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*APPLICATION NUMBER:*

**761072Orig1s000**

**SUMMARY REVIEW**

## Cross-Discipline Team Leader Review/ Division Director Summary

<b>Date</b>	<i>Electronic Stamp Date</i>
<b>From</b>	Banu A. Karimi-Shah, M.D. Badrul A. Chowdhury, M.D., Ph.D.
<b>Subject</b>	Cross-Discipline Team Leader Review Division Director Summary Review
<b>BLA #</b>	351(k) BLA 761072
<b>Applicant</b>	Pfizer
<b>Date of Submission</b>	February 13, 2017
<b>Scientific BsUFA Goal Date</b>	December 13, 2017
<b>Proprietary Name (Proposed) / Nonproprietary names</b>	Ixifi PF-06438179 <sup>1</sup> , infliximab-qbtx
<b>Dosage Forms / Strength</b>	Sterile lyophilized powder in a 15 mL capacity vial/ 100 mg per vial
<b>Route of Administration</b>	Intravenous
<b>Proposed Indication(s)</b>	<ul style="list-style-type: none"><li>• Crohn's Disease (Adult and Pediatric)</li><li>• Ulcerative colitis (Adult and Pediatric<sup>2</sup>)</li><li>• Rheumatoid arthritis</li><li>• Ankylosing spondylitis</li><li>• Psoriatic arthritis</li><li>• Plaque psoriasis</li></ul>
<b>Recommended:</b>	<i>Approval as a biosimilar to US-licensed Remicade for the same indications except for pediatric ulcerative colitis, as Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity</i>

### 1) Introduction

Pfizer (referred to as Pfizer or “the Applicant” in the rest of this document) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for PF-06438179, a proposed biosimilar to Remicade (infliximab). BLA 103772 for Remicade was initially licensed by FDA on August 24, 1998, and the BLA is currently held by Janssen Biotech, Inc. US-licensed Remicade is the reference product for Pfizer’s

<sup>1</sup> In this document, we generally refer to Pfizer’s proposed product by the Pfizer descriptor “PF-06438179” which was the name used to refer to this product during development. Subsequently, the nonproprietary name for this proposed product was determined to be “infliximab-qbtx.”

<sup>2</sup> This reflects information for PF-06438179 that Pfizer submitted in the BLA. We note that 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/oopd/index.cfm>. Accordingly, FDA will not license PF-06438179 for this indication until the orphan drug exclusivity expires.

351(k) BLA. Pfizer is seeking licensure of PF-06438179 for the same indications as US-licensed Remicade:<sup>3</sup>

- 1) Crohn's Disease (CD):
  - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
  - reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
- 2) Pediatric Crohn's Disease (pediatric CD):
  - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
- 3) Ulcerative Colitis (UC):
  - reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.
- 4) Pediatric Ulcerative Colitis (pediatric UC):
  - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.<sup>4</sup>
- 5) Rheumatoid Arthritis (RA) in combination with methotrexate:
  - reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.
- 6) Ankylosing Spondylitis (AS):
  - reducing signs and symptoms in patients with active ankylosing spondylitis.
- 7) Psoriatic Arthritis (PsA):
  - reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
- 8) Plaque Psoriasis (PsO):
  - treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

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<sup>3</sup> Remicade USPI

<sup>4</sup> 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/ood/index.cfm>. Accordingly, FDA will not license PF-06438179 for this indication until the orphan drug exclusivity expires.

Although the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology and Inborn Errors Products (DGIEP), and the Division of Dermatology and Dental Products (DDDP) during the course of the review.

The application consists of:

- Extensive analytical data intended to support (i) a demonstration that PF-06438179 and US-licensed Remicade are highly similar, (ii) a demonstration that PF-06438179 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet appropriate quality standards and (iii) a justification of the relevance of comparative data generated using the European Union (EU)-approved Remicade to support a demonstration of biosimilarity of PF-06438179 to US-licensed Remicade.
- A single-dose pharmacokinetic (PK) study (Study B5371001) providing a 3-way comparison of PF-06438179, US-licensed Remicade, and EU-approved Remicade intended to (i) support PK similarity of PF-06438179 and US-licensed Remicade and (ii) provide a PK bridge to support the relevance of the comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of PF-06438179 to US-licensed Remicade.
- A comparative clinical study (Study B5371002) between PF-06438179 and EU-approved Remicade in patients with RA. This was a 78-week, randomized, double-blind, parallel group study conducted in 650 patients with moderate to severely active RA on background methotrexate (MTX). Subjects were randomized 1:1 to PF-06438179 or EU-approved Remicade at a dose of 3 mg/kg through a 2-hour intravenous (IV) infusion at Weeks 0, 2, 6, and every 8 weeks thereafter, and remained on the background of methotrexate (MTX) throughout the study.
- A scientific justification for extrapolation of data to support biosimilarity in each of the additional indications for which Pfizer is seeking licensure, specifically Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis,<sup>5</sup> ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

Pfizer submitted comparative analytical data on the PF-06438179 lots used in clinical studies intended to support a demonstration of biosimilarity ("clinical product lots") and on the proposed commercial product. Based on our review of the data provided, Pfizer's comparative analytical data for PF-06438179 demonstrate that PF-06438179 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components.

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<sup>5</sup> 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/ood/index.cfm>. Accordingly, FDA will not license PF-06438179 for this indication until the orphan drug exclusivity expires.

Pfizer used a non-US-licensed comparator (EU-approved Remicade) in some studies intended to support a demonstration of biosimilarity to US-licensed Remicade. Accordingly, Pfizer provided scientific justification for the relevance of data from those studies to support a demonstration of biosimilarity of PF-06438179 to US-licensed Remicade by establishing an adequate scientific bridge (analytical and PK) between EU-approved Remicade, US-licensed Remicade, and PF-06438179.

The results of the comparative clinical efficacy, safety, immunogenicity, and PK studies indicate that Pfizer's data support a demonstration of "no clinically meaningful differences" between PF-06438179 and US-licensed Remicade in terms of safety, purity, and potency in the indications studied. Further, the single transition from EU-approved Remicade to PF-06438179 during the second part of Study B5371002 in RA did not result in different safety or immunogenicity profiles. This supports the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition from US-licensed Remicade to PF-06438179.

In considering the totality of the evidence, the data submitted by Pfizer support a demonstration that PF-06438179 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between PF-06438179 and US-licensed Remicade in terms of the safety, purity, and potency of the product, in the studied indication of RA.

The Applicant has also provided an extensive data package to address the scientific considerations for the extrapolation of data to support biosimilarity in other conditions of use and licensure of PF-06438179 for each of the indications for which US-licensed Remicade is currently licensed and for which Pfizer is seeking licensure.<sup>6</sup>

## 2) Background

### *The BPCI Act*

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

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<sup>6</sup> We note that 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/ood/index.cfm>. Accordingly, FDA will not license PF-06438179 for this indication until the orphan drug exclusivity expires.

Section 351(i) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a “stand-alone” marketing application). The goal of a “stand-alone” development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and, once the applicant has established that the proposed biosimilar product meets the analytical similarity prong of the biosimilarity standard, the amount of residual uncertainty remaining can be assessed with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

The ‘totality of the evidence’ submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

### ***Reference Product***

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with a reference product. When an applicant's proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

### ***Relevant Regulatory History***

FDA and Pfizer had a number of pre-submission meetings and interactions to discuss the PF-06438179 development program. During the pre-submission interactions, FDA provided product quality, nonclinical, and clinical comments, including recommendations to the Applicant regarding clinical development, such as:

- Design, endpoints, and selection of the similarity margin for the comparative clinical study in RA.
- Assessment of safety and immunogenicity in the setting of patients who undergo a single transition from EU-approved Remicade to PF-06438179 to provide a descriptive comparison with patients who continue on EU-approved Remicade in the RA comparative clinical study.
- Demonstration of PK similarity between PF-06438179, US-licensed Remicade, and EU-approved Remicade.
- Expectations for the scientific justification for extrapolation of biosimilarity.

Three key regulatory interactions are listed below:

- Biosimilar Biological Product Development (BPD) Type 2 Meeting: December 18, 2013
  - Discussed the proposed comparative efficacy study protocol B5371002
- BPD Type 3 Meeting: August 5, 2014
  - Reviewed the adequacy of the functional, structural and PK similarity data to support the comparative clinical development plan
- BPD Type 2 Meeting: July 8, 2016
  - Discussed the extent of clinical data to be included in the BLA, as well as CMC/Stability, blinding strategy and proposed statistical analyses for Study B5371002.
- BPD Type 4 Meeting: November 22, 2016
  - Discussed the format and content of the proposed BLA submission.

Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP).

### 3) CMC/Product Quality

*CMC Reviewer: Yanming Yan, Ph.D. (for drug substance) and Sarah Arden, PhD (for drug product);*

*CMC Statistical Reviewer: Yu-Ting Weng, Ph.D.; CMC Statistical Supervisor: Meiyu Shen, Ph.D.;*

*Immunogenicity Reviewer: Sarah Arden, Ph.D.;*

*Microbiology Reviewers: Kathleen Jones, Ph.D. (for drug substance) and Aimee*

*Cunninghman, Ph.D. (for drug product); Microbiology Team Lead: Patricia Hughes, Ph.D.;*

*Facilities Reviewer: Marion Michaelis; Facilities Team Lead: Zhihao (Peter) Qiu, Ph.D.*

*OBP Labeling: Vicky Borders-Hemphill, Pharm.D.*

*OBP Director: Steven Kozlowski, M.D.*

*Application Technical Lead: Christopher Downey, Ph.D.*

- **General product quality considerations**

PF-06438179 (infliximab-qbtx) is a recombinant chimeric human/mouse IgG1 $\kappa$  monoclonal antibody that binds to TNF- $\alpha$ . PF-06438179 consists of 4 polypeptide chains (2 heavy chains and 2 light chains) comprised of 1328 amino acids and has a molecular weight of approximately 149.1 kDa. The PF-06438179 drug substance (DS) manufacturing process involves (b) (4)

(b) (4). All drug substance lots were manufactured at (b) (4)

(b) (4). The stability data support an PF-06438179 DS expiration dating period of (b) (4) months when stored at (b) (4) °C.

PF-06438179 drug product (DP) is a sterile, white, lyophilized concentrate for intravenous injection in a single-use, 15 mL vial. Lyophilized PF-06438179 DP is reconstituted with 10 mL of sterile water for injection (WFI) to yield a single dose formulation of 10 mg/mL infliximab-qbtx at pH 6, and is further diluted in 0.9% sodium chloride solution for infusion. PF-06438179 DP does not contain preservatives. The PF-06438179 DP is manufactured by Pfizer Manufacturing Belgium NV, Rijksweg 12, Belgium. The stability data support PF-06438179 DP expiration dating period of 42 months when stored at 2°C to 8°C.

The PF-06438179 final DS and DP processes are fully validated, and the manufactured product is of a consistent quality. The controls that have been established for the routine manufacture of PF-06438179 DS and PF-06438179 DP meet regulatory requirements. However, the product quality review team recommends, and we agree with, six post-marketing commitments (PMCs) which are listed at the end of this memorandum.

- **Analytical Similarity Assessment**

To determine whether PF-06438179 is highly similar to US-licensed Remicade, and to establish the adequacy of the analytical portion of the scientific bridge (i.e., justification) between PF-06438179, US-licensed Remicade, and EU-approved Remicade to permit the use of comparative data generated with EU-approved Remicade, Pfizer evaluated and compared analytical data from multiple lots of each of the three products. The FDA performed confirmatory statistical analysis of the submitted data. All methods were validated or qualified prior to the time of testing and demonstrated to be suitable for intended use.

Pfizer's analytical comparison of multiple lots of PF-06438179, US-licensed Remicade, and EU-approved Remicade included comparison of the following attributes:

- Amino acid sequence/primary structure
- TNF- $\alpha$  binding and neutralization
- Fc-mediated *in vitro* biological activities (bioactivities)
- Fc receptor binding affinity
- Additional *in vitro* bioactivities (membrane TNF- $\alpha$  binding, reverse signaling, regulatory macrophage induction)
- Purity
- Protein concentration after reconstitution
- Protein content
- Physicochemical attributes
- High Molecular Weight Variants/Aggregates
- Higher order structure

Pfizer's analytical comparisons of the above attributes support a demonstration that PF-06438179 is highly similar to US-licensed Remicade and support the scientific bridge between PF-06438179, US-licensed Remicade, and EU-approved Remicade to permit the use of comparative data generated with EU-approved Remicade.

TNF- $\alpha$  binding and neutralization, the main mechanisms of action of infliximab products, were assessed by two assays: 1) inhibition of cellular apoptosis induced by TNF- $\alpha$  and 2) relative binding affinity to TNF- $\alpha$  assayed by surface plasmon resonance (SPR). The product quality team concluded, and we agree, that the data from the TNF- $\alpha$  binding and neutralization assays met the criteria for statistical equivalence between PF-06438179, US-licensed Remicade, and EU-approved Remicade supporting a demonstration that PF-06438179 is highly similar to US-licensed Remicade. These data also support, in part, the scientific bridge to justify the relevance of the data obtained using EU-approved Remicade in the clinical study, B5371002.

Additional potential mechanisms of action have been proposed for infliximab in the scientific literature. These include antibody dependent cell-mediated cytotoxicity (ADCC) against cells expressing membrane-bound TNF- $\alpha$  (mTNF- $\alpha$ ), complement dependent cytotoxicity (CDC) against mTNF- $\alpha$  positive cells, "reverse signaling" (signal transduction into cells by activation mTNF- $\alpha$ ), and induction of regulatory macrophages in mucosal healing. To the extent these potential mechanisms of action are relevant for infliximab, it is likely that the relative role for

each of these mechanisms differs between indications. The Applicant conducted functional assays to assess similarity between PF-06438179, US-licensed Remicade, and EU-approved Remicade with regard to each of these potential mechanisms. In each case, the results were similar and met pre-determined similarity criteria between PF-06438179, US-licensed Remicade, and EU-approved Remicade.

Each protein biochemistry and biological activity attribute met the pre-determined criteria for the pairwise comparisons between PF-06438179, US-licensed Remicade, and EU-approved Remicade, with the following exceptions:

- Percent basic product-related variants
- C1q binding by ELISA
- Predominant form of sialic acid

In each of these cases, the differences were modest and the impact of the slight differences in the attributes and resulting residual uncertainty was adequately mitigated by additional information and analysis provided by the Applicant. The additional information and analysis is summarized in the OPQ Review.

Based on the above considerations, the product quality team concluded, and we agree, that the totality of analytical similarity data supports a demonstration that PF-06438179 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components, and supports the scientific bridge between the three products to justify the relevance of comparative data generated from the clinical study that used EU-approved Remicade, to support a demonstration of biosimilarity of PF-06438179 to US-licensed Remicade.

- **Facilities review/inspection**

FDA's Office of Process and Facilities (OPF) conducted an assessment of the manufacturing facilities for this BLA. As part of this BLA, there were three pre-license inspections (PLI) conducted for manufacturing:

- (b) (4) - Drug Substance (DS) Manufacturing Inspection conducted (b) (4). The outcome of the inspection was classified as Voluntary Action Indicated (VAI).
- Pfizer Manufacturing Belgium NV (Pfizer) – Drug Product (DP) Manufacturing Inspection Conducted June 12-21, 2017. The outcome of the inspection was classified as No Action Indicated (NAI) for the PLI and VAI for GMP Surveillance
- (b) (4) - Cell bank manufacture and storage, biosimilarity assessment. Inspection conducted (b) (4). The outcome of this inspection was also classified as NAI.

The OPF team recommended that BLA 761072 be approved from the standpoint of facilities assessment. We concur with this recommendation.

## 4) Nonclinical Pharmacology/Toxicology

*Pharmacology/Toxicology Reviewer: Matthew Whittaker, Ph.D.*

*Pharmacology/Toxicology Team Leader: Timothy W. Robison, Ph.D.*

The PF-06438179 nonclinical development program was considered adequate to support clinical development.

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 $\alpha$  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; therefore, repeat dose toxicology studies were not conducted. This was agreed upon in pre-submission communications with the Agency.

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<sub>max</sub>, C<sub>max</sub>, and AUC<sub>0-1344</sub>) were comparable between PF-06438179 and EU-approved Remicade. An additional 2-week, repeated dose (once weekly) GLP toxicology study conducted with 10 or 50 mg/kg PF-06438179 (no comparator) did not identify any novel toxicities that were judged to be clinically relevant.

In summary, the animal studies submitted demonstrate the similarity of PF-06438179 to US-licensed Remicade in terms of the nonclinical pharmacology and pharmacokinetics data. The Pharmacology and Toxicology team concluded, and we agree, that the results of these animal studies can be taken together with the data from the analytical bridging studies (refer to the CMC section of this document for details) to support a demonstration that PF-06438179 is biosimilar to US-licensed Remicade. No residual uncertainties have been identified by this discipline.

## 5) Clinical Pharmacology/Biopharmaceutics

*Clinical Pharmacology Reviewer: Manuela L.T. Grimstein, Ph.D.*  
*Clinical Pharmacology Team Leader: Anshu Marathe, Ph.D.*

- **General clinical pharmacology/biopharmaceutics considerations**

The objectives of the PF-06438179 clinical pharmacology program were to evaluate the pharmacokinetic similarity between PF-06438179 and US-licensed Remicade, and to support the scientific bridge between PF-06438179, US-licensed Remicade, and EU-approved Remicade in order to justify the relevance of comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of PF-06438179 to US-licensed Remicade.

The clinical development for PF-06438179 relevant to the submission in the United States (US) included two clinical studies, and the key design features of the studies are summarized in Table 1. Pharmacokinetic (PK) similarity of PF-06438179 to US-licensed Remicade was evaluated in a pivotal three-way PK similarity study to compare the PK, safety, tolerability, and immunogenicity of PF-06438179, EU-approved Remicade and US-licensed Remicade in 151 healthy subjects (B5371001). PK and immunogenicity were also assessed for PF-06438179 and EU-approved Remicade in 650 patients with active rheumatoid arthritis (RA) in Study B5371002.

**Table 1. Key Design Features of PF-06438179 Clinical Studies**

Study ID Dates	Design	Study Duration	Treatment Arms	N	Population	Endpoint
<b>PK Similarity Study</b>						
B5371001  May 2013- November 2013	R, DB, PG, SD, 3-arm, comparative PK study	12 weeks	PF-06438179 US-licensed Remicade EU-approved Remicade  10 mg/kg IV over a period of not less than 2 hours	52 49 50	HV	PK parameters for similarity and bridging: C <sub>max</sub> , AUC <sub>t</sub> , and AUC <sub>inf</sub>
<b>Comparative Clinical Study</b>						
B5371002  August 2014- June 2016	R, DB, PG  TP1: Week 0- Week 30  TP2: Week 30- Week 54  TP3* W54- Week 78	Primary Endpoint: Week 14  Total Duration: 78 weeks	<u>TP1:</u> PF-06438179 EU-approved Remicade  <u>TP2: Transition</u> PF-06438179/ PF-06438179  EU-approved Remicade/ EU-approved Remicade  EU-approved Remicade/ PF-06438179  <u>Induction:</u> 3 mg/kg IV Weeks 0, 2 and 6  <u>Maintenance:</u> 3 mg/kg IV Q8 wk  one-time escalation to 5 mg/kg per infusion for subjects who failed to achieve a minimum clinical response or lost clinical response	324 326  280  143  143	Moderately to severely active RA w/ inadequate response to MTX	Proportion of subjects achieving an ACR20 Response at Week 14
R=randomized, DB=double-blind, PG=parallel-group, SD=single dose, HV=healthy volunteers, TP=treatment period, RA=rheumatoid arthritis, MTX=methotrexate, PK-pharmacokinetics *: Data from Week 54 to 78 not submitted at the time of this review Total N represents the Intent-to-Treat (ITT) population. The ITT population was defined as all subjects who were randomized to study treatment. Source: Module 5.3.3.1, CSR B5371001, Synopsis B5371001, CSR B5371002, Synopsis B5371002						

In the pivotal PK study, Study B5371001, the 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of PF-06438179 to EU-approved Remicade, PF-06438179 to

US-licensed Remicade, and EU-approved Remicade to US-licensed Remicade for the tested PK parameters (i.e., AUC0-inf, AUC0-t, and Cmax) were all within the PK similarity acceptance interval of 80-125% as shown in Table 2. These pairwise comparisons met the pre-specified criteria for PK similarity between PF-06438179, US-licensed Remicade, and EU-approved Remicade. Thus, PK similarity was established between PF-06438179 and the US-licensed Remicade and a PK bridge was established to support the relevance of the data generated using EU-approved Remicade in the comparative clinical efficacy study (Study B5371002). In Study B5371002, serum peak and trough concentrations assessed at treatment period 1 (up to Week 30) were generally comparable between PF-06438179 and EU-approved Remicade treatment groups.

**Table 2. Statistical Analysis for PK Parameters, Study B5371001**

Comparison	Parameter	GMR%	90% CI (%)
PF-06438179 vs US-licensed Remicade	Cmax	107.05	98.53, 116.31
	AUC0-t	107.67	98.85, 117.28
	AUC0-inf	107.06	97.49, 117.58
PF-06438179 vs EU-approved Remicade	Cmax	110.03	101.32, 119.49
	AUC0-t	111.98	102.85, 121.92
	AUC0-inf	110.49	100.67, 121.28
EU-approved Remicade vs US-licensed Remicade	Cmax	97.29	89.72, 105.50
	AUC0-t	96.15	88.45, 104.53
	AUC0-inf	96.90	88.42, 106.18
Source: FDA analysis of data from Pfizer 351(k) BLA submission			

The Office of Clinical Pharmacology (OCP) has determined that PK similarity has been demonstrated between PF-06438179 and US-licensed Remicade and that the PK data support, in part, the scientific bridge justifying the relevance of the comparative data generated using EU-approved Remicade to support a demonstration of the biosimilarity of PF-06438179 to US-licensed Remicade. The OCP has concluded that the clinical pharmacology results from the PF-06438179 program add to the totality of evidence to support a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade. We concur with this assessment. The PK studies have not raised any new uncertainties and the clinical pharmacology data support a demonstration of biosimilarity between PF-06438179 and US-licensed Remicade.

## 6) Clinical Microbiology

Not applicable.

## 7) Clinical/Statistical-Efficacy

*Primary Statistical Reviewer: William Koh, Ph.D.*

*Statistical Team Leader: Robert Abugov, Ph.D.*

*Primary Clinical Reviewer: Erika Torjusen, M.D., M.H.S.*

*Clinical Team Leader: Banu Karimi-Shah, M.D.*

### ***Overview of the Clinical Program***

To support the demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade, in addition to the PK similarity study in healthy volunteers (Study B5371001) discussed in the section on Clinical Pharmacology above, Pfizer submitted clinical safety, immunogenicity, and efficacy data from one comparative clinical study (B5371002) in patients with RA, described in detail in this section below. The key design features of these studies are summarized in Table 1 above. Of note, the comparative clinical efficacy data in B5371002 were derived using EU-approved Remicade as the comparator. However, Pfizer provided sufficient analytical and clinical PK bridging data (Study B5371002) between PF-06438179, US-licensed Remicade, and EU-approved Remicade to justify the relevance of the comparative data generated using EU-approved Remicade in Study B5371002 to support a demonstration of no clinically meaningful differences between PF-06438179 to US-licensed Remicade.

Study B5371002 was a randomized, double blind, parallel group, multicenter, comparative clinical study to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of PF-06438179 compared to EU-approved Remicade in 650 subjects with moderate to severe RA despite MTX therapy. The study was conducted in approximately 174 investigator sites worldwide, including 40 sites in the US. The study consisted of three distinct treatment periods:

- Treatment period 1 (TP1): began with the first dose of study drug on Day 1 and ended with the completion of Week 30 pre-dose assessments.
- Treatment period 2 (TP2): began with dosing at Week 30, when patients treated with EU-approved Remicade were randomized to undergo a single transition to PF-06438179 or continue on EU-approved Remicade to Week 54.
- Treatment period 3 (TP3): began with Week 54 dosing, when all patients remaining on EU-approved Remicade were transitioned to PF-06438179. All subjects continued to receive open-label PF-06438179 treatment for an additional 24 weeks, with last study drug dosing scheduled for Week 70, and the end of treatment (EOT) visit at Week 78. The data from TP3 were not submitted at the time of this review, but were not deemed necessary to our review, as the treatment duration up to Week 54 was considered adequate for regulatory decision-making.

Treatment groups were balanced with respect to demographics and disease characteristics.

The primary endpoint of the study was the proportion of patients who remained in the study and achieved an American College of Rheumatology 20% (ACR20) response at Week 14. This endpoint is considered sufficiently sensitive for the assessment of similarity in clinical efficacy. Further, the similarity margin has been informed by the published literature. As shown in Table 3, the proportion of patients who achieved an ACR20 response at Week 14 was similar between PF-06438179 and EU-approved Remicade, and contained within the pre-specified asymmetric similarity margin of [-12%, +15%] recommended by FDA.

At Week 14, 63.8% of the patients randomized to EU-approved Remicade and 61.1% of the patients randomized to PF-06438179 remained in the study and achieved an ACR20 response, with an estimated absolute response rate -2.7% lower in the PF-06438179 treatment group compared to the EU-approved Remicade treatment group (90% CI: -9.1, 3.6). Additional supportive analysis based on all-observed data demonstrated similar findings. The per-protocol analysis with non-responder imputation (NRI) or all-observed data collected similarly ruled out the FDA asymmetric margin (see Table 3).

**Table 3. Analysis of ACR20 Response Rate at Week 14<sup>a</sup>, Study B5371002**

	n/N	%	Difference in Response (%)	90% CI Lower (%)	90% CI Upper (%)
<b>Primary analysis of ACR20 response rate at Week 14 (ITT-NRI)</b>					
<b>PF-06438179 (N=324)</b>	198/324	61.1	-2.7	-9.1	3.6
<b>EU-Remicade (N=326)</b>	208/326	63.8			
<b>Analysis of ACR20 response rate at Week 14 (Observed)<sup>b</sup></b>					
<b>PF-06438179 (N=311)</b>	203/311	65.3	-1.2	-8.4	6.6
<b>EU-Remicade (N=316)</b>	210/316	66.5			
<b>Analysis of ACR20 response rate at Week 14 (Per Protocol – NRI)</b>					
<b>PF-06438179 (N=279)</b>	186/279	66.7	-0.9	-7.5	5.7
<b>EU-Remicade (N=290)</b>	196/290	67.6			
<b>Analysis of ACR20 response rate at Week 14 (Per Protocol – Observed)</b>					
<b>PF-06438179 (N=279)</b>	186/279	66.7	-0.9	-7.5	5.7
<b>EU-Remicade (N=290)</b>	196/290	67.6			
Observed analysis included efficacy data collected regardless of adherence to study treatment. NRI: Patients who discontinued the study treatment or withdraw from the study were imputed as non-responder. a: This differs from original submission (Seq0001) after a data entry was noted by the Applicant in a later submission (Seq0022) for subject (b) (6) at Week 14. b: Two patients from infliximab-EU and five from PF-06438179 discontinued study treatment but were followed up beyond week 14. This analysis was based on data from the original submission and included (b) (6) as an ACR20 responder at Week 14. Abbreviations: ACR=American College of Rheumatology; CI=confidence intervals; ITT=intent to treat; NRI=non-responder imputation; PP=per protocol Source: FDA analysis of data from PF-06438179 351(k) BLA submission					

The ACR20 response probabilities over time comparing the two treatments up to Week 30 also supported similarity (data not shown).

The comparative analyses of secondary endpoints, such as ACR components, HAQ-DI scores, and DAS28(CRP) also showed similar efficacy between the two treatment groups (data not shown).

Up to Week 14, 23 (4%) patients had withdrawn from the study: 13 patients (4%) from the PF-06438179 treatment group and 10 patients (3%) from the EU-approved Remicade treatment

group, with similar distributions for early withdrawal. To assess the impact of missing data in Study B5371002, the FDA statistical team conducted tipping point sensitivity analyses. The results from these analyses largely support the findings of the key efficacy analyses in Study B5371002.

The FDA statistical review team concluded, and we concur, that the totality of the evidence from the comparative clinical study B5371002 supports a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade.

- **Discussion of statistical and clinical efficacy reviews with explanation for CDTL's conclusions**

In summary, the Applicant has provided statistically robust comparative clinical data demonstrating similar efficacy between PF-06438179 and US-licensed Remicade in patients with moderate-to-severe RA despite methotrexate in Study B5371002. The primary analyses were supported by the analyses of key secondary endpoints and sensitivity analyses accounting for missing data. The FDA statistical and clinical teams concluded, and we agree, that the results from Study B5371002 support a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

None.

## 8) Safety

*Primary Clinical Reviewer: Erika Torjusen M.D., MPH*

*Clinical Team Leader: Banu Karimi-Shah, M.D.*

*OBP Immunogenicity Reviewer: Sarah Arden, Ph.D.*

- **Studies contributing to safety analyses**

The primary safety data were derived from one comparative clinical study in 650 patients with moderate-to-severe RA (Study B5371002).

In Treatment Period 2 of the study at Week 30, a total of 143 subjects underwent a single transition from EU-approved Remicade to PF-06438179 to assess additional risks, if any, in safety and immunogenicity resulting from a single transition from EU-approved Remicade to PF-06438179 to address the safety of the clinical scenario where non-treatment naïve patients transition to PF-06438179. Of note, Study B5371002 used EU-approved Remicade. To justify the extrapolation of comparative data, including safety data, generated using EU-approved Remicade to support a demonstration of the biosimilarity of PF-06438179 to US-licensed Remicade, Pfizer provided robust comparative analytical data and clinical PK bridging data (Study B5371002). Supportive safety and immunogenicity information was also

provided from one single dose PK study in healthy subjects (Study B5371001). The safety and immunogenicity data were reviewed for each individual study. Overall, the safety database is adequate to provide a reasonable comparative safety assessment to support a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Overall, there were no major differences in adverse events (AEs), serious adverse events (SAEs), or AEs leading to discontinuations between the treatment groups. Adverse events leading to discontinuation were infrequent and balanced between treatment arms. Reports of hypersensitivity and injection site reactions were balanced between treatment arms with a single case of anaphylaxis in each treatment arm in Study B5371002. No new safety signals were identified in the PF-06438179 group compared to the known adverse event profile of US-licensed Remicade, as described in the FDA-approved labeling for Remicade.<sup>7</sup>

### ***Deaths***

Five (5) deaths were reported in the PF-06438179 clinical program through treatment periods (TPs) 1 and 2. In TP1, there were three deaths reported, with two events occurring in the PF-06438179 treatment arm and one in occurring in the EU-approved Remicade treatment arm. The two deaths in the PF-06438179 treatment arm were attributed to acute myocardial infarction, and the death in the EU-approved Remicade arm was ascribed to shock/multi-organ dysfunction. In addition, one patient who received EU-approved Remicade experienced an SAE during TP1 (community acquired pneumonia which resulted in a fatal outcome outside of TP1, and after the June 29, 2016 data cut-off). Finally, one patient died due to sudden cardiac death during TP2 in the PF-06438179/PF-06438179 treatment group. There were no deaths in the other two treatment groups during TP2. Overall, death was an infrequent occurrence in the clinical program, with no clinically meaningful differences identified.

### ***Nonfatal Serious Adverse Events (SAE)***

The proportion of patients who experienced at least one SAE was similar between the treatment groups during Treatment Periods 1 and 2. The most frequently reported SAEs were infections which were overall similar between the treatment groups. SAEs across the system organ classes (SOCs) showed a similar distribution with minor numerical differences between each group. There was no notable difference in the incidence of SAEs following a single transition in Treatment Period 2 from EU-approved Remicade to PF-06438179 in Study B5371002. The different SOC of SAEs or the pattern of SAEs in the PF-06438179 clinical program were consistent with the known safety profile of US-licensed Remicade as presented in the FDA-approved Remicade labeling. In the comparative PK study (B5371001), there

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<sup>7</sup> FDA-approved Remicade labeling

were two subjects who experienced SAEs; one subject reported myalgia in the US-licensed Remicade treatment arm and one subject reported a mental disorder in the PF-06438179 treatment arm.

### ***Discontinuations due to Adverse Events***

The proportion of patients discontinuing due to an adverse event was similar between PF-06438179 and EU-approved Remicade. In Treatment Period 1, the SOCs with the highest proportion of subjects who had AEs leading to permanent treatment discontinuations were Skin and Subcutaneous Tissue Disorders [(2.5%) PF-06438179, (2.1%) EU-approved Remicade], Injury, Poisoning and Procedural Complications [(1.9%) PF-06438179, (1.8%) EU Approved Remicade], and Infections and Infestations [(1.5%) PF-06438179, (1.8%) EU Approved Remicade]. There was no notable difference in the incidence of treatment discontinuation due to adverse events following the single transition from EU-approved Remicade to PF-06438179 in Treatment Period 2 of Study B5371002.

### ***Adverse Events of Special Interest (AESI)***

The selection of AESI was informed by the known safety profile of US-licensed Remicade as presented in the FDA-approved Remicade labeling and other published data. Overall, the incidence of AESI, including serious infections, tuberculosis, infusion-related reaction, anaphylaxis,<sup>8</sup> malignancy, between the PF-06438179, US-licensed Remicade, and EU-approved Remicade treatment arms was similar across the controlled portions of the clinical studies. No increase in AESI was observed following a single transition from EU-approved Remicade to PF-06438179 in Period 2 of Study B5371002.

### ***Common Adverse Events (AEs)***

In Treatment Period 1, infusion-related reactions, nasopharyngitis, and ALT/AST elevations, were the most common adverse events in Study B5371002 with event rates similar between PF-06438179 and EU-approved Remicade. Following the single transition in Treatment Period 2 of Study B5371002, the common adverse event profile remained consistent and similar between subjects who underwent the single transition from EU-approved Remicade to PF-06438179 and those who continued on EU-approved Remicade. The incidence and types of common adverse events were similar between the treatment arms and were consistent with the known safety profile of US-licensed Remicade as presented in the FDA-approved Remicade labeling, further supporting a demonstration that there are no clinically meaningful differences between PF-06438179 and US-licensed Remicade in the indication studied.

### ***Laboratory Abnormalities, Vital Signs and Electrocardiograms (ECGs)***

No unexpected laboratory findings were reported in the PF-06438179 clinical program.

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<sup>8</sup> Sampson HA et al., J Allergy Clin Immunol. 2006 Feb;117(2):391-7

- **Immunogenicity**

In the PF-06438179 clinical studies, determination of anti-drug antibodies (ADA) consisted of a multi-tiered approach with sequential screening, confirmation, and characterization.

A group of validation exercises were performed to demonstrate and ensure the ability of the assays to reliably quantify levels of ADA and Neutralizing Antibodies (NABs). The screening assays demonstrated adequate sensitivity and precision. Of note, the validated drug tolerance for the screening assays ranged from 0.5 – 5.0 µg/mL when challenging high and low positive control antibody concentrations. The impact of on-board drug on the assay sensitivity will be the same when testing sera from patients treated with either PF-06438179 or EU-approved Remicade; in other words, it is unlikely that there would be differential underestimation of the ADA rate between products. The drug tolerance study results were discussed with the clinical pharmacology and clinical teams, and it was concluded that the  $C_{trough}$  levels of PF-06438179 or EU-approved Remicade at the relevant timepoints in the clinical efficacy study were within the levels demonstrated to be tolerated by the assay validation study. Thus, the data are sufficient to support that the assay is sensitive to ADA in the relevant clinical samples, and the screening assay is suitable for assessing and comparing ADA levels between PF-06438179 and EU-approved or US-licensed Remicade. The validation data support that the NAB assays are adequate to sensitively determine the level of neutralizing activity of confirmed ADA positive patient sera.

*Immunogenicity in Study B5371002*

In Study B5371002, ADAs were assessed at sequential time points starting at baseline (screening), Weeks 0, 2, 6, 14, 30, 38, 54, and any post-treatment follow-up.

As shown in Table 4, at Week 30, 157 (48.6%) subjects in the PF-06438179 treatment group and 167 (51.2%) subjects in the EU-approved Remicade treatment group tested positive for ADA. Of these, 124 (79%) subjects in the PF-06438179 treatment group and 143 (85.6%) subjects in the EU-approved Remicade treatment group tested positive for NAb. The distribution of ADA titers was also comparable between the treatment groups over the 30-week treatment period (data not shown).

**Table 4. Proportion of ADA Positive Patients Following Repeat Dosing in Treatment Period 1, Study B5371002 (Week 0-30)**

		PF-06438179 N=323		EU-approved Remicade N=326	
		n'	n (%)*	n'	n (%)*
Screening	ADA	322	9 (2.8)	323	9 (2.8)
Week 30 Overall <sup>a</sup>	ADA	320	157 (48.6)	325	167 (51.2)
	NAb	157	124 (79.0)	167	143 (85.6)

Source: FDA analysis of data from PF-06438179 351(k) BLA submission  
 ADA: anti-drug Antibody, NAb: Neutralizing Antibody (Proportion of ADA positive patients with a positive Nab)  
 n'-number of patients with available ADA/NAb results  
 \* percentage is reported as a percentage of N, all randomized patients  
<sup>a</sup>Overall ADA: defined as "positive" for patients with at least one ADA (or NAb) positive up to Week 30 after Week 0

To further supplement the immunogenicity assessment of PF-06438179, the Applicant provided immunogenicity data out to Week 54, including immunogenicity in patients undergoing a single transition from EU-approved Remicade to PF-06438179 compared to that of patients who continued EU-approved Remicade or PF-06438179. Of 326 subjects who received EU-approved Remicade through Week 54, 143 subjects underwent a single transition to PF-06438179 (EU-approved Remicade/PF-06438179 treatment group) and 143 subjects continued on EU-approved Remicade (EU-approved Remicade/EU-approved Remicade treatment group). The subjects who received PF-06438179 during the randomized, double-blind period continued to receive PF-06438179 (PF-06438179/PF-06438179 treatment group). Blood samples for determination of immunogenicity were collected at Weeks 30, 38, and 54 (Week 30 is from the randomized, double-blind period). As summarized in Table 5, in Treatment Period 2, at Week 54, similar proportions of patients tested positive for ADA in all three treatment groups. The proportion of ADA-positive patients who developed NAb was also comparable between the three groups. Importantly, the ADA rates did not increase differentially between patients who underwent a single transition from EU-approved Remicade to PF-06438179 as compared with those who continued EU-approved Remicade or PF-06438179. Consistent with the observations through Week 30, a majority of ADA-positive samples were confirmed to be NAb.

**Table 5. Proportion of ADA Positive Patients Following Repeat Dosing in Treatment Period 2, Study B5371002 (Week 30-54)**

		PF-06438179/ PF-06438179 N=280		EU-approved Remicade			
				EU-approved Remicade/ PF-06438179 N=143		EU-approved Remicade/ EU-approved Remicade N=143	
				n'	n (%)*	n'	n (%)*
Week 54	ADA	279	146 (52.1)	141	83 (58.0)	141	86 (60.1)
Overall <sup>a</sup>	NAb	146	118 (80.8)	83	65 (78.3)	86	73 (84.9)

Source: FDA analysis of data from PF-06438179 351(k) BLA submission  
 Extension Period Baseline: Extended Study Baseline; Nab: Neutralizing Antibody (Proportion of ADA positive patients with a positive Nab)  
 n' - number of patients with available ADA/NAb results  
 \* percentage is reported as a percentage of N, all randomized patients  
<sup>a</sup> Overall ADA: defined as "positive" for patients with at least one ADA (or NAb) positive up to Week 54 after Week 0

*Impact of immunogenicity on clinical endpoints*

To investigate the potential impact of the ADA on clinical outcomes in study B5371002, the relationship between ADA, primary efficacy endpoints (ACR20), and select relevant safety outcomes associated with ADA (such as infusion-related reactions, IRRs) was examined. We acknowledge that such analyses are exploratory in nature and limited by the small sample sizes within subgroups and the non-randomized nature of comparisons, as ADA status is a post-randomization variable and observed differences in efficacy or safety outcomes (or lack thereof) could be attributable to ADA formation or to other confounding variables.

Within each ADA subpopulation there were no notable differences between PF-06438179 and EU-approved Remicade in IRRs. As summarized in Table 6, in a sub-group analysis evaluating these adverse events up to Week 30, the incidence of IRRs was higher in ADA positive patients compared to ADA negative patients with similar rates in both treatment groups. These results suggest that ADA formation against PF-06438179 or EU-approved Remicade had similar impact on clinically relevant safety.

**Table 6. Incidence of Infusion-related Reactions by ADA Status in Treatment Period 1, Study B5371002 (Week 0-30)**

	ADA Subgroup	PF-06438179 N = 323	EU-approved Remicade N = 326
Infusion-related Reaction	ADA-positive	11/157 (7.0%)	14/167 (8.4%)
	ADA negative	8/163 (4.9%)	7/158(4.4%)

Source: FDA analysis of data from PF-06438179 351(k) BLA submission

Overall, in Treatment Period 1, the incidence of IRRs appeared comparable between PF-06438179 and EU-approved Remicade in ADA-positive subjects. A total of 11 (7.0%) subjects in the PF-06438179 group and 14 (8.4%) subjects in the EU-approved Remicade group reported IRRs; 4 (2.5%) and 2 (1.2%) subjects reported Grade 3 IRRs, respectively. No subjects reported IRR SAEs.

When examining ADA-positive subjects Treatment Periods 1 and 2 combined, a total of 9 (5.8%) subjects in the PF-06438179 group, 6 (6.7%) in the EU-approved Remicade/PF-06438179 group, and 11 (12.5%) subjects in the EU-approved Remicade/EU-approved Remicade group reported infusion-related reactions. The percentage of subjects reporting an IRR was highest in the EU-approved Remicade/EU-approved Remicade treatment arm. While this difference is noted, study discontinuation and  $\geq$  Grade 3 adverse events were generally balanced across the treatment arms. Overall, the data do not indicate an increase in IRRs with extended exposure to PF-06438179 during TP2, nor do they indicate an increase in IRRs after switching treatment from EU-Remicade to PF-06438179.

Immunogenicity was assessed at the same time as the efficacy endpoint (ACR20) assessment, i.e. at Weeks 14 and 30 in Treatment Period 1. ACR20 response was observed in a majority of the patients despite ADA status. ACR20 response was lower in ADA-positive patients compared to ADA-negative patients; however, it was consistent between the PF-06438179 and EU-approved Remicade groups. Table 7 provides a summary of results from the randomized, double-blind period at Week 14. Similar trends were noted at later time points. These results suggest that ADA formation against PF-06438179 or EU-approved Remicade had similar impact on clinical efficacy.

**Table 7. ACR20 Response by ADA Status at Week 14, Study B5371002**

	Treatment	n/N (%)
ADA positive	PF-06438179	51/100 (51.0)
	EU-approved Remicade	51/103 (49.5)
ADA negative	PF-06438179	152/220 (69.1)
	EU-approved Remicade	158/222 (71.2)
Nab positive	PF-06438179	37/74 (50.0)
	EU-approved Remicade	37/81 (45.7)
Nab negative	PF-06438179	166/246 (67.5)
	EU-approved Remicade	172/244 (70.5)
Source: FDA analysis of data from PF-06438179 351(k) BLA submission		

**In Study B5371002, mean serum concentrations of PF-06438179 and EU-approved Remicade appeared to be comparable in each ADA group at each individual time point during the 30-week treatment period ( Table 8), with mean concentrations of serum PF-06438179 and EU-approved Remicade being lower in ADA-positive subjects compared to ADA-negative subjects.**

**Table 8. Median (5th-95th percentile) Value of Serum Concentrations of PF-06438179 and EU-approved Remicade by Anti-Drug Antibody (ADA) Status, Study B5371002**

Visit (Week)	ADA-positive subjects		ADA-negative subjects	
	PF-06438179	EU-Approved Remicade	PF-06438179	EU-Approved Remicade
<b>Ctrough (µg/mL)</b>				
2	15.5 (5.68-26.8)	14.2 (5.24-26.1)	18.2 (6.32-28.8)	18.0 (9.08-29.6)
4	17.8 (0.77-37.4)	16.4 (0.256-32.5)	27.9 (10.7-49.2)	26.9 (13.0-41.4)
6	6.16 (0-20.2)	5.1 (0-17.4)	14.0 (3.96-29.9)	12.8 (4.32-26.4)
14	0 (0-4.01)	0 (0-3.43)	3.35 (0.492-15.7)	3.06 (0.197-8.44)
22	0 (0-2.26)	0 (0-1.15)	2.98 (0.206-10.6)	2.49 (0-7.58)
30	0 (0-0.53)	0 (0-0.575)	2.85 (0.386-10.1)	2.39 (0.192-7.58)
<b>Cmax (µg/mL)</b>				
0 (Day 1)	63.8 (35.6-101)	59.3 (1.60-93.2)	59.3 (1.60-93.2)	59.3 (1.60-93.2)
14	68.3 (0-157)	62.0 (1.09-118)	62.0 (1.09-118)	62.0 (1.09-118)

Source: FDA analysis of data from PF-06438179 351(k) BLA submission

Based on the above considerations, the small numerical differences in ADA incidence, did not have a differential impact on clinically relevant endpoints and do not preclude a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade.

*Immunogenicity in Study B5371001*

In this single-dose PK study, the only study to directly compare PF-06438179 and US-licensed Remicade, a total of 146 healthy subjects were enrolled and randomized, with 49, 48, and 49 subjects in the PF-06438179, EU-approved Remicade, and US-licensed Remicade treatment groups, respectively. Blood samples were collected on Day 1 (pre-dose), 15, 29, 43, 57, 85(end-of study) for assessment of immunogenicity. The products were administered as a single dose of 10mg/kg intravenous infusion for at least 2 hours. Of the total 146 subjects who received the assigned study treatment, 118 and 119 subjects completed immunogenicity assessments through Days 57 (week 8) and 85 (week 12), respectively. No subjects were tested positive for ADA at baseline. A total of 5 (4.2%) and 31 (26.1%) subjects tested positive for ADA through Days 57 (pre-specified PK profiling period) and 85, respectively. The ADA formation rates for PF-06438179, EU-approved Remicade, and US-licensed Remicade in healthy subjects were 16.2%, 32.6%, and 28.2%, respectively. On Day 85, the PF-06438179 treatment group showed a lower incidence of ADA compared to that for the EU-approved Remicade or US-licensed Remicade treatment groups. While small differences in the proportion of subjects with ADA-positive response were evident after single dose administration in Study B5371001, it should be noted that assessment of immunogenicity after multiple doses in Study B5371002 is considered clinically more relevant. Assessment of PK similarity (pre-specified to be conducted at Day 57) in Study B5371001 was limited, as only 5 subjects tested positive for ADA at that time; however, the data are available (Table 8) for Study B5371002.

In study B5371001, of the 31 subjects who tested positive for ADA at Day 85, 26 (84%) subjects tested positive for Nab. In study B5371002, of the ADA-positive subjects, 79.0% and 85.6% also tested positive for NAb in the PF-06438179 and EU-approved Remicade treatment

groups, respectively. The rates of NAb positive subjects appeared to be comparable in study B5371002.

*Conclusions about immunogenicity*

Collectively, these data do not indicate that the ADA formation differentially impacts safety or efficacy between patients treated with PF-06438179 and EU-approved Remicade (Study B5371002). Therefore, there are sufficient data supporting similar immunogenicity between PF-06438179, US-licensed Remicade, and EU-approved Remicade, and immunogenicity data adds to the totality of the evidence to support a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade. Further, the product quality immunogenicity review team recommends approval of the BLA from an immunogenicity perspective, and we agree with this recommendation.

- **Discussion of primary reviewer's comments and conclusions**

The safety database submitted for PF-06438179 is adequate to provide a reasonable descriptive comparison between the PF-06438179 and US-licensed Remicade. The safety and immunogenicity analysis of the PF-06438179 clinical program in the studied condition of use, RA, and in healthy subjects in the PK single dose Study B5371001, has not identified notable differences in the safety profile between PF-06438179, US-licensed Remicade, and EU-approved Remicade. No new safety signals have been identified compared to the known adverse event profile of US-licensed Remicade. Further, the single transition from EU-approved Remicade to PF-06438179 after Week 30 in Study B5371002 did not result in an increase in adverse events, supporting the safety of the clinical scenario where non-treatment naïve patients transition to PF-06438179. The FDA safety analysis is consistent with the Applicant's analysis.

The clinical safety and immunogenicity data using the lowest labeled dose for US-licensed Remicade in combination with methotrexate in patients with RA, showed a similar safety profile between PF-06438179 and EU-approved Remicade. Dr. Torjusen and we are in agreement that the submitted safety and immunogenicity data and analyses are adequate to support the conclusion of no clinically meaningful differences between PF-06438179 and US-approved Remicade in the indication studied.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion**

None.

- **Discussion of notable safety issues (resolved or outstanding)**

None.

## 9) Extrapolation of Data to Support Biosimilarity in Other Conditions of Use

Pfizer is seeking licensure for the following indications for which US-licensed Remicade is licensed (i.e., RA, PsA, AS, CD, pediatric CD, UC, pediatric UC,<sup>9</sup> and PsO). The PF-06438179 clinical program however, provides direct comparative clinical data from one clinical study in patients with RA and safety and immunogenicity data in healthy subjects.

The Agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on totality of the data in the application, including data from a clinical study(ies) performed in another condition of use. This concept is known as extrapolation. As described in the Guidance for Industry: *“Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,”* if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed.<sup>10</sup> The Applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA) in each condition of use for which licensure is sought,
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations,
- The immunogenicity of the product in different patient populations,
- Differences in expected toxicities in each condition of use and patient population,
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. Consistent with the principles outlined in the above FDA guidance, Pfizer has provided a justification for the proposed extrapolation of data, including direct comparative clinical data in RA, to support a demonstration of biosimilarity in each of the other indications approved for US-licensed Remicade for which Pfizer is seeking licensure of

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<sup>9</sup> We note that 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/oopd/index.cfm>. Accordingly, FDA will not license PF-06438179 for this indication until the orphan drug exclusivity expires.

<sup>10</sup> Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (April 2015)

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf>

PF-06438179, as summarized in this section.

First, Pfizer's extensive analytical characterization data support a demonstration that PF-06438179 is highly similar to US-licensed Remicade notwithstanding minor differences in clinically inactive components, and that the data support a demonstration there are no clinically meaningful differences between PF-06438179 and US-licensed Remicade in terms of safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in RA.

Further, the additional points considered in the scientific justification for extrapolation of data to support biosimilarity in the indications for which Pfizer is seeking licensure of PF-06438179 (adult and pediatric CD, adult and pediatric UC, PsA, AS, and PsO) include:

- Similar PK was demonstrated between PF-06438179 and US-licensed Remicade, as discussed in the section on Clinical Pharmacology above. Importantly, PF-06438179 was demonstrated to be highly similar to US-licensed Remicade based on comparative analytical data, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between PF-06438179 and US-licensed Remicade in the indications sought for licensure. Thus, a similar PK profile would be expected between PF-06438179 and US-licensed Remicade in patients across all the indications being sought for licensure.
- In general, immunogenicity of the US-licensed Remicade was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used.<sup>11</sup> As stated previously in this document, the Agency has concluded that there is sufficient data to support similar immunogenicity between PF-06438179 and EU-approved Remicade with repeat dosing in patients with RA, and between PF-06438179, EU-approved Remicade, and US-licensed Remicade after a single dose in healthy subjects. Accordingly, similar immunogenicity would be expected between PF-06438179 and US-licensed Remicade for adult and pediatric CD, adult and pediatric UC, PsA, AS, PsO.
- A similar clinical safety profile with chronic dosing was demonstrated between PF-06438179 and EU-approved Remicade in patients with RA, and between PF-06438179, EU-approved Remicade, and US-licensed Remicade following single doses in healthy subjects. As analytical and PK similarity was demonstrated between PF-06438179 and US-licensed Remicade, a similar safety profile would be expected between PF-06438179 and US-licensed Remicade for adult and pediatric CD, adult and pediatric UC, PsA, AS, PsO.
- The mechanism(s) of action (MOA) relevant to the extrapolation of data to support

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<sup>11</sup> FDA-approved Remicade labeling

biosimilarity in specific indications are summarized in Table 9 and discussed below.

**Table 9. Known and Potential (Likely or Plausible) Mechanisms of Action of US-licensed Remicade in the Conditions of Use Sought for Licensure of PF-06438179**

MOA of Remicade	RA	AS	PsA	PsO	CD, Pediatric CD	UC, Pediatric UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
6yInduction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors <sup>12,13,14</sup>						

*Extrapolation of Data to Support Biosimilarity in PsA, AS, and PsO*

The primary MOA of infliximab products is to block TNF receptor-mediated biological activities (see Table 9 above). Infliximab binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The published scientific literature indicates that this MOA is the primary MOA in RA, PsA, AS, and PsO. The *in vitro* data provided by Pfizer showed similar TNF binding and potency to neutralize TNF- $\alpha$ , supporting the demonstration that PF-06438179 and US-licensed Remicade utilize the same MOA. Therefore, based on the above considerations, it is scientifically justified to conclude that PF-06438179 is biosimilar to US-licensed Remicade in PsA and AS. Further, the DDDP review team concluded, and we agree, that based on the totality of the data establishing analytical similarity, PK similarity, and no clinically meaningful differences in RA between PF-06438179 and EU-approved Remicade, the extrapolation of data to support a finding of biosimilarity for PF-06438179 and US-licensed Remicade to PsO is scientifically justified.

<sup>12</sup> Oikonomopoulos A et al., *Current Drug Targets*, 2013, 14, 1421-1432.

<sup>13</sup> Tracey D et al., *Pharmacology & Therapeutics* 117 (2008) 244-279.

<sup>14</sup> Olesen, C.M, et al., *Pharmacology & Therapeutics* 159 (2016), 110-119.

*Extrapolation of Data to Support Biosimilarity in Inflammatory Bowel Disease (IBD) Indications*

TNF plays a central role in the pathogenesis of the IBD indications (Crohn's disease, pediatric Crohn's disease, ulcerative colitis and pediatric ulcerative colitis<sup>15</sup>), and TNF inhibition is important in treating the diseases, as evidenced by the efficacy of the approved TNF monoclonal antibodies, but the detailed cellular and molecular mechanisms involved have not been fully elucidated.<sup>16</sup> However, the available scientific evidence suggests that for TNF inhibitors in IBD, in addition to binding and neutralization of sTNF, other MOA, listed in Table 9 may play a role.<sup>17</sup> Binding to sTNF and tmTNF involves the Fab region of the antibody, while the other plausible mechanisms of action involve the Fc region of the molecule.

As outlined in the section on CMC/Product Quality above, Pfizer provided experimental data supporting a demonstration that PF-06438179 and US-licensed Remicade are highly similar based on extensive structural and functional analytical characterization. Further, Pfizer addressed each of the known and potential mechanisms of action of US-licensed Remicade listed in Table 9 and submitted data to support the conclusion that PF-06438179 and US-licensed Remicade have the same mechanisms of action for each of the requested indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Thus, the DGIEP review team concluded, and we agree, that based on the totality of the data establishing analytical similarity, PK similarity, and no clinically meaningful differences in RA between PF-06438179 and EU-approved Remicade, the extrapolation of data to support a finding of biosimilarity for PF-06438179 and US-licensed Remicade to the IBD conditions of use is scientifically justified.

In aggregate, based on the above considerations, extrapolation of data to the additional indications for which Pfizer is seeking licensure (CD, pediatric CD, UC, pediatric UC,<sup>18</sup> AS, PsA, and PsO) is scientifically justified and supports licensure of PF-06438179 for the

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<sup>15</sup> 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/oopd/index.cfm>. Accordingly, FDA will not license PF-06438179 for this indication until the orphan drug exclusivity expires.

<sup>16</sup> Oikonomopoulos A et al., "Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?", *Current Drug Targets*, 2013, 14, 1421-1432

<sup>17</sup> Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", *Pharmacology & Therapeutics* 117 (2008) 244-279

<sup>18</sup> 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/oopd/index.cfm>. Accordingly, FDA will not license PF-06438179 for this indication until the orphan drug exclusivity expires.

indications being sought; however, PF-06438179 currently is eligible for licensure for only certain indications (RA, CD, pediatric CD, UC, AS, PsA and PsO).

## 10) Advisory Committee Meeting

An Advisory Committee (AC) meeting was determined not to be necessary as there were no issues where the Agency needed input from the committee.

## 11) Pediatrics

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, pediatric assessment**

The Applicant submitted an agreed initial pediatric study plan (iPSP) to address the PREA requirements for the indications sought for licensure as detailed below:

- Rheumatoid Arthritis (RA): Pfizer proposed that the pediatric assessment is fulfilled for polyarticular juvenile idiopathic arthritis (PJIA) patients between 4 and 17 years old by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to PF-06438179. The Applicant requested a waiver of the requirement to submit a pediatric assessment for (1) patients ages 2 to < 4 years old because PF-06438179 does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients with the condition and (2) patients < 2 years old because the condition is rare in this age group and such studies would be impossible or highly impracticable.
- Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA): The Applicant requested a waiver of the requirement to submit a pediatric assessment for juvenile AS and juvenile PsA because the studies would be impossible or highly impracticable due to the difficulty of making specific diagnoses of juvenile PsA or juvenile AS in the pediatric age range.
- Crohn's Disease (CD), Pediatric CD, Ulcerative Colitis (UC), Pediatric UC: The Applicant proposed that the pediatric assessment is fulfilled for pediatric CD and pediatric UC patients 6 years of age and older, by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to PF-06438179. It should be noted that the reference product has orphan drug exclusivity for pediatric UC, which precludes approval of PF-06438179 for the protected indication until the expiration of orphan exclusivity on September 23, 2018. Accordingly, the following statement will be included in the labeling for PF-06438179: "A pediatric assessment for Ixifi demonstrates that Ixifi is safe and effective in another pediatric indication. However, Ixifi is not approved for

such indication due to marketing exclusivity for Remicade (infliximab).” The Applicant requested a waiver of the requirement to submit a pediatric assessment for pediatric CD and pediatric UC patients younger than 6 years of age because such studies are impossible or highly impracticable. As a scientific matter, the Agency has determined that, based on recent epidemiologic data, a pediatric assessment for pediatric CD and pediatric UC patients should be conducted in patients 2 years and older, as opposed to previously recommended cut-off of 6 years of age and older. However, FDA acknowledges that, in this case, designing dedicated pediatric studies in pediatric CD and pediatric UC patients limited to ages 2 to 5 years old would be impossible or highly impracticable due to the low incidence of the disease in this specific pediatric age group.

- **Plaque Psoriasis (PsO):** The Applicant requested a waiver of the requirements for a pediatric assessment in patients with pediatric chronic severe plaque psoriasis ages 0 to less than 17 years old due to safety concerns with increased risk of lymphoma and other cancers associated with the use of TNF blockers in children and adolescents. The Agency’s current view is that this safety information does not necessarily apply across the class of TNF-alpha inhibitors, and thus would not necessarily support a waiver of the pediatric assessment for PF-06438179 in PsO patients on safety grounds. However, unlike certain other TNF-alpha inhibitors with a broader PsO indication, Remicade is approved only for treatment of adult patients with chronic severe (i.e., extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. Accordingly, a waiver of the requirement for a pediatric assessment in PsO is justified because such studies would be impossible or highly impracticable for this narrow indication of chronic severe PsO.

The Division of Pediatric and Maternal Health (DPMH) agreed that the pediatric assessment for PF-0648179 is complete, provided that biosimilarity to Remicade is demonstrated. The PF-06438179 pediatric study plan was also reviewed by the Pediatric Review Committee (PeRC) on November 29, 2016 and PeRC agreed that the pediatric assessment is complete, including granting the waivers described above. We agree with DPMH and PeRC’s conclusions.

## 12) Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues.
- **Exclusivity**—There is no unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Remicade (infliximab) (BLA # 103772, Janssen Biotech, Inc) that would prohibit the approval of PF-06438179.
- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **OSIS inspection** - The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study B5371001 conducted at Vince & Associates Clinical Research, Inc., Overland Park, KS, USA. No significant deficiencies were observed and Form

FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

- **OSI audits**—Two clinical sites that enrolled patients in the comparative clinical study were selected for inspection. Site 1100 received a classification of "no action indicated" (NAI). Site 1103 received a preliminary classification of NAI; preliminary classifications are based on communication with the ORA investigator. Inspection classification becomes final when the Establishment Inspection Report is received from the field, has been reviewed, and a letter is issued to the inspected entity.
- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**—Not applicable.

### 13) Labeling

- **Proprietary name**

The Applicant submitted the proposed proprietary name Ixifi for review on February 13, 2017. The name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and was found to be conditionally acceptable. We agree with this assessment.

- **Non-proprietary/Proper name**

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Pfizer's Ixifi product is necessary to distinguish this proposed product from Remicade (infliximab). As explained in FDA's Guidance for Industry, Nonproprietary Naming of Biological Products, FDA expects that a nonproprietary name that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance of biological products.<sup>19</sup>

On February 13, 2017, the Applicant submitted a list of suffixes to be used in the nonproprietary name of PF-06438179 along with supporting analyses intended to demonstrate that the proposed suffixes satisfied the factors described in section V of the Draft Guidance for Industry, Nonproprietary Naming of Biological Products. The DMEPA review concluded, and we agree, that Pfizer's proposed distinguishing suffix "qbtx" is acceptable and the nonproprietary name "infliximab-qbtx" should be reflected in the product label and labeling accordingly.

- **Important issues raised by brief discussion of OPDP and OSE Division comments**

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<sup>19</sup> See the FDA Guidance for Industry on Nonproprietary Naming of Biological Products (January 2017). The guidances referenced in this document are available on the FDA Drugs guidance Web page at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>

None

- **Physician labeling**

The Applicant-proposed labeling closely tracks the labeling of US-licensed Remicade. In addition, the Applicant proposed revisions to Section 8, to conform to PLLR formatting requirements.

During the BLA labeling review, revisions were made for consistency with the Draft Guidance for Industry, *Labeling for Biosimilar Products* (March 2016).

The proprietary name “Ixifi,” and the non-proprietary name “infliximab-qbtx,” should be reflected in the product labeling as appropriate.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

As discussed above.

- **Carton and immediate container labels**

As discussed above in the DMEPA review and recommendations, the proprietary name “Ixifi” and the non-proprietary name “infliximab-qbtx,” should be reflected in the product Patient labeling/Medication guide as appropriate.

- **Patient labeling/Medication guide**

The Applicant proposed a Patient labeling/Medication guide that closely tracks that of US-licensed Remicade. The proprietary name “Ixifi” and the non-proprietary name “infliximab-qbtx,” should be reflected in the product Patient labeling/Medication guide as appropriate.

## 14) Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

We recommend approval of the 351(k) BLA 761072 for PF-06438179 to receive licensure as a biosimilar product to US-licensed Remicade for each of the indications for which US-licensed Remicade is currently licensed and for which Pfizer is seeking licensure of PF-06438179; however, PF-06438179 currently is eligible for licensure for only certain indications (RA, CD, pediatric CD, UC, AS, PsA and PsO).<sup>20</sup>

- **Totality of the Evidence**

The conclusion of the comparison of the structural and functional properties of the clinical and commercial product lots of PF-06438179 and US-licensed Remicade was that they were highly similar, notwithstanding minor differences in clinically inactive components.

Pfizer provided extensive analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved Remicade to support a demonstration of biosimilarity of PF-06438179 to US-licensed Remicade.

The submitted clinical pharmacology studies are adequate to (1) support the demonstration of PK similarity between PF-06438179 and US-licensed Remicade, and (2) establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved Remicade.

The results of the clinical development program indicate that Applicant's data meet the requirement for a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade in terms of safety, purity, and potency in the indication studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, which included the use of a chronic dosing regimen of PF-06438179 and EU-approved Remicade in patients with RA, adequately support a demonstration that there are no clinically meaningful differences between PF-06438179 and US-licensed Remicade in RA. The single transition from EU-approved Remicade to PF-06438179 during the second part of Study B5371002 did not result in a different safety or immunogenicity profile. This would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to PF-06438179.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support a finding of biosimilarity in conditions of

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<sup>20</sup> 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/ood/index.cfm>. Accordingly, FDA will not license PF-06438179 for this indication until the orphan drug exclusivity expires.

use not directly studied to support licensure of PF-06438179 for each of the indications for which US-licensed Remicade is currently licensed and for which Pfizer is seeking licensure of PF-06438179; however, PF-06438179 currently is eligible for licensure for only certain indications (RA, CD, pediatric CD, UC, AS, PsA and PsO).

In considering the totality of the evidence submitted, the data submitted by the Applicant show that PF-06438179 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between PF-06438179 and US-licensed Remicade in terms of the safety, purity, and potency of the product. The information submitted by the Applicant demonstrates that PF-06438179 is biosimilar to US-licensed Remicade and should be licensed.<sup>21</sup>

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

None.

- **Recommendation for other Postmarketing Requirements and Commitments**

We do not recommend any post-marketing required studies for this application.

#### **Postmarketing Commitments (PMC):**

We concur with the post-marketing commitments recommended by the product quality review team, as listed below:

1) Repeat the capping/crimping validation using a dye ingress method which has been shown to reliably detect breaches  $\leq 20 \mu\text{m}$ .

Final Report Submission: June 2018

2) Perform 3 consecutive media fills simulating the entire PF-06438179 DP manufacturing process using the PF-06438179 container closure system. The media fills will include worst-case hold and processing times, and be performed on (b) (4)

Final Report Submission April 2018

3) Complete PQ shipping validation studies (b) (4) using PF-06438179 DP and submit the validation report.

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<sup>21</sup> The proposed Ixifi labeling states: "Biosimilarity of Ixifi has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information."

Final Report Submission

August 2018

4) Conduct bioburden method qualification using in-process samples from 2 additional batches of PF-06438179 DS.

Final Report Submission

January 2019

5) Reassess and tighten all in-process drug substance endotoxin acceptance criteria based on process capability after 20-30 data points have been collected.

Final Report Submission

January 2019

6) Implement an assay assessing binding to FcγRIIIa into the Drug Substance release specification. Submit the proposed release specification as a Prior Approval Supplement described under 21 CFR 601.12 (b).

Final Report Submission

January 2019

- **Recommended Comments to Applicant**

None.

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/s/  
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12/12/2017

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