10	5	21-30	51-60	NA	NA
4	0	0	5	NA	NA	501-503	512-514
5	10	2	5	NA	NA	504-507	515-518
6	50	10	5	NA	NA	508-511	519-522

NA = Not Applicable

a. All doses are expressed as mg of protein per kg of body weight.

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

- Animals received IV bolus injections on study days 1, 8, and 15
- Hematology, coagulation, and clinical chemistry parameters were evaluated in Main Study animals on Day 16; samples were collected at necropsy. Urinalysis parameters were evaluated in Main Study animals on Day 16.
- Main study animals were fasted overnight and euthanized on Day 16. Necropsy, tissue collection, organ weights, macroscopic tissue evaluation, and microscopic examination were performed. A complete battery of tissues were examined microscopically in control and HD males and females.

Observations and Results

There were no treatment-related findings in any parameter evaluated, with the exception of histopathology (see below).

Histopathology

Adequate Battery

Yes

Peer Review

Yes

Histological Findings

- Liver sinusoidal cell hyperplasia was observed in 9/10 HD males and 9/10 HD females vs. 0/10 in control or LD males and females (Table 4)
 - This finding is not attributable to binding of PF-06438179 to TNF- α , as this molecule does not bind to rat TNF- α
 - This finding likely represents an adaptive biological response to the large doses of human-mouse chimeric protein administered to rats and is not considered relevant to humans
 - The lack of a reference product comparator makes it impossible to

establish whether these findings are unique to PF-06438179

- Liver sinusoidal hyperplasia was an expected finding in light of comparable observations in repeated dose rat toxicology studies with other infliximab biosimilar products and EU-approved infliximab
- Injection site findings in vehicle and PF-06438179 treated animals were consistent with expected findings of intravenously administered products (inflammation, hemorrhage/necrosis) and were of minimal severity

Table 4. Summary of treatment-related microscopic findings after 3 once-weekly doses of PF-06438179 in rats.

	Males			Females		
	0	10	50	0	15	40
DRUG (mg/kg)	0	10	50	0	15	40
number of animals	10	10	10	10	10	10
LIVER (# examined)	10	10	10	10	10	10
Hyperplasia: sinusoidal cell						
Minimal	0	0	8	0	0	6
Mild	0	0	1	0	0	3
TOTAL	0	0	9	0	0	9
INJECTION SITE (# examined)	10	0	10	10	0	10
Inflammation/necrosis						
Minimal	5	NE	3	2	NE	5
Hemorrhage						
Minimal	3	NE	5	4	NE	6

Toxicokinetics

- PF-06438179 exposure increased approximately proportionally with dose (Table 5).
- There was no evidence for decreased exposure in individual rats that could be attributable to anti-drug antibodies
- There were no observed differences in exposure between males and females
- Slight accumulation was observed with once weekly dosing
 - 10 mg/kg: 1.7-fold
 - 50 mg/kg: 1.6-fold

Table 5. Mean toxicokinetic parameters in rats on study day 1 and 8 after once weekly IV administration of PF-06438179 in rats

Dose (mg/kg) ^a	Study Day	Sex	C _{max} (µg/mL)			T _{max} (h)			AUC ₁₆₈ (µg•h/mL)		
			Mean	SD	n	Mean	SD	n	Mean	SD	n
10	1	Male	205	9.47	4	1.0	0.0	4	15000	850	4
		Female	223	11.6	4	1.0	0.0	4	16200	222	4
		Overall	214	13.8	8	1.0	0.0	8	15600	882	8
	8	Male	300	21.8	4	1.0	0.0	4	25500	1220	4
		Female	308	19.6	4	1.0	0.0	4	26300	1170	4
		Overall	304	19.6	8	1.0	0.0	8	25900	1200	8
50	1	Male	1050	84.4	4	1.0	0.0	4	74600	7240	4
		Female	933	98.2	4	1.0	0.0	4	70100	7930	4
		Overall	993	107	8	1.0	0.0	8	72300	7420	8
	8	Male	1420	86.9	4	1.0	0.0	4	117000	13100	4
		Female	1300	106	4	1.0	0.0	4	114000	13600	4
		Overall	1360	111	8	1.0	0.0	8	115000	12500	8

AUC₁₆₈ = Area under the serum drug concentration-time curve from 0-168 hours; C_{max} = Highest drug concentration observed in serum; h = hours; n = Sample size; Overall = Combined male plus female; SD = Standard deviation; T_{max} = Time at which C_{max} was first observed.
a. Doses were administered on Study Days 1 and 8.

11 Integrated Summary and Safety Evaluation

Pfizer submitted BLA 761072 on February 13, 2017 seeking approval of PF-06438179 as a biosimilar to US-licensed REMICADE (infliximab). Pfizer's analytical assessment of PF-06438179 (including physicochemical characterization as well as in vitro functional evaluation), submitted at the time that the initial IND was opened (IND 114828, March 28, 2013), was judged to be sufficient to allow for a limited in vivo nonclinical assessment of this molecule.

The clinical PF-06438179 formulation uses a succinate (b) (4). This formulation differs from the reference product which uses a phosphate (b) (4) formulation. There is sufficient data for the safety qualification of succinic acid administered by the IV route with particular reference to potential systemic toxicity. The nonclinical assessment of similarity between PF-06438179 and REMICADE was based on in vivo pharmacokinetic and toxicology data in rats only; it is noted that rats are not a pharmacologically relevant species with infliximab.

After a single IV dose at 10 or 50 mg/kg to male SD rats, pharmacokinetic parameters (T_{max}, C_{max}, and AUC₀₋₁₃₄₄) were comparable between PF-06438179 and EU-approved infliximab. Mean C_{max} and AUC₀₋₁₃₄₄ values in PF-06438179 treated rats were 88 – 116% and 96 – 99% of mean EU-approved infliximab values, respectively.

The effects of repeated IV doses of PF-06438179 were investigated in a two week study in male and female SD rats. There was no REMICADE comparator arm included in this study. Three once-weekly IV doses of PF-06438179 at 0, 10, or 50 mg/kg resulted in injection site findings including hemorrhage and inflammation/necrosis in vehicle and high dose animals. The findings were of minimal severity, and are consistent with expected injection site observations in IV studies in rats. Liver sinusoidal cell hyperplasia (minimal – mild) was observed in HD males and females. This finding likely represents an adaptive biological response to the large doses of infliximab, a human-mouse chimeric protein, administered to rats and was judged to have little or no relevance to humans.

The in vivo nonclinical data in rats provided in the BLA support a demonstration of pharmacokinetic similarity between PF-06438179 and EU-approved infliximab. This study also provides support for the use of succinate (b) (4) in the DP formulation.

Recommendation: BLA 761052 is recommended for approval from the nonclinical toxicology perspective. There are no outstanding nonclinical issues.

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/s/

MATTHEW T WHITTAKER
10/20/2017

TIMOTHY W ROBISON
10/20/2017
I concur

PHARMACOLOGY/TOXICOLOGY REVIEW
Safety Assessment of Extractables and Leachables

Date: October 19, 2017

BLA number: 761072

Sponsor: Pfizer

Drug substance: PF-06438179 (proposed biosimilar to infliximab)

Indication(s): All approved indications for REMICADE

Route of administration: Intravenous

Reviewer name: Matthew Whittaker, Ph.D.

Division: Pulmonary, Allergy, and Rheumatology Products (DPARP)

EXECUTIVE SUMMARY

Pfizer has adequately identified leachable compounds from the stopper of the PF-06438179 drug product container closure system. All potential leachables are qualified for safety from the nonclinical perspective.

Introduction

BLA 761072 was submitted by Pfizer, Inc. on February 13, 2017 under section 351(k) of the Public Health Service Act (PHS Act) to support registration of PF-06438179 as a biosimilar to US-licensed REMICADE (infliximab). This review provides a safety evaluation of extractables and leachables for the PF-06438179 container closure system. The overall nonclinical toxicology evaluation and labeling recommendations for this application are provided in a separate review.

Extractables Study

The container closure system for PF-06438179 consists of the following components:

- (1) Vial (15 mL, (b) (4) glass, clear).
- (2) Stopper (20 mm (b) (4) (b) (4)). The specific stopper type is: (b) (4) .
- (3) Crimp seal (20 mm (b) (4) (b) (4))

Extraction studies were conducted on the rubber stoppers to be used in the PF-06438179 container closure system to identify compounds for monitoring in subsequent leachables studies.

Briefly, for each extraction condition, 10 stoppers were cut into thin strips of approximately 0.1” thickness. The following solvents were used for extraction: (1) purified water, (2) acidified water (pH 3, formic acid), (3) alkaline water (pH 10, sodium hydroxide), (4) isopropanol (IPA), and (5) hexane.

Two different extraction techniques were used: (1) Sealed pressure vessel extraction and (2) Controlled extraction using a reflux apparatus. The sealed pressure vessel technique is reported to be a more sensitive technique for detection of volatile compounds. The sealed vessel retains volatile compounds that are extracted, whereas in the reflux technique, volatile compounds can escape through the reflux condenser.

Extractions were carried out under the following conditions:

	Sealed Pressure Vessel method		Reflux Apparatus method	
Solvent	Solvent Volume (ml)	Conditions	Solvent Volume (ml)	Conditions
Aqueous	50	90°C for 24 h	50	Reflux 16 h
Purified water	50	90°C for 24 h	50	Reflux 16 h
Acidified water (pH 3)	50	90°C for 24 h	50	Reflux 16 h
Alkaline water (pH 10)	50	90°C for 24 h	50	Reflux 16 h
IPA	50	72°C for 24 h	50	Reflux 16 h
Hexane	50	58°C for 24 h	50	Reflux 16 h

Extracts were then analyzed for quantitation of extractable materials using the following methodologies:

- (1) Volatile extractables: headspace gas chromatography/mass spectrometry (HS GC/MS)
- (2) Semi-volatile extractables: GC/MS
- (3) Non-volatile extractables: liquid chromatography/ultraviolet mass spectrometry (LC/UV/MS)

Results

Extraction studies with rubber stoppers identified volatile, semi-volatile, and non-volatile compounds. Volatile compounds included [REDACTED] (b) (4)

Semi-volatile compounds included [REDACTED] (b) (4)

[REDACTED] was the most abundant volatile and semi-volatile extractable.

There were no non-volatile compounds observed in the aqueous extractions, which was considered the more relevant condition. Non-volatile compounds confirmed to be present in the

IPA and hexane extracts included: (b) (4). Based on Product Quality Research Institute (PQRI) recommendations and projected dosing strategy, these studies identified the following potential leachable compounds for leachables study monitoring:

(b) (4)

Leachables Study (Study INX100236564)

Leachables studies are ongoing to determine the levels of (b) (4) in lyophilized PF-06483179 drug product (**Lot A02637**) under storage conditions of $5 \pm 3^\circ\text{C}$ and $30 \pm 2^\circ\text{C}$. These studies are designed to extend out to 60 months. Leachable data up to the 24 month time point has been provided in the BLA.

Safety assessment was conservatively based on the highest detected level of each leachable at any time point and storage condition. Leachable total intake values ($\mu\text{g}/\text{dose}$) were calculated using a maximal PF-06438179 dose of 600 mg (based on a 10 mg/kg dose and 60 kg body weight). The PF-06438179 DS concentration is 10 mg/ml.

Results

The leachable quantities after 6, 12, and 24 months of storage at 5°C and 30°C are reported in Table 1. (b) (4) levels were below the quantitation limit at all time points.

Table 1. Summary of leachable concentrations measured in PF-06483179 DP under storage at 5°C or 30°C .

Compound	Quantitation limit (ng/ml)	Initial (ng/ml)	6 months (ng/ml)	12 months (ng/ml)	24 months (ng/ml)
5°C					
(b) (4)					
30°C					
(b) (4)					
ND: Not detected					

The maximum potential exposure of each leachable on a per dose basis is presented in Table 2.

Table 2. Maximum potential exposure for leachables detected in PF-06483179 drug product. Values are derived from the maximum leachable concentration measured from any time point under any storage condition.

Compound	Maximum potential exposure (µg/dose)
	(b) (4)

Safety assessment

Safety evaluations are based on an assumption of daily exposure. It is noted that infliximab products are administered only every 2 – 8 weeks.



(b) (4)



Conclusions

(b) (4) were identified as potential leachables from the PF-06438179 DP container closure system. The maximum potential exposures of both compounds on a per dose basis are considered qualified from the nonclinical perspective.

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/s/

MATTHEW T WHITTAKER

10/19/2017

This is a review of extractables and leachables from the CCS.

TIMOTHY W ROBISON

10/19/2017

I concur