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APPLICATION NUMBER:

761072Orig1s000

CLINICAL REVIEW(S)

Medical Officer Review

Division of Gastroenterology & Inborn Errors Products

Application Type and Number: 351(k) BLA 761072

Applicant: Pfizer

Date of Submission: 2/13/2016

PDUFA Goal Date: 12/13/2017

DGIEP Clinical Reviewer/Team Leader: Tara Altepeter, MD

DGIEP Division Director: Donna Griebel, MD

Date Review Completed: 12/11/2017

Drug: PF-06438179 / "IXIFI" (infliximab-qbtx) -a proposed biosimilar to US licensed Remicade (infliximab)

Drug Class: TNF- α antagonist

Dosage Form/Presentation: Sterile lyophilized powder in a 15ml capacity vial / 100mg per vial

Route of Administration: Intravenous infusion

Proposed Indications: Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis¹, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis

1 Introduction

On February 13, 2017, Pfizer Inc. (the applicant) submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for PF-06438179, a proposed biosimilar to US-licensed Remicade (infliximab). US-licensed Remicade (US-Remicade) (BLA103772) received marketing approval in the U.S. on August 24, 1998 and its license is currently held by Janssen Biotech, Inc.

This application (BLA761054) was submitted to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for review. The application included a 3-arm comparative PK study in healthy volunteers (B5371001) demonstrating that the study drug is similar to both EU-approved Remicade (EU-Remicade) and US-licensed Remicade (and supporting, along with analytical data, a scientific bridge between US-Remicade and EU-Remicade for the purpose of justifying the relevance of the data obtained using EU-Remicade) and a comparative clinical study (B5371002) in patients with Rheumatoid Arthritis (RA) on methotrexate. The primary review team has concluded that the totality of the evidence submitted supports that there are no clinically meaningful differences between the study drug and US-licensed Remicade.

As a part of the collaborative review process of this application, this memorandum provides DGIEP's assessment on the justification for extrapolating data, including clinical safety and efficacy data, from studies of RA patients, to support approval of PF-06438179 for the inflammatory bowel disease (IBD) indications (which include Crohn's disease (CD), pediatric Crohn's disease, ulcerative colitis (UC) and pediatric ulcerative colitis¹). The reader is referred to the primary clinical review by Dr. Erika Torjusen

¹ The reviewer notes that Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. Accordingly, FDA will not be able to license SB2 for this indication until the orphan exclusivity expires.

(DPARP), and the CDTL memo by Dr. Banu Karimi-Shah for detailed review of the submitted clinical study in patients with rheumatoid arthritis (RA).

2 Extrapolation of Existing Data to Support Biosimilarity to IBD indications

The applicant seeks licensure for PF-06438179 for the same indications for which US-Remicade is licensed (Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis¹, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis). If a proposed 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 applicant may seek licensure for one or more additional conditions of use for which the reference product is licensed.² However, the applicant would need to provide sufficient scientific justification for extrapolating data, including clinical data, to support a determination of biosimilarity for each condition of use for which licensure is sought. Hence, it is potentially acceptable to include, among the totality of evidence to support a demonstration of biosimilarity for IBD indications, a clinical study in RA patients, provided that adequate scientific justification of how this population is relevant to IBD patients is included. The scientific justification for extrapolation should address the following issues as described in the FDA guidance²:

- 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 and efficacy of the product in each condition of use and patient population for which licensure is sought.

All of these factors were adequately addressed by the applicant, as summarized below. Therefore, this reviewer agrees that the totality of the evidence supports a demonstration of biosimilarity for the IBD indications for this product.

1. Mechanism of Action

The mechanisms of action of infliximab that are relevant to RA (the clinical study population) are also relevant to IBD. The applicant provided data to support that PF-06438179 has the same known and potential mechanisms of action as US-licensed Remicade, which supports extrapolation to these other indications.

The primary mechanism of action of infliximab is to neutralize the biological activity of tumor necrosis factor alpha (TNF- α) by binding to the soluble and transmembrane forms of TNF- α and inhibit binding of TNF- α with its receptors.³ Similar to the studied indication (RA), TNF- α plays a central role in the pathogenesis of IBD, and TNF- α inhibition is important in treating the disease, as evidenced by the efficacy of the approved TNF- α monoclonal antibodies, though the detailed cellular and molecular

² FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (April 2015), available at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf>

³ Prescribing Information for Remicade (last revised on October 2, 2015), accessed on August 26, 2016: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103772s5373 bl.pdf

mechanisms involved have not been fully elucidated.⁴ However, the available scientific evidence suggests that for TNF- α inhibitors in IBD, in addition to binding and neutralization of the soluble form of TNF- α (sTNF- α), other mechanisms of action, listed in Table 1, may play a role.⁵ Binding to sTNF- α and transmembrane TNF- α (tmTNF- α) involves the fragment antigen-binding (Fab) region of the antibody, while the other plausible mechanisms of action involve the fragment crystallizable (Fc region) region of the antibody.

Table 1: Mechanisms of Action of Infliximab across indications

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
Induction of ADCC on tmTNF-expressing target cells (via Fc γ RIIIa 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 table, based on summary of current literature^{4,5})

The Product Quality reviewers determined that the applicant has adequately addressed each of the known and potential mechanisms of action of US-licensed Remicade listed in Table 1 through the analytical similarity assessment. TNF- α binding and neutralization, believed to be the primary function of infliximab, met Tier 1 acceptance criteria and were demonstrated to be statistically equivalent between PF-06438179 and US-Remicade, as well as to EU-Remicade. Other mechanisms of action, such as reverse signaling, antibody dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), were evaluated based on Tier 2 and Tier 3 similarity criteria, and were within the quality range set by the applicant's data, supporting a determination that PF-06438179 is highly similar to US-Remicade. Induction of regulatory macrophages was evaluated via mixed lymphocyte reaction assay, met Tier 3 acceptance criteria, and the data support similarity between PF-06438179, US-Remicade and EU-Remicade. Refer to the Product Quality reviews for additional detail.

⁴ Oikonomopoulos A, et al. "Anti-TNF Ant bodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?" Current Drug Targets 2013;14:1421-32.

⁵ Tracey D, et al. "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review." *Pharmacology & Therapeutics* 2008;117:244-79.

Based on review of the data included in the BLA submission, the product quality reviewers have concluded that the applicant provided adequate data to support a conclusion that PF-06438179 is highly similar to US-Remicade. For attributes where there were minor potential differences detected, additional data support that there are no impacts on function, activity or stability in vitro.

Additionally, the product quality reviewers also concluded that data provided were adequate to support the scientific bridge and justify use of clinical data generated with EU-Remicade to support a demonstration of biosimilarity.

Overall, based on the Product Quality assessment, this reviewer agrees that the applicant has adequately addressed Mechanism of Action, in support of extrapolation to IBD indications.

2. Pharmacokinetics (PK)

The applicant's BLA submission included data from a pivotal three-way PK similarity study comparing the PK, safety, tolerability and immunogenicity of PF-06438179, US-licensed Remicade, and EU- Remicade. The clinical pharmacology reviewer concluded that the data support a demonstration of PK similarity between PF-06438179 and US-licensed Remicade, which also supports the scientific bridge between PF-06438179, US-licensed Remicade and EU-Remicade. PK similarity was demonstrated in healthy volunteers in the PK similarity study, and at steady state in RA patients in the comparative clinical study. Refer to the clinical pharmacology review by Manuela Grimstein PhD, for additional details.

Available data on US-licensed Remicade do not indicate any major differences in PK based on disease state.³ Therefore, it is reasonable to conclude that PK for the study drug is expected to be similar between RA patients (the studied population) and those with IBD. In addition, it should be noted that the PK of infliximab is also influenced by immunogenicity. Specifically, the clearance of infliximab has been shown to be higher in patients who developed anti-drug-antibodies (ADA).³ Immunogenicity considerations are discussed further below.

3. Immunogenicity

Immunogenicity, measured by the development of anti-drug antibodies (ADA), is an important factor influencing safety and efficacy of anti-TNF α agents. Immunogenicity data are highly dependent on assay methodology, and may be influenced by sample handling, timing of sample collection, underlying disease and concomitant medication use.³

In the PF-06438179 development program, immunogenicity assessment was conducted in healthy subjects (study B5371001), as well as RA patients (study B5371002). In the healthy subjects (study B5371001), 151 subjects were randomized, and 146 subjects received at least one dose of drug and were included for analysis. There were numerical differences between the rates of ADA development at day 57 and Day 85⁶, though they appeared relatively insignificant, given the small sample size and other limitations of immunogenicity testing described above. Further, the importance of immunogenicity is the effect it may have on efficacy and/or safety. In that regard, the PK profile was demonstrated to be similar within pre-specified criteria of 80-125% in this study, so there was no basis for concern that this ADA development would result in decreased efficacy. Further there were no immunogenicity related safety concerns noted in this study.

⁶ Data from Clinical Study Report for Study B5371001, applicant's Table 16, page 58/320. Summary of ADA Results by treatment group, safety analysis set: Day 57: 2/38 (5.3%) in PF-06438179 vs 3/41 (7.3%) in US-Remicade. Day 85: 6/37 (16.2%) in PF-06438179 vs 11/39 (28.2%) in US-Remicade.

In RA patients receiving concomitant methotrexate therapy (study B5371002), 650 patients were randomized 1:1 to receive PF-06438179 or EU-Remicade. Rates of ADA development, as well as the rates of neutralizing antibody development (Nab) were similar at Week 30 in patients treated with PF-06438179 or EU-Remicade. After week 30, patients in the EU-Remicade group were re-randomized 1:1 to either transition to PF-06438179, or to continue on EU-Remicade. This permitted week 54 assessment of immunogenicity associated with a single transition from EU-Remicade to PF-06438179. The rate of ADA positivity by the end of treatment period 2 (at Week 54) was no higher (58%) for the patients who underwent a single transition from EU-Remicade to PF-06438179 than it was for patients who received only EU-Remicade (60%). Rates of infusion related reactions in this study were comparable between patients treated with PF-06438179 and EU-Remicade (5.3% vs 6.1%).

The primary review team did not identify any major differences in immunogenicity that would preclude a determination of no clinically meaningful differences between PF-06438179 and EU-Remicade. The applicant provided an adequate bridge between EU-Remicade and US-Remicade, to support utilizing EU-Remicade in the similarity assessment. There are limitations in comparing historically reported rates of immunogenicity across patient populations, mostly due to variability in assay methodology used in different development programs. However, the Agency has concluded that RA patients, despite background therapy with methotrexate, are a sufficiently sensitive population in which to conduct the immunogenicity assessment for infliximab biosimilars. This is supported by the fact that where RA patients (on background immunosuppression) were compared to a patient population receiving infliximab monotherapy (AS patients) utilizing the same assay methodology, the RA patients were noted to have higher rates of ADA development⁷. For this reason, this population was considered sufficiently sensitive to assess the potential for immunogenicity, and the similarity demonstrated in this population is relevant to IBD patients as well. RA patients on background methotrexate received a lower (3mg/kg) dose of infliximab, whereas the AS patients received the higher (5mg/kg) dose as monotherapy, analogous to the dosing regimen approved for IBD indications.

As the sponsor has demonstrated no clinically meaningful differences in immunogenicity profile in RA patients, and acknowledging that ADA development is thought to be driven mostly by dose, dosing interval, and concomitant therapies (rather than the disease state itself), this reviewer finds that these data support extrapolation to the IBD population.

4. Toxicity

In controlled clinical trials that supported approval of the US-licensed Remicade, patients with IBD experienced similar adverse reactions as other indications, including RA. Similar common and serious adverse reactions have been reported across licensed indications and are described in the prescribing information. Since the safety profile of PF-06438179 has been shown to be similar to that of US-licensed Remicade (see Dr. Erika Torjusen's primary clinical review and Dr. Banu Karimi-Shah's CDTL memorandum) and submitted analytical data did not identify reasons to expect differential safety profiles between patient populations, a similar safety profile would be expected for pediatric and adult patients with IBD receiving PF-06438179. Major toxicities of infliximab are serious infections, including tuberculosis and opportunistic infections, and malignancies, which are shared amongst disease populations. Given the similar product quality attributes, PK, and immunogenicity, there is no reason to

⁷ Ji Soo Kim, Sung Hwan Kim, ByoungOh Kwon & SeungSuh Hong (2015) Comparison of immunogenicity test methods used in clinical studies of infliximab and its biosimilar (CT-P13), Expert Review of Clinical Immunology, 11:sup1, 33-41, DOI: 10.1586/1744666X.2015.1090312

expect that the safety profile in the IBD population would be different from that demonstrated in RA patients.

3 Summary and conclusions

Consistent with the principles of the FDA Guidance outlined in section 2, above, this reviewer concludes that the applicant has provided sufficient scientific justification (based on the mechanism of action, PK, immunogenicity and toxicity profile), and sufficient information, including clinical data from the studied population (RA patients on concomitant methotrexate therapy), to support licensure of PF-06428179 for the inflammatory bowel disease indications.

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/s/

TARA A ALTEPETER
12/11/2017

DONNA J GRIEBEL
12/11/2017

Medical Officer's Review of BLA 761072
Division of Dermatology and Dental Products

Type: Biosimilar 351(k)
Serial Amendment: 000
Supporting Document Number: 001

Correspondence date: 13-FEB-2017
CDER Stamp date: 13-FEB-2017
Review Date: 20-NOV-2017

Applicant: Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Drug: PF-06438179, a proposed biosimilar to infliximab
Name: IXIFI (infliximab-qbtx)
Route of Administration: Intravenous
Dosage Form: lyophilized 100mg/15 mL vial for reconstitution
Pharmacologic Category: Anti-human tumor necrosis factor alpha (TNF α) human-murine immunoglobulin G1 (IgG1) monoclonal antibody
Proposed Indication:

- 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 disease.
- 2) Pediatric Crohn's Disease:
 - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active 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 disease who have had an inadequate response to conventional therapy.
- 4) Pediatric Ulcerative Colitis:
 - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.¹
- 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 disease.

¹ 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 be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

- 6) Ankylosing Spondylitis (AS):
 - reducing signs and symptoms in patients with active disease
- 7) Psoriatic Arthritis (PsA):
 - reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.
- 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.

Project Manager: Barbara Gould

Team Leader: David Kettl, MD

Medical Officer: Gary Chiang, MD, MPH.

Executive Summary:

The Division of Dermatology and Dental Products has concluded that the proposed drug product PF-06438179, a proposed biosimilar to US-licensed Remicade (infliximab), has provided sufficient scientific evidence under section 351(k) of the Public Health Service Act (PHS Act) to demonstrate that the proposed 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 proposed biosimilar product and the reference product in terms of the safety, purity and potency of the product.

No clinical data was submitted specifically related to the psoriasis indication. To support the use of PF-06438179 for plaque psoriasis, Pfizer Inc. has provided adequate scientific justification for the extrapolation of biosimilarity to non-studied indications, including plaque psoriasis. For additional information on the clinical data submitted to support the indications evaluated in this application, please refer to the clinical review from DPARP, the review memo from the Division of Gastrointestinal and Inborn Errors Products (DGIEP), or the Cross-Discipline Team Leader (CDTL) review for details of the submitted application.

It is the Division's conclusion that sufficient scientific evidence is presented for use of PF-06438179 in "the 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."

Introduction:

Pfizer Inc. is developing PF-06438179 as a proposed biosimilar to US-licensed Remicade (infliximab). Remicade was licensed in the United States (US) in 1998. Remicade is also licensed in many countries worldwide, including the European Union (EU) via the Centralized Procedure.

PF-06438179 is a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to human tumor necrosis factor alpha (TNF α). The active substance is a glycoprotein with 1 N-linked glycosylation site in the CH2 domain of each heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteines in the heavy and light chains are involved in either intra- or inter-disulfide bonding.

A total of seven drug substance (DS) batches, eight drug product (DP) lots and two reference materials of PF-06438179 were included in the similarity assessment. The results from analytical similarity assessments support Tier 1, Tier 2, and Tier 3 analytical similarity between PF-06438179 and EU-approved Remicade. In addition, the three-arm comparative PK study B5371001 demonstrated the PK bioequivalence of PF-06438179 to both US-licensed Remicade and the EU-approved Remicade, and of EU-approved Remicade to US-licensed Remicade.

As part of the totality of the evidence for a demonstration of biosimilarity, the clinical development program for PF-06438179 is to support a demonstration that no clinically meaningful differences exist between PF-06438179 and the reference product, US-licensed Remicade in terms of its pharmacokinetics, efficacy, safety, and immunogenicity. The following two controlled studies provide the primary evidence to support the determination of no clinically meaningful differences between PF-06438179 and the reference product, US-licensed Remicade:

- Study B5371001 is a randomized, double-blind, three-arm, parallel group, single-dose study to compare the PK, safety/tolerability and immunogenicity of PF-06438179, US-licensed Remicade, and EU-approved Remicade in healthy subjects. The study demonstrated similarity of PK between PF-06438179, US-licensed Remicade, and EU-approved Remicade; and supported the PK element of the scientific bridge between PF-06438179, US-licensed Remicade and EU-approved Remicade. This scientific bridge between the products is necessary to justify the relevance of comparative data generated using EU-approved Remicade to support demonstration of biosimilarity of PF-06438179 to US-licensed Remicade.
- Study B5371002 is a randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy, safety/tolerability and immunogenicity of PF-06438179 compared to EU-approved Remicade in moderately to severe active RA with inadequate response to methotrexate. This clinical trial is the comparative clinical study that provides the efficacy and safety data for PF-06438179 in subjects with moderate to severe rheumatoid arthritis (RA) despite MTX therapy, to support a demonstration of no clinically meaningful differences.

Additional long-term safety and immunogenicity data was collected in Treatment Period 2 (TP2) of study B53710023 beginning with the dosing on Week 30, when subjects initially assigned to the EU-approved Remicade study arm were re-randomized in a 1:1 ratio, with 50% of the EU-approved Remicade arm switching to PF-06438179 and the

other 50% remaining on EU-approved Remicade. All subjects initially assigned PF-06438179 remained blindly assigned to continue on PF-06438179. Treatment continued in TP2 for another 24 weeks and ended with the completion of the Week 54 pre-dose assessments. Treatment Period 3 (TP3) began with the Week-54 dosing, when all subjects remaining on EU-approved Remicade were switched to PF-06438179. All subjects continued to receive open-label PF-06438179 treatment for an additional 24 weeks, with last study drug dosing scheduled on Week 70, and the end of treatment (EOT) visit on Week 78 (8 weeks after dosing on Week 70).

Extrapolation to Plaque Psoriasis:

Pfizer Inc. is seeking licensure for the indication studied in the clinical program, RA, as well as for ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, and adult and pediatric ulcerative colitis¹ for which they have not submitted clinical data. To support the use of PF-06438179 for the non-studied indications, Pfizer Inc. has provided adequate scientific justification for the extrapolation of biosimilarity to those indications.

The justification addresses the issues for the testing and extrapolation to conditions of use outlined in Guidance for Industry: *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.²

If a biological product meets the statutory requirements for licensure as a biosimilar biological 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 applicant may seek licensure for one or more additional conditions of use for which the reference product (i.e., US-licensed Remicade) is licensed.² However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

Such scientific justification for extrapolation 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

²Guidance for Industry “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product”, April 2015
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>

Differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity.

Consistent with the principles outlined in the Guidance for Industry: *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*², Pfizer Inc. has provided sufficient justification to extrapolate data from the comparative clinical studies of PF-06438179 in RA to support a determination of biosimilarity for the additional indications for which US-licensed Remicade is licensed. Considerations specific to plaque psoriasis include:

- The primary mechanism of action (MOA) of infliximab is direct binding and blocking of TNF receptor-mediated biological activities. 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 scientific literature indicates that this MOA is the primary MOA in RA, AS, PsA, PsO. The data provided by Pfizer Inc. showed similar TNF binding and potency to neutralize TNF α , supporting the determination of analytical similarity pertinent to this MOA. Therefore, the totality of the evidence provided by Pfizer supports a demonstration of biosimilarity of PF-06438179 to U.S. licensed Remicade in adult patients with chronic severe plaque psoriasis based on common mechanism of action.
- Because similar PK was demonstrated between PF-06438179 and US-licensed Remicade, a similar PK profile would be expected for PF-06438179 in adult patients with chronic severe plaque psoriasis.

In general, immunogenicity of the US-licensed Remicade was affected primarily by 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. In plaque psoriasis the recommended dose is 5 mg/kg. US-licensed Remicade is used without methotrexate in plaque psoriasis. Pfizer Inc. provided adequate bridging data to justify the relevance of comparative data with EU-approved Remicade in the PK healthy subject and RA clinical trial to support a demonstration of biosimilarity of PF-06438179 to US-licensed Remicade.

- No differences in expected toxicities that are relevant to the plaque psoriasis population were noted between the PF-06438179 product and the EU-approved Remicade arms in the clinical trial.
- Based on the above considerations, the Division concluded that it is reasonable to conclude that the available PF-06438179 data supports a demonstration of biosimilarity of PF-06438179 in plaque psoriasis.

PeRC

Pfizer Inc. provided an Initial Pediatric Study Protocol Agreement (iPSP) to the Agency at the time of the BLA submission. The iPSP included a waiver to study the pediatric population in ages 0-17 years old. This is based on a lack of efficacy and safety profile with infliximab in pediatric psoriasis and the reports of AEs associated with infliximab in the pediatric indications.

The initial waiver agreement was based on evidence of cancer risks due to TNF α class biologics; however, the Agency has since approved etanercept (a TNF α class biologic) for use in pediatrics. With the approval, TNF α biologics will be required to study appropriate pediatric populations under the Pediatric Research Equity Act (PREA).

The PeRC agreed that in a general, a class-wide waiver for TNF alpha inhibitors based on safety reasons should no longer be assumed for the indication of plaques psoriasis. However, the PeRC and division also agreed that the data available to support approval of any biosimilar should be based on the data available for adult and pediatric patients for the specific TNF α product. Because the reference product, US-licensed Remicade, is approved for chronic severe plaque psoriasis (i.e., extensive and/or disabling), which is a subset of moderate to severe plaque psoriasis, a waiver of the requirement for pediatric studies may be justified for the reason that such studies would be impossible or highly impracticable for this narrower indication of severe plaque psoriasis.

Overall Conclusion:

The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires a demonstration that the proposed 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 proposed biosimilar product and the reference product in terms of the safety, purity and potency of the product.

This review from DDDP concludes that the applicant has provided proper justification and information to support the proposed use of PF-06438179 in the 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.

Gary Chiang, M.D., M.P.H.
Medical Officer
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GARY T CHIANG
11/20/2017

DAVID L KETTL
11/20/2017

CLINICAL REVIEW

Application Type	351(k) BLA
Application Number(s)	761072
Priority or Standard	Standard
Submit Date(s)	February 13, 2017
Received Date(s)	February 13, 2017
BsUFA Goal Date	December 13, 2017
Division / Office	DPARP/ODEII- Lead Division Collaborative review with DGIEP and DDDP
Reviewer Name(s)	Erika Torjusen, MD, MHS
Review Completion Date	October 30, 2017
Nonproprietary Name	PF-06438179
(Proposed) Trade Name	Ixifi
Therapeutic Class	TNF-inhibitor
Applicant	Pfizer
Formulation(s)	Intravenous (IV)
Dosing Regimen	<ul style="list-style-type: none">• Rheumatoid Arthritis: In conjunction with methotrexate, 3mg/kg at 0, 2, and 6 weeks, then every 8 weeks increasing up to 10mg/kg or treating every 4 weeks• Ankylosing Spondylitis: 5mg/kg at 0, 2, and 6 weeks, then every 6 weeks• Psoriatic Arthritis, Plaque Psoriasis and Ulcerative Colitis: 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks• Crohn's disease: 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks increasing up to 10mg/kg in patients who initially respond but lose their response later
Indication(s)	<ul style="list-style-type: none">• Rheumatoid Arthritis in combination with methotrexate• Ankylosing Spondylitis• Psoriatic Arthritis• Plaque Psoriasis• Crohn's Disease• Pediatric Crohn's Disease

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- Ulcerative Colitis
 - Pediatric Ulcerative Colitis¹
- Intended Population(s)
- Rheumatoid Arthritis: moderate to severe disease
 - Ankylosing Spondylitis: active disease
 - Psoriatic Arthritis: active disease
 - Plaque Psoriasis: chronic, severe disease
 - Crohn’s Disease: moderate to severe disease
 - Pediatric Crohn’s Disease: moderate to severe disease
 - Ulcerative Colitis: moderate to severe disease
 - Pediatric Ulcerative Colitis: moderate to severe disease¹

¹ We note that the 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>.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This biologic licensing application (BLA 761072) seeks approval of the product PF-06438179 (proposed trade name: Ixifi) which is a proposed biosimilar to US-licensed Remicade (also referred to as US-Remicade in this review) with the active ingredient infliximab, a TNF α -inhibitor. The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires that the proposed 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 proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, with the foundation being an extensive structural and functional characterization to support a demonstration that the products are highly similar.

The product quality review by OBP (Office of Biotechnology Products) team, of structural and functional characterization, concluded that PF-06438179 is highly similar to US-licensed Remicade notwithstanding minor differences in clinically inactive components. The submitted clinical pharmacology, efficacy, safety, and immunogenicity data from the clinical development program of PF-06438179, support a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade.

Therefore, PF-06438179 meets both parts of the statutory definition to demonstrate biosimilarity to the reference product in that PF-06438179 is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between PF-06438179 and the US-licensed Remicade in terms of safety, purity and potency. The applicant has also provided adequate scientific justification to allow for extrapolation of data to support biosimilarity in all indications that US-licensed Remicade is licensed for, and Pfizer is seeking licensure of PF-06438179, namely, Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Psoriasis (PsO), adult and pediatric Crohn's Disease (CD), and adult and pediatric Ulcerative Colitis (UC)².

Therefore, from a clinical perspective, we recommend **approval** of BLA 761072 for PF-06438179 as a biosimilar to US-licensed Remicade.

² We note that the 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>.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

The following two controlled studies provide the primary evidence to support the determination of no clinically meaningful differences between PF-06438179 and US-licensed Remicade:

- Study B5371001, is a single-dose, 3-way pharmacokinetics (PK) study that assessed the similarity in PK between PF-06438179 and US licensed Remicade. It also helped in establishing the PK bridge between PF-06438179, US-licensed Remicade, and EU approved Remicade. This bridge is necessary because the reference product of interest for this application is US-licensed Remicade, but the majority of the clinical program utilized EU approved Remicade as the comparator. This study therefore provides the PK component of the scientific justification for the extrapolation of data using EU approved Remicade for the demonstration of biosimilarity of PF-06438179 to US-licensed Remicade. Study B5371001 also provides the immunogenicity data comparing PF-06438179 and US-licensed Remicade following single dose administration.
- Study B5371002, is the comparative clinical study that provides efficacy, safety and immunogenicity data for PF-06438179 in rheumatoid arthritis (RA) in comparison with EU approved Remicade. The comparative clinical study is a randomized, double-blind, parallel-group study to compare efficacy, safety and immunogenicity between the two products for 30 weeks. Following the first randomized controlled period, additional long-term safety and immunogenicity data from Week 30 to Week 54 were reported for patients who either continued PF-06438179 or underwent a randomized single transition at Week 30 from EU approved Remicade to PF-06438179 or continued to receive EU approved Remicade in a randomized, double-blind fashion.

Clinical Efficacy Overview and Conclusions

Study B5371002, the comparative clinical study in RA patients, met its primary objective of demonstrating that the proportion of patients achieving ACR20 response at Week 14 was similar between the PF06438179 and EU approved Remicade treatment groups [(n=198, 61%) and (n=207, 64%), respectively]. The 90% CI for the estimate of treatment difference (-2.39) was contained within the prespecified asymmetric similarity margin of -12% to 15% (90% CI: -8.75, 4.02). In light of the scientific justification that allowed extrapolation, these results support the finding that there are no clinically meaningful differences between the proposed biosimilar, PF06438179, and U.S.-licensed Remicade.

Analysis of secondary efficacy endpoints in Study B5371002 including ACR20, ACR50, ACR70 responses and disease activity score (DAS28-CRP) at various time points through Week 54, showed similar results between PF06438179 and EU approved Remicade treatment groups.

The transition-extension period of study B5371002 had a single transition from EU approved Remicade to PF06438179 at Week 30 and was supportive of the primary endpoint. ACR20

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response rates over time up to Week 54 were comparable between the different treatment arms. Efficacy endpoint analysis demonstrated consistent efficacy up to Week 54 in each treatment group, PF06438179 maintenance, EU approved Remicade maintenance and EU approved Remicade to PF06438179 transition group.

Clinical Safety Overview and Conclusions

The safety evaluation plan of PF-06438179 was based on the known safety profile of US-licensed Remicade as described in the USPI and other published data.

The safety of PF-06438179 compared to EU approved Remicade (with extrapolation to US-licensed Remicade) was assessed in Study B5371002, the comparative clinical study, comparing PF-06438179 with EU approved Remicade in patients with RA as well as the single dose, healthy subject, comparative PK study, B5371001. Safety assessments in these studies included adverse events (AEs), physical examinations, vital signs, ECGs, clinical laboratory testing and immunogenicity assessments. Study B5371001 was a single-dose study and provided information regarding short-term exposure to PF-06438179. Study B5371002 provided information regarding longer term exposure to PF-06438179, up to 54 weeks, as well as data for patients who underwent a single transition from EU approved Remicade to PF-06438179.

The safety database submitted for PF-06438179 is adequate to provide a reasonable descriptive comparison between the products. The safety risks identified are consistent with the known adverse event profile of US licensed Remicade. The analysis of the data indicates a safety profile of PF-06438179, similar to that of US licensed Remicade. No new safety signals were identified in the PF-06438179 group compared to the known adverse event profile of US licensed Remicade. There were no notable differences between PF-06438179 and US licensed or EU approved Remicade in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, or deaths between the treatment groups. Infusion related reactions, hypersensitivity events and anaphylaxis were generally balanced between the treatment groups, with a slight increase in infusion related reactions (IRRs) noted in the EU Remicade/ EU Remicade treatment arm during treatment period two (TP2) of the comparative clinical study. It is notable that IRRs and hypersensitivity events did not increase following transition from EU approved Remicade to PF-06438179.

The safety database is adequate to assess the comparative safety of PF-06438179. In summary, the safety data for PF-06438179 did not reveal any new safety concerns. Adverse events were few and consistent with those observed with similar approved TNF inhibitor biologic products. In addition, transitioning of non-treatment naïve patients, i.e., patients previously treated with EU approved Remicade, to PF-06438179 does not appear to result in an increase of clinically significant adverse reactions.

Immunogenicity Overview and Conclusions

Small numerical differences in ADA formation were seen between PF-06438179, EU-Remicade and US-Remicade in the clinical program. These differences were slightly greater in the comparative PK study, B5371001. However, in light of the totality of the information discussed in Section 7.4.6 Immunogenicity in this review, these do not represent clinically meaningful differences and do not preclude a demonstration of biosimilarity between PF-06438179 and US-licensed Remicade.

Risk-Benefit Assessment

Overall, the efficacy, safety and immunogenicity data from the PF-06438179 clinical development program (studies B5371001 and B5371002) provide evidence of no clinically meaningful differences between PF-06438179 and US licensed Remicade. Safety and immunogenicity analyses indicate a safety profile of PF-06438179, similar to that of US licensed Remicade.

Extrapolation to Non-studied Indications

Pfizer is seeking licensure for the indication studied in the clinical program, i.e. RA as well as for ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, and adult and pediatric ulcerative colitis³ which have not been directly studied in PF-06438179 clinical program. To support the use of PF-06438179 for those indications, Pfizer has provided adequate scientific justification to permit the use of data generated with EU-approved Remicade in support of the demonstration of biosimilarity for those indications. The justification addresses issues for the testing and extrapolating conditions of use outlined in Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009." Also refer to BLA 761054 Division Memos from the collaborating review Divisions, Division of Dermatology and Dental Products (DDDP) and Division of Gastroenterology and Inborn Errors Products (DGIEP), outlining their conclusion that extrapolation of biosimilarity to indications in dermatology and gastroenterology, respectively is scientifically justified.

Recommended Regulatory Action

From a clinical perspective, based on the finding that there are no clinically meaningful differences between PF-06438179 and US licensed Remicade, the risk-benefit assessment supports the approval of BLA 761072 for PF-06438179 as a biosimilar to US-licensed Remicade.

³We note that the 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>.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements or commitments are recommended at this time.

2 Introduction and Regulatory Background

Summary

PF-06438179 has been developed as a proposed biosimilar product to US-licensed Remicade (infliximab). The applicant, Pfizer, submitted a BLA (biologics licensing application) for PF-06438179 under the abbreviated licensure pathway 351(k) of the PHS Act for a proposed biosimilar product. The reference product, US-licensed Remicade (US-Remicade), was approved by the FDA in 1998 on the basis of a complete stand-alone drug development program.

Biosimilar Regulatory Background

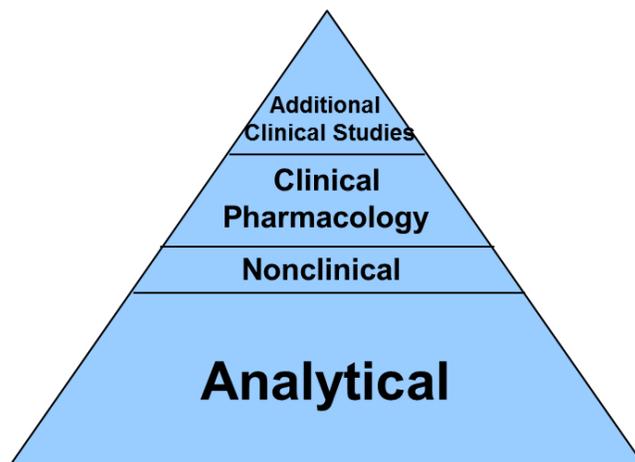
The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law in 2010, amended the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biological products that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product. This pathway is provided in the part of the law known as the *Biologics Price Competition and Innovation Act* (BPCI Act). Under the BPCI Act, a biological product may be demonstrated to be “biosimilar” if data show that, among other things, the product is “highly similar” to an already-approved biological product. Of note, PF-06438179 has been developed as a proposed biosimilar to US-Remicade and not as interchangeable product. As such, there will no discussion of interchangeability in this review.

To help clarify definitions surrounding biosimilars, it is important to note that a biosimilar product must utilize the same mechanism of action to the extent the mechanisms are known for the reference product, and must have the same route of administration, dosage form and strength as the reference product.

In the abbreviated licensure pathway (under 351(k)), (see Figure 1 below) the goal is to demonstrate biosimilarity between the proposed biosimilar product and the reference product with analytical similarity being the foundation of this assessment. The goal is not to independently establish safety and effectiveness of the proposed product. The abbreviated pathway means that a biosimilar product can be approved based on less than a full complement of product-specific preclinical and clinical data because FDA can rely on certain existing scientific knowledge and FDA’s finding of safety, purity and potency regarding the reference product

Figure 1. Abbreviated Licensure Pathway for Biosimilar Products under 351(k) Pathway of PHS Act

“Abbreviated” Development Program, 351(k)
Goal: To demonstrate biosimilarity
(or interchangeability)



The biosimilar licensure pathway under section 351(k) of the PHS Act requires that the a) proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and b) that there are no clinically meaningful differences between the proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

The PF-06438179 Story under 351(k) pathway (Product Development Rationale)

The development of PF-06438179 began with demonstration of analytical similarity between PF-06438179 and the reference product, US-licensed Remicade. To demonstrate that PF-06438179 is highly similar to the reference product, the applicant conducted a robust analytical program to compare physico-chemical and biological (structure & functional) characteristics including assessment of primary, secondary and tertiary structure; post-translational profile and in-vitro functional characteristics, purity, stability, potency, including TNF-alpha binding and neutralization to name a few of the key quality attributes. See OBP review for the detailed assessment of analytical similarity. The applicant also conducted a small nonclinical program including in-vitro and in-vivo studies to support the clinical program.

To support that there are no clinically meaningful differences between PF-06438179 and US-licensed Remicade, the applicant conducted two clinical studies. A phase 1 PK study (Study B5371001) was conducted in healthy subjects to show similarity in PK between the two

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products. Lastly, a comparative clinical study (Study B5371002) in RA patients was conducted to address residual uncertainties or clinically meaningful differences, if any, that remained between PF-06438179 and the reference product. Both these studies assessed safety, efficacy and immunogenicity of PF-06438179 in comparison with Remicade.

Of note, the comparative clinical study compared PF-06438179 with EU-approved Remicade. To justify the relevance of the data generated using EU-approved Remicade to support a demonstration of biosimilarity between PF-06438179 and US-licensed Remicade, the applicant provided adequate bridging data between PF-06438179, US-licensed Remicade and EU-approved Remicade. The analytical, and nonclinical studies in addition to the PK study, provided the data to establish a scientifically justified bridge between EU-approved Remicade and US licensed Remicade.

This review focuses on the clinical program conducted to support a demonstration of no clinically meaningful differences between PF-06438179 and Remicade.

2.1 Product Information

PF-06438179 is a proposed biosimilar biological product to US-licensed Remicade. PF-06438179 is a chimeric human murine immunoglobulin G1 (IgG1) monoclonal antibody that binds to the human tumor necrosis factor alpha (TNF α). The active PF-06438179 Drug Product (DP) is 100 mg lyophilized infliximab in a 15 mL vial for injection, for intravenous use, and its strength is 100 mg per vial.

2.2 Tables of Currently Available Treatments for Proposed Indications

Available therapies may be approved for treatment of more than one condition. Currently approved non-biologic and biologic systemic therapies and the indications for which they are approved are listed in Table 1 and Table 2, respectively.

Plaque Psoriasis

The available approved systemic treatments for moderate to severe PsO in candidates for systemic therapy or phototherapy is described in Table 1 and Table 2 below. While multiple topical therapies are available, and may be used in combination with systemic treatments, topical therapies are not typically used alone for patients with psoriasis of moderate to severe severity. Phototherapy involves exposure to UVB (including narrowband) or to UVA in combination with the photosensitizer, Psoralen, a photochemotherapy that goes by the acronym PUVA. Phototherapy requires frequent office visits (e.g. three times per week) and carries an increased risk of squamous cell carcinoma (of the skin).

Rheumatoid Arthritis

Many effective therapies are approved for the treatment of patients with RA including nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors, corticosteroids, disease modifying anti rheumatic drugs (DMARDs) and biologics. Currently approved non-biologic and biologic systemic therapies for RA are listed in Table 1 and Table 2, respectively.

Polyarticular Juvenile Idiopathic Arthritis (JIA)

Similar to RA, effective therapies for the treatment of patients with JIA include NSAIDs, selective COX-2 inhibitors, corticosteroids, DMARDs, and biologics. Currently approved non-biologic and biologic therapies for polyarticular JIA are listed in Table 1 and Table 2 below.

Psoriatic Arthritis (PsA)

The first-line therapy for the treatment of psoriatic arthritis is typically the off-label use of small molecular immunomodulators (DMARDs, such as methotrexate (MTX), sulfasalazine, and leflunomide). NSAIDs and corticosteroids are also used. The TNF-inhibitors, infliximab, etanercept, adalimumab, certolizumab, and golimumab, as well as the IL-12/IL-23 inhibitor, ustekinumab, have been approved for treatment of active psoriatic arthritis. More recently, apremilast, a small molecule phosphodiesterase 4 inhibitor, and secukinumab, an IL-17 inhibitor, were also approved for treatment of active psoriatic arthritis. Currently approved therapies for treatment of adult patients with psoriatic arthritis are listed in Table 1 and Table 2.

Ankylosing Spondylitis (AS)

Initial treatment for AS typically includes the use of NSAIDs. Sulfasalazine may be used off-label for management of peripheral arthritis. For persistent axial symptoms, patients may be

treated with TNF-inhibitors or secukinumab, an IL-17 inhibitor. Currently approved therapies for treatment of adult patients with ankylosing spondylitis are listed in Table 1 and Table 2.

Table 1. US-licensed Non-Biologic DMARDs by Indication

Product Name (Trade Name) [Applicant] {year}	Mechanism of Action	Approved Indications					
		RA	PsA	AS	pJIA	PsO	Other
Sulfasalazine (AZULFIDINE) [Pfizer]{1950}	<i>Anti-inflammatory and/or immunomodulator</i>	X			X		UC
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple] {1953}	<i>Folate anti-metabolite</i>	X			X	X	Oncology indications
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]{1955}	<i>Unknown</i>	X					SLE, Malaria
Prednisone [Multiple sponsors]{1955}	<i>Anti-inflammatory and other unspecified mechanisms</i>	X					Many
Azathioprine (IMURAN) [Prometheus Labs]{1968}	<i>Anti-metabolite</i>	X					Renal transplant
Penicillamine (CUPRIMINE) [Aton]{1970}	<i>Unknown</i>	X					Wilson's Disease, cystinuria
Auranofin (RIDAURA) [Prometheus Labs]{1985}	<i>Unknown</i>	X					
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]{1990, 1995}	<i>T-cell inhibitor</i>	X				X	Organ rejection, KCS
Acitretin (SORIATANE) (Stiefel){1996}	<i>Retinoid</i>					X	
Leflunomide (ARAVA) [Sanofi-Aventis]{1998}	<i>Anti-metabolite</i>	X					
Tofacitinib (XELJANZ) [Pfizer] (2012)	<i>JAK kinase inhibitor</i>	X					
Tofacitinib (XELJANZ XR) [Pfizer] (2016)	<i>JAK kinase inhibitor</i>	X					
Apremilast (Otezla) [Celgene] {2014}	<i>PDE4 inhibitor</i>		X			X	
* Year = Year of first approval	UC=Ulcerative Colitis, CD=Crohn's Disease, SLE=Systemic Lupus Erythematosus, KCS=Keratoconjunctivitis sicca						

Table 2. US-Licensed Biologic DMARDs by Indication

Product Name (Trade Name) [Applicant] {year}	Description and Mechanism of Action	Approved Indications					
		RA	PsA	AS	pJIA	PsO	Other
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Fusion protein consisting of TNF-R and human IgG1 Fc <i>TNF inhibitor</i>	X	X	X	X	X	
Infliximab (REMICADE) [Centocor] {1999}	Chimeric IgG1 k mAb <i>TNF inhibitor</i>	X	X	X		X	CD, UC, Pediatric CD/UC
Anakinra (KINERET) [Amgen] {2001}	Recombinant polypeptide <i>IL-1 receptor antagonist</i>	X					NOMID
Adalimumab (HUMIRA) [Abbott] {2002}	Human IgG1 k mAb <i>TNF inhibitor</i>	X	X	X	X	X	CD, UC, Pediatric CD, HS, Uveitis
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Fusion protein consisting of CTLA-4 and human IgG1 Fc <i>T cell activation inhibitor</i>	X	X		X		
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Chimeric murine/human IgG1 k mAb <i>Anti CD20, B cell depletor</i>	X					GPA, MPA, NHL, CLL
Golimumab (SIMPONI) [Centocor] {2009}	Humanized IgG1 k mAb <i>TNF inhibitor</i>	X	X	X			UC
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Humanized Fab fragment <i>TNF inhibitor</i>	X	X	X			CD
Ustekinumab (STELARA) [Centocor Ortho Biotech] {2009}	Humanized IgG1 k mAb <i>IL-12, IL-23 antagonist</i>		X			X	
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Humanized IgG1 k mAb <i>IL-6 receptor inhibitor</i>	X			X		SJIA
Golimumab (SIMPONI ARIA) [Janssen Biotech] {2013}	Humanized IgG1 mAb <i>TNF inhibitor</i>	X					
Secukinumab (Cosentyx) [Novartis] {2015}	Humanized IgG1 mAb <i>IL-17 inhibitor</i>		X	X		X	
Infliximab-dyyb (INFLECTRA) [Celltrion] {2016}	Chimeric IgG1 k mAb <i>TNF inhibitor</i>	X	X	X		X	CD, UC, Pediatric CD
Etanercept-szszs (ERELZI) [Sandoz] {2016}	Fusion protein consisting of TNF-R and human IgG1 Fc <i>TNF inhibitor</i>	X	X	X	X	X	
Adalimumab-atto (AMJEVITA) [Amgen] {2016}	Human IgG1 k mAb <i>TNF inhibitor</i>	X	X	X	X	X	CD, UC
*Year = Year of first approval	CD=Crohn's Disease, UC=Ulcerative Colitis, NOMID=Neonatal Onset Multisystem Inflammatory Disease, GPA=Granulomatosis with Polyangiitis, MPA=Microscopic Polyangiitis, NHL=Non-Hodgkin's Lymphoma, CLL=Chronic Lymphocytic Leukemia, SJIA= Systemic Juvenile Idiopathic Arthritis, HS=Hidradenitis Suppurativa						

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Product Name (Trade Name) [Applicant] {year}	Description and Mechanism of Action	Approved Indications					
		RA	PsA	AS	pJIA	PsO	Other
Infliximab-abda (RENFLEXIS) [Samsung] {2017}	Chimeric IgG1 k mAb <i>TNF inhibitor</i>	X	X	X		X	CD, UC, Pediatric ¹ CD
Sarilumab (KEVZARA) [Sanofi-Aventis] {2017}		X					
Adalimumab-adbm (CYLTEZO) [Boehringer Ingelheim] {2017}	Human IgG1 k mAb <i>TNF inhibitor</i>	X	X	X	X	X	CD, UC
Year = Year of first approval ¹ We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018.	CD=Crohn's Disease, UC=Ulcerative Colitis, NOMID=Neonatal Onset Multisystem Inflammatory Disease, GPA=Granulomatosis with Polyangiitis, MPA=Microscopic Polyangiitis, NHL=Non-Hodgkin's Lymphoma, CLL=Chronic Lymphocytic Leukemia, SJIA= Systemic Juvenile Idiopathic Arthritis, HS=Hidradenitis Suppurativa						

2.3 Availability of Proposed Active Ingredient in the United States

PF-06438179 is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety program for PF-06438179 was designed based on the well-known safety profile of US-licensed Remicade. Potential risks based on class of drug (TNF α) and of the drug substance (foreign protein) were considered. Potential risks associated with immunomodulating biologic therapies may include infections, cardiovascular safety, malignancies and autoimmune disorders. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, infusion reactions and immunogenicity.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

January 28, 2013 Pre-IND Meeting

- Provided advice for the proposed biosimilar development program

July 8, 2013 Parallel Qualification Advice Meeting with FDA (b) (4)

- Discussed clinical evaluation methodologies in RA of anti-cytokine products

December 18, 2013 BPD Type 2 Meeting

- Discussed proposed the comparative clinical efficacy study protocol B5371002 including population, endpoints, and endpoint timing (primary endpoint: ACR20 response at Week 14) and the randomized single transition to PF-06438179 at Week 30

August 5, 2014 BPD Type 3 Meeting

- Discussed the adequacy of the functional, structural, and PK similarity data to support the comparative clinical development plan (no determination of similarity was made as the full analytical data package had not been submitted for review), and provided final comments on the comparative clinical efficacy study, B5371002

April 8, 2015 (Post Meeting Written Responses to Similarity Margin Proposal)

- The statistical team for the primary review Division suggested an asymmetric similarity margin (-12%, +15%), with adequate justification, and a 90% confidence interval

January 29, 2016 BPD Type 2 Meeting (TCON)

- Discussed statistical tiering assignments for QA similarity assessments, number of PF-06438179 lots proposed to demonstrate similarity is insufficient for a robust estimate of the variability and the mean of PF-06438179 (should use at least 10 lots of PF-06438179)

July 8, 2016 BPD Type 2 Meeting

- Discussed the extent of clinical data to be included in the BLA (study B5371002: efficacy and safety data for treatment period 1, first 8 weeks of treatment period 2 single transition, remaining data extending to Week 54 provided in the 4-Month safety update), as well as CMC/Stability, blinding strategy and proposed statistical analyses for Study B5371002.

November 22, 2016 BPD Type 4 Meeting

- Discussed and obtained concurrence on the overall structure and format of a future 351(k) BLA for PF-06438179, and FDA request for 'independent' DS/DP lots in the similarity assessment.

January 11, 2017 BPD Type 4 Meeting (Post Meeting Written Responses to CMC questions)

- Discussed DS/DP lot independence for analytical assessment and similarity data.

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The data quality and integrity of the studies were considered reliable.

OSI Inspection

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The BLA submission was in electronic common technical document (eCTD) format and was adequately organized. The Office of Scientific Investigations (OSI) was consulted to conduct routine clinical site and applicant/monitor inspection for PF-06438179, a proposed biosimilar to US-licensed Remicade.

The inspection audited the clinical study B5371002. Two clinical sites (1100 and 1103- both in Bosnia & Herzegovina), which were among the highest enrollers of patients and represented the extremes for the number of protocol violations, were selected for inspection.

Per OSI, the final CDER classification of site 1103, was pending at the time of this review. However, the preliminary classification of this site was “no action indicated”. The second site, 1100, was also deemed “no action indicated” and it was determined that the clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. The data submitted by this clinical site appeared acceptable in support of this specific indication.

The Division of New Drug Bioequivalence Evaluation (DNDBE) Office of Study Integrity and Surveillance recommended that the analytical data from the comparative PK study (B5371001) be accepted without an on-site inspection as an inspection was not needed at this time.

3.2 Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in this BLA were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators. The applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54.

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Covered Clinical Studies (Name and/or Number): B5371001 and B5371002.

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified:		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>5</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: <u>5</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this BLA application. No potentially conflicting financial interests were identified for the investigators participating in study B5371001. Compensation beyond the acceptable limits for study B5371002 are outlined below:

Dr. [REDACTED] (b) (6): Total \$48,450.00

- Speaker honorarium
- Consulting

Dr. [REDACTED] (b) (6): Total \$33,640.59

- Speaker honorarium
- Consulting

Dr. [REDACTED] (b) (6): Total \$63,500.00

- Speaker honorarium

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Dr. [REDACTED] (b) (6): Total \$57,817.35

- Speaker honorarium
- Consulting

[REDACTED] (b) (6): Total \$294,786.42

- Speaker honorarium
- Consulting

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

PF-06438179 is a proposed similar biological product to US-licensed Remicade (infliximab). PF-06438179 is an IgG1 kappa monoclonal antibody (mAb) with two identical heavy (H) chains and two identical light (L) chains, covalently linked with four inter-chain disulfide bonds.

To support a determination that PF-06438179 is highly similar to the reference product, Pfizer submitted an extensive analytical similarity package consisting of multiple orthogonal physicochemical and biological assays.

Further, the clinical development program was conducted using EU-approved Remicade. To obtain licensure of PF-06438179 under section 351(k) of the PHS Act, Pfizer had to demonstrate that PF-06438179 is biosimilar to a single reference product that previously has been licensed by FDA, i.e. US-licensed Remicade. As outlined in the draft FDA Guidance for Industry “*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product - February 2012*”, Pfizer had to provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the US-licensed reference product. To that extent, Pfizer submitted a 3-way analytical similarity assessment comparing PF-06438179 to both EU- approved and US-licensed Remicade to establish an acceptable bridge to US-licensed Remicade. These analyses were intended to demonstrate:

- Identical primary structure
- Highly similar secondary and higher order structure
- Highly similar disulfide bonding
- Highly similar glycosylation profile with very minor differences in core fucose content
- Highly similar critical quality attributes such as TNF binding and neutralization and other functional characteristics, including, Fc receptor binding, induction of cell-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), Induction of regulatory macrophages and mucosal healing.

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The product quality review was pending at the time of this review. For a detailed review and analysis of the CMC data, refer to the review by the Product Quality review team.

4.2 Clinical Microbiology

The clinical microbiology review was pending at the time of this review.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology review was pending at the time of this review.

4.4 Clinical Pharmacology

The clinical pharmacology review was pending at the time of this review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Sources of Clinical Data							
Study ID <i>Dates</i>	Design	Study Duration	Treatment Arms	N	Population	Endpoint	Sites % US Sites
Phase 1 Comparative PK study							
B5371001 <i>May 2013- November 2013</i>	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 _{max} , AUC _t , and AUC _{inf}	US 100%
Phase 3 Comparative Clinical Study							
B5371002 <i>August 2014- June 2016</i>	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	US 13% <u>5 Regions:</u> North America and Western Europe, Japan, Republic of Korea, Latin America, and the rest of the world
<p>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.</p>							
Source: Module 5.3.3.1, CSR B5371001, Synopsis B5371001, CSR B5371002, Synopsis B5371002							

5.2 Review Strategy

The focus of this review are the clinical efficacy and safety in the two controlled clinical studies (B5371001 and B5371002) conducted to support the determination that there no clinically meaningful differences between PF-06438179 IV and US-licensed Remicade (See Table 3). An analysis of the comparative PK data can be found in the clinical pharmacology review by Manuela Grimstein, PhD.

Section 5.3 Discussion of Individual Studies/Clinical Trials, describes the protocols in detail for each individual study. Section 6 Review of Efficacy, reviews the efficacy results for the comparative clinical study (B5371002) in patients with RA through Week 54. As the applicant submitted the data in blocks for each treatment period, efficacy results are displayed at Week 14 (the primary endpoint), weekly through Week 30 (treatment period 1, TP1) and weekly through Week 54 (treatment period 2, TP2). Section 7 Review of Safety, describes the individual safety results for the two pivotal studies (B5371001 and B5371002). The safety section is organized by treatment period; Week 0-Week 30 (TP1) and Week 30- Week 54 (TP2). Display of the data by treatment period also permits evaluation of any differences in efficacy, safety and immunogenicity after the transition from EU-approved Remicade to PF-06438179 at Week 30.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study B5371001

Administrative Information

Study B5371001

- **Study title:** A Phase 1, Double-Blind, Randomized, Parallel Group, Single-Dose, 3-arm, Comparative Pharmacokinetic Study of PF-06438179 and Infliximab sourced from US and EU administered to healthy volunteers
- **Study dates:** May 2013- November 2013
- **Study sites:** 1 site in the USA
- **Study report date:** March 18, 2014

Objectives/Rationale

Primary Objectives

- To compare the pharmacokinetics (PK) of PF-06438179 to EU approved Remicade and PF-06438179 to US licensed Remicade.
- To compare the PK of infliximab-EU to infliximab-US.
- To evaluate the single-dose safety, tolerability, and immunogenicity.

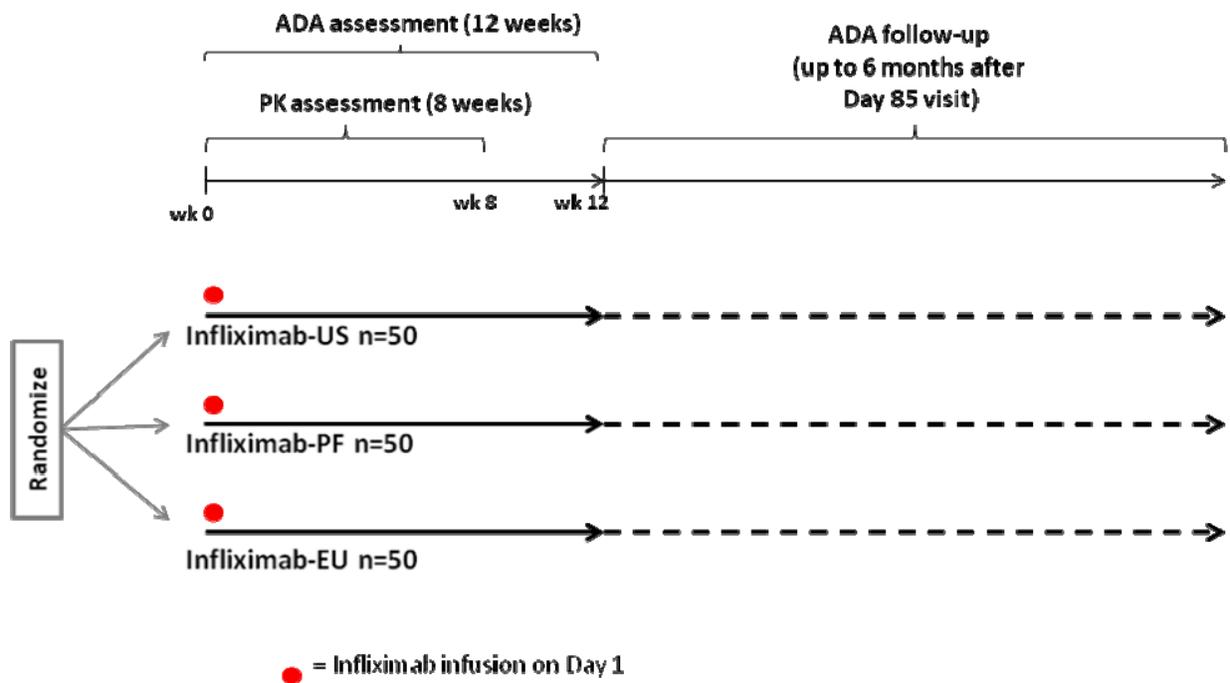
Study Design and Conduct

Overview

B5371001 was a Phase 1, double-blind (Sponsor unblinded), randomized (1:1:1), parallel-group, single-dose, 3-arm, comparative PK study of (PF-06438179), US licensed Remicade and EU-approved Remicade administered IV to healthy volunteers.

The study design for the study is depicted in Figure 2.

Figure 2. Study Design: B5371001



Source: Module 5.3.5.1, CSR B5371001, Figure 1, Page 19

The schedule of assessments is shown in Table 4.

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Table 4. Schedule of Assessments: B5371001

Protocol Activity	Screen	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	OPV Day 15	OPV Day 22	OPV Day 29	OPV Day 36	OPV Day 43	OPV Day 50	OPV Day 57	OPV Day 85	Extended Follow-up Visits ¹		
Visit Window (days)*	(-28 to -1)	0	0										±1	±2	±2	±3	±4	±5	±5	±8	±7
Time (hr) Post-dose			0 ²	2	4	8	24	48	72	96	120	144	168	336	504	672	840	1008	1176	1344	2016
Informed Consent ³	X	X																			
Medical History ⁴	X	X																			
Demography and Height	X																				
Weight	X	X																			X
History of Drug, Alcohol, and Tobacco Use	X																				
Inclusion/Exclusion Criteria	X	X																			
Physical Examination ⁵	X	X				X					X	X		X		X		X			
Randomization		X																			
Admission to CRU		X																			
CRU Confinement		X	X-----X																		
Discharge from CRU ⁶											X										
Safety Laboratory	Hematology	X	X							X	X		X						X		
	Chemistry	X	X							X	X		X						X		
	Urinalysis	X	X								X								X		
Urine Drug and Alcohol Test ⁷	X	X									X	X	X	X	X	X	X	X			
FSH ⁸	X																				

Protocol Activity	Screen	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	OPV Day 15	OPV Day 22	OPV Day 29	OPV Day 36	OPV Day 43	OPV Day 50	OPV Day 57	OPV Day 85	Extended Follow-up Visits ¹		
Visit Window (days)*	(-28 to -1)	0	0										±1	±2	±2	±3	±4	±5	±5	±8	±7
Time (hr) Post-dose			0 ²	2	4	8	24	48	72	96	120	144	168	336	504	672	840	1008	1176	1344	2016
HBsAg, HBcAb, HBsAb, anti-HCV serology, HIV-1, HIV-2	X																				
QuantiFERON [®] -TB Gold In-Tube Test	X																				
Chest X-Ray ⁹	X																				
Single ECG (12 lead)	X		X							X			X					X			
Vital Signs ¹⁰	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry ¹¹			X-----X																		
Continuous Cardiac Telemetry Monitoring ¹²		X	X-----X																		
Insert IV Catheter for Blood Collection/Drug Administration ¹³			X																		
Premedication and Study Treatment Administration ¹⁴			X																		
Serum Samples for Study Drug Concentrations ¹⁵			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹⁸	X ¹⁸
Serum Samples for ADA and Nab			X								X		X		X			X	X	X	X
Assess Baseline Symptoms/Adverse Event Monitoring ¹⁶		X-----X																			
Prior/Concomitant Medication ¹⁷		X-----X																			

*All visits and procedures should occur when scheduled, but visit windows provide some flexibility as necessary.
 Abbreviations: ADA = anti-drug antibodies; CRU = Clinical Research Unit; ECG = electrocardiogram; FSH = Follicle Stimulating Hormone;
 HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HBsAb = antibody to hepatitis B surface antigen; HCV = Hepatitis C virus;
 HIV = human immunodeficiency virus; IV = Intravenous; OPV = outpatient visit; Nab = neutralizing antibodies; PK = pharmacokinetic; TB = tuberculosis

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1. Subjects having an unresolved adverse event (AE) will be followed up until the AE or its sequelae resolve or stabilize per the investigator's assessment. If the unresolved AE is considered by the investigator as possibly related to or associated with ADA formation, the subject will be asked to return for additional drug concentration and ADA/Nab blood sampling at up to 3-month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and the sponsor concurs with the investigator's assessment, up to 6 months from the Day 85 visit or the day of early withdrawal.
2. Activities scheduled at Time 0 are done pre-dose. Infusion starts at Time 0.
3. Informed consent must be obtained prior to undergoing any study specific procedure.
4. Medical history and medication history are updated at the Day 0 visit.
5. After Day 0, limited examinations will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.
6. Subject may be discharged from the research unit following the post-infusion blood collection (168 hrs) and following assessments of adverse events (Day 8).
7. In the event that a subject is not able to receive the full planned dose, urine drug and alcohol tests on Day 22, Day 36 and Day 50 may be assessed at the investigator's discretion.
8. To confirm non-childbearing status in females who are amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause.
9. The allowable window for the chest x-ray is 24 weeks prior to Day 1.
10. Vital signs include blood pressure, pulse rate, respiratory rate, and temperature. Blood pressure should be taken with the subject in the supine position after the subject has been resting quietly for at least 5 minutes. In the event that a subject is not able to receive the full planned dose, vital signs on Day 22, Day 36 and Day 50 may be assessed at the investigator's discretion.
11. On Day 1 (immediately prior and during infusion, and for at least 4 hours after the start of the infusion). Monitoring may be extended for safety purposes at the discretion of the investigator.
12. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing. This may be done immediately prior to dosing or at some 2 hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the subject is awake. Continuous cardiac monitoring will be conducted minus 5 minutes pre-dose and through the 8 hours after the start of the infusion.
13. Site may insert IV catheter for blood sample collection/drug administration prior to study drug administration (optional). For blood draws taken within the first 24 hours following study drug administration, blood samples must be drawn from the arm contralateral to the arm in which the infusion was administered. In no case may blood samples be obtained via the catheter through which the study drug was administered.
14. Infliximab will be administered intravenously at a dose of 10 mg/kg over a period of not less than 2 hours using a calibrated infusion pump. In the event that there is an infusion interruption, the entire duration of drug infusion, from the initial start of infusion to the completion of infusion, should not exceed 4 hours. Unless contraindicated, all subjects will receive premedication with 650 mg acetaminophen and 25 mg diphenhydramine 90 minutes prior to infliximab administration, which is consistent with institutional guidelines to ensure subject comfort and safety. Premedication will not include corticosteroids.
15. Blood samples for determination of infliximab drug concentration will be collected within 2 hours prior to initiation of infliximab infusion (time 0), within 5 min prior to end of infusion (2 hrs after start of infusion), and at 4 (± 0.5 hrs), 24 (± 2 hrs), 48 (± 4 hrs), 72 (± 6 hrs), 96 (± 8 hrs), 168 (± 8 hrs), 336 (± 24 hrs), 504 (± 48 hrs), 672 (± 48 hrs), 840 (± 72 hrs), 1008 (± 96 hrs), 1176 (± 120 hrs), and 1344 hrs (± 120 hrs) after start of infusion. Every effort should be made to draw samples at the scheduled time points, but sampling within the specified time window is allowed. If the infusion length is more than 120 minutes, the sample with nominal time of 2 hr after the start of infusion will be collected immediately prior to the end of infusion. In the event that a subject is not able to receive the full planned dose within 4 hrs on Day 1, the subject will be excluded from the PK similarity assessment, and blood sampling for drug concentration will only be conducted at the time points of ADA sample collection.
16. Reporting of serious adverse events (SAEs) begins at the time of informed consent. AEs will be collected from the time the subject has taken at least one dose of study treatment through last subject visit. Long-term follow-up will include reporting of SAEs. If subject discontinues early, adverse events must be followed for 50 days post study drug administration.
17. Collected at each visit/contact from the time the consent form is signed to the final study visit/contact. If subject discontinues early, concomitant medications must be followed for 50 days post study drug administration.
18. This drug concentration sample is collected at the same time of ADA/Nab sampling to facilitate the immunogenicity assessment.

Source: Module 5.3.5.1, CSR B5371001, Page 4

If a subject did not return for a scheduled visit, every effort was made to contact the subject. The investigator was instructed to attempt to contact the subject twice. After two attempts, CRU staff was permitted to send a registered letter. If no response was received from the subject, the subject was considered lost-to-follow up. The investigator was instructed to inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

Key Inclusion Criteria

- Healthy female subjects of non-childbearing potential and healthy male subjects between the ages of 18 and 55 years, inclusive (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG and clinical laboratory tests).

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- Achieved postmenopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum FSH level within the laboratory's reference range for postmenopausal females;

- Have undergone a documented hysterectomy and/or bilateral oophorectomy.

All other female subjects (including females with tubal ligations and females that do NOT have a documented hysterectomy or bilateral oophorectomy) will be considered to be of childbearing potential.

- Body Mass Index (BMI) of 17.5 to 32.0 kg/m²; and a total body weight >50 kg (110 lbs).
- Currently smoking less than the equivalent of 5 cigarettes per day. Occasional use of other nicotine containing products is allowed at the discretion of the investigator. Subjects will not be allowed to smoke or use nicotine containing products for 24 hours prior to dosing and during confinement.

Key Exclusion Criteria

- Evidence or history of clinically significant infectious, hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, autoimmune, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).
- Evidence or history of heart failure, seizures or nervous system demyelinating diseases (including multiple sclerosis, optic neuritis, Guillain-Barré syndrome).
- Previous history of cancer, except for adequately treated basal cell or squamous cell carcinoma of the skin.
- Clinically significant abnormalities in laboratory test results and vital signs
- 12-lead ECG demonstrating QTc >450 or a QRS interval >120 msec at Screening. If QTc exceeds 450 msec or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc and QRS values should be used to determine the subject's eligibility.
- Pregnant females; breastfeeding females; females of childbearing potential; males who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for 6 months following study drug administration.
- Previous exposure to a monoclonal antibody, or current use of other biologics.
- Exposure to any live vaccines within 28 days prior to study drug administration. Exposure to any live vaccines is also prohibited for at least 3 months after study drug administration.
- Positive urine drug or alcohol screen at Screening or Day 0.
- History of febrile illness within 7 days prior to dosing.
- History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.
- History of hypersensitivity reaction to inactive components of the study drugs or any murine proteins or anaphylactic reactions to therapeutic drugs.
- Treatment with an investigational drug within 30 days (or as determined by the local requirement, whichever is longer) or 5 half-lives preceding the first dose of study medication.

- Prior or current use of azathioprine or 6-mercaptopurine.
- Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication. Herbal supplements must be discontinued 28 days prior to the first dose of study medication. As an exception, acetaminophen/paracetamol may be used at doses of ≤ 1 g/day. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.
- Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to dosing.
- History of sensitivity to heparin or heparin-induced thrombocytopenia.
- Positive hepatitis B, hepatitis C or human immunodeficiency virus (HIV) tests at
- Screening indicative of a current or past infection.
- History of tuberculosis (TB) or a positive latent TB test at Screening.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results
- Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate. The exclusion criteria address potential risks due to mechanism of action such as exclusion of patients with a history of tuberculosis or a positive latent TB test at screening.

Treatment Groups

Treatment groups are outlined in Table 5.

Table 5. Treatment groups: Study B5371001			
Substance	PF-06438179	US-licensed Remicade	EU-approved Remicade
Pharmaceutical Form	Lyophilized Powder for Infusion		
Dose (mg)	10 mg/kg		
Frequency	Once a day (single dose)		
Route of Administration	Intravenous (IV)		
PF-06438179, US-licensed Remicade, or EU-approved Remicade was administered intravenously at a dose of 10 mg/kg over a period of not less than 2 hours using a calibrated infusion pump per the randomization schedule			
Source: Module 5.3.3.1: Study B5371001 CSR, Page 27			

Efficacy Endpoints

Study B5371001 was a comparative PK study to compare the PK of PF-06438179, US-licensed Remicade, or EU-approved Remicade; efficacy was not evaluated in this study. The study also provided single-dose safety, tolerability, and immunogenicity data.

PK Endpoints

- PK parameters for similarity and bridging: C_{max}, AUC_t, and AUC_{inf}.
- Other PK parameters including clearance (CL), t_{1/2}, and volume of distribution at steady state (V_{ss}), as data permit.

Safety Endpoints

- Safety as measured by type, incidence, severity, timing, seriousness and relatedness of adverse events, and abnormalities in laboratory parameters.
- Incidence of ADA and neutralizing antibodies (Nab).

PK and Safety Parameters

The total blood sampling volume for individual subjects in this study was approximately 215 mL. Additional blood samples could be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study did not exceed 550 mL during any period of 30 consecutive days.

PK Parameters

During all study periods, blood samples (5 mL) were collected to provide approximately 2 mL of serum for measurement of the drug concentration. Every effort was made to draw samples at the scheduled time points, but sampling within the specified time window was allowed. If the infusion length was more than 120 minutes, the sample with a nominal time of 2 hours after the start of infusion was collected immediately prior to the end of infusion. In the event that a subject was not able to receive the full planned dose within 4 hours on Day 1, the subject was excluded from the PK similarity assessment, and blood sampling for drug concentration was only conducted at the time points of ADA sample collection.

Safety Parameters

Immunogenicity

Blood samples for the detection of ADA and Nab were collected at the times specified in the protocol. Samples were analyzed using validated analytical methods in compliance with standard operating procedures of a Pfizer designated bioanalytical lab. Two parallel ADA assays with the same immunoassay platform will be used to detect ADA against infliximab-Pfizer and ADA against infliximab, respectively. Samples were first tested in the assay that was specific to the product with which the subject is dosed. If a sample was positive for antibodies to the dosed product, the sample was analyzed in the alternative assay. Samples confirmed as positive for

ADA were further tested for Nab using validated Nab assays. Samples collected for detecting ADA and Nab were retained in accordance to local regulations and if not used within this timeframe, will be destroyed. Additional exploratory testing of samples could be performed to further characterize the ADA response.

Laboratory Tests

The safety laboratory tests were performed at times defined in the study protocol. Unscheduled clinical labs could be obtained at any time during the study to assess any perceived safety concerns.

Table 6. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea and Creatinine	pH	FSH ^b
Hematocrit	Glucose (fasting)	Glucose (qual)	Urine drug screen ^c
RBC count	Calcium	Protein (qual)	QuantiFERON [®] -TB Gold
MCV	Sodium	Blood (qual)	In-Tube Test ^e
MCH	Potassium	Ketones	HIV-1 ^e
MCHC	Chloride	Nitrites	HIV-2 ^e
Platelet count	Total CO2 (Bicarbonate)	Leukocyte esterase	HBs Ag ^e
MPV	AST, ALT	Urobilinogen	HBs Ab ^e
WBC count	Total Bilirubin	Urine bilirubin	HBc Ab ^e
Total neutrophils (Abs)	Alkaline phosphatase	Microscopy ^a	Anti-hepatitis C virus serology ^e
Eosinophils (Abs)	Uric acid		
Monocytes (Abs)	Albumin		
Basophils (Abs)	Total protein		
Lymphocytes (Abs)			
	Additional Tests ^d		
	AST, ALT (repeat)		
	Total bilirubin (repeat)		
	Albumin (repeat)		
	Alkaline phosphatase (repeat)		
	Direct bilirubin		
	Indirect bilirubin		
	Creatine kinase		
	GGT		
	PT/INR		

- a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
- b. At Screening only, in females who amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause.
- c. At Screening, Day 0 and all scheduled outpatient visits only.
- d. Additional testing for potential Hy's Law cases only.
- e. Only performed at Screening.

Physical Examinations

Physical examinations were conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A complete physical examination included head, ears, eyes, nose, mouth, throat, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. Limited examinations were focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

Vital Signs

Supine blood pressure was measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after 5 minutes of rest. Respiratory rate was measured after 5 minutes of rest in supine position by observing and counting the respirations of the subject for 30 seconds and multiplied by 2. Temperature was measured using oral or tympanic methods. Scheduled 12-lead ECGs were performed after the subject rested quietly for at least 10 minutes in a supine position. ECGs were compared to Day 1 pre-dose ECGs and any clinically significant changes were recorded as adverse events and evaluated further, as clinically warranted.

Chest X-Ray

Subjects must have had a chest radiograph (posterior-anterior and lateral views were recommended; however, local guidelines were followed) with no evidence of current, active TB or previous inactive TB, general infections, heart failure, malignancy, or other clinically significant abnormalities taken at Screening or within 24 weeks prior to Day 1 and read by a qualified radiologist.

Continuous Cardiac Monitoring by Telemetry

Telemetry was collected using a centralized system that also allowed for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. To establish a baseline, telemetry was recorded for at least 2 hours before dosing. Telemetry could be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it was expected that the telemetry leads would be in place and the system connected prior to dosing. Continuous cardiac monitoring by telemetry began prior to the start of infusion (minus 5 minutes) and continued through 8 hours after the start of infusion. All abnormal rhythms were recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event were recorded in the CRF/DCT.

Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) were recorded and reported accordingly. AEs (serious and non-serious) were recorded on the CRF/DCT from the time the subject took at least one dose of study treatment through last subject visit. For SAEs, the active reporting period to Pfizer or its designated representative began from the time that the subject provided informed consent,

through and including 50 calendar days after the last administration of the investigational product.

Ethics

The study was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study was conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

5.3.2 Study B5371002

Administrative Information

- **Study title:** A Phase 3 Randomized, Double-Blind Study Assessing the Efficacy and Safety of PF-06438179 and Infliximab in Combination With Methotrexate in Subjects With Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Methotrexate
- **Study dates:** August 2014- December 2016 (TP2), full study planned study completion, including TP3, May 2017
- **Study sites:** 174 sites worldwide, including 40 sites in the US
- **Study report date:** May 24, 2017

Objectives/Rationale

Primary Objectives

To compare the efficacy between PF-06438179 and EU approved Remicade in subjects with moderately to severely active rheumatoid arthritis (RA) who are treated with infliximab in combination with methotrexate.

Secondary Objectives

- To evaluate the overall safety and tolerability of PF-06438179 and EU approved Remicade.
- To evaluate the immunogenicity of PF-06438179 and EU approved Remicade.
- To evaluate the overall safety, tolerability and immunogenicity of PF-06438179 after treatment transition from EU approved Remicade to PF-06438179.
- To evaluate the population pharmacokinetics (PK) of PF-06438179 and EU approved Remicade (TP1 only).
- To evaluate the pharmacodynamic (PD) response to PF-06438179 and EU approved Remicade.

- To evaluate the individual ACR (American College of Rheumatology criteria) parameters of clinical response to PF-06438179 and EU approved Remicade.

Study Design and Conduct

Overview

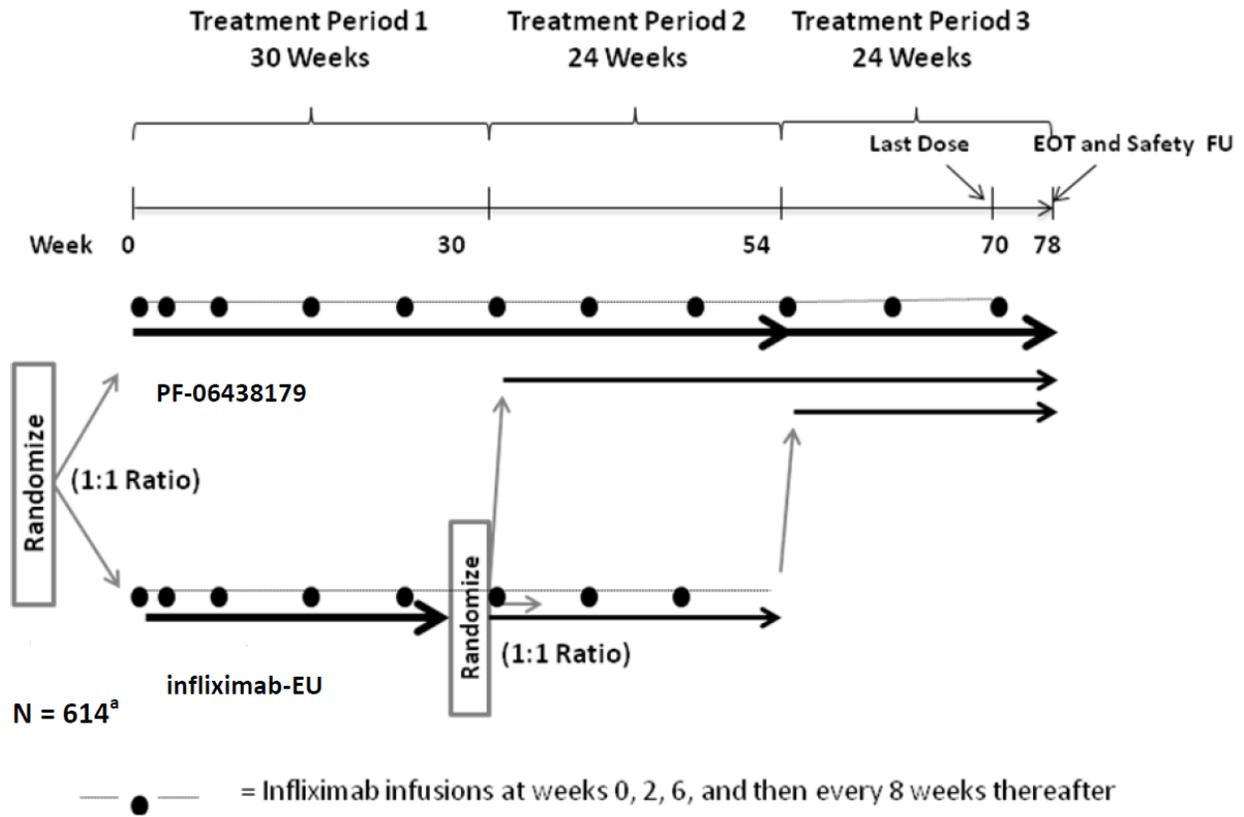
Study B5371002 was a multi-national, randomized, double-blind, 2-arm, parallel group study designed to compare the safety, efficacy, and immunogenicity of intravenously (IV) administered PF-06438179 to EU approved Remicade in combination with methotrexate to treat subjects with moderately to severely active RA who have had an inadequate response to methotrexate therapy. This study was also designed to blindly evaluate clinical response, safety and immunogenicity after study drug single transition from EU approved Remicade to PF 06438179 after 30 or 54 weeks of EU approved Remicade treatment.

Upon completion of screening, 650 subjects were randomized (1:1 ratio) into 2 study treatment arms to receive either PF-06438179 or EU approved Remicade, stratified by geographic region. Upon completion of TP1, 566 subjects were re-randomized into TP2. Study treatment was provided through 3 treatment periods. The report for TP3 was not finalized at the time of this review.

- TP1 began with the first dose of study drug on Week 0 (Day 1) and ended with the completion of Week 30 pre-dose assessments.
- TP2 began with the dosing on Week 30, when subjects initially assigned to the EU approved Remicade study arm were re-randomized in a 1:1 ratio, with 50% of the EU approved Remicade arm switching to PF-06438179 and the other 50% remaining on EU approved Remicade. All subjects initially assigned to PF-06438179 remained blindly assigned to continue on PF-06438179. Treatment continued in TP2 for another 24 weeks and ended with the completion of the Week 54 pre-dose assessments.
- TP3 began with Week 54 dosing, when all subjects remaining on EU approved Remicade were switched 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 on Week 78 (8 weeks after dosing Week 70). [This data is not available at the time of this review].

A limited number of Sponsor's personnel were unblinded to conduct the analyses up to Week 30. The review and conduct of the study continued in a blinded manner by study team members who were blinded to all study data until all randomized subjects completed the Week 54 visit and the TP2 database was unblinded. The study site personnel, investigators, and study subjects continued to be blinded for the treatment assignments in TP1 and TP2 until the final database release following the last subject completing all protocol defined visits and assessments. A final supplemental clinical study report will be prepared to report the results from TP3.

Figure 3. Study B5371002 Schematic



Abbreviations: EOT = end of treatment; FU = follow-up; N = number of subjects.

a. This study originally planned to enroll approximately 614 subjects; the actual number of subjects randomized was 650.

Source: Module 5.3.5.1 CSR B5371002, Figure 1, Page 30

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The schedule of assessments is summarized in Table 7.

Table 7. Schedule of Assessments Study B5371002

Study Period	Screen	Treatment Period 1								Treatment Period 2			Treatment Period 3		
		TX 2 (BL)	TX 3	4	TX 5	6	TX 7	TX 8	TX 9 (SW ^a)	TX 10	TX 11	TX 12 (SW ^a)	TX 13	TX 14 (LD)	15 (EOT/ET ^{b, c, d})
Study Week ^e	-3 to -1	0	2	4	6	12	14	22	30	38	46	54	62	70	78
Study Day	-21 to -1	1	15	29	43	85	99	155	211	267	323	379	435	491	547
Visit Window in Days			±2	±2	±2	±2	±2	±7	±7	±7	±7	±7	±7	±7	+7
Informed consent	X														
Inclusion/Exclusion criteria	X	X													
Medical history	X														
Demography	X														
Global functional status in RA	X														
Prior treatments for RA	X														
Urine drug screen	X														
HIV, Hepatitis B & C ^f	X														
Anti-dsDNA antibody (Japan only)	X								X			X			X
Beta-D-glucan (Japan only)	X														
FSH ^g	X														
TB test ^h	X								X			X			
Chest radiography ⁱ	X														
Single ECG (12-Lead)	X														X
Randomization ^a		X							X						
Complete physical examination ^j	X											X			X
Vital signs ^k	X	X ^l	X ^l	X	X ^l		X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X
Body weight	X ^m								X			X			
Pregnancy test ⁿ	X	X							X			X			X
Safety laboratory	Hematology	X	X ^o	X	X	X		X	X	X	X	X	X	X	X
	Chemistry	X	X ^o	X	X	X		X	X	X	X	X	X	X	X
	Urinalysis	X	X ^o		X			X		X		X			X
Total RF and anti-CCP		X							X		X				X
hs-CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA/NAbs Samples		X ^p	X ^p		X ^p		X ^p		X ^p	X ^p		X ^p	X ^p		X ^q
Drug concentration samples		X ^r	X ^p	X ^q	X ^p		X ^r	X ^p	X ^p	X ^p		X ^p	X ^p		X ^q

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Study Period	Screen	Treatment Period 1								Treatment Period 2			Treatment Period 3		
		TX 2 (BL)	TX 3	4	TX 5	6	TX 7	TX 8	TX 9 (SW ^a)	TX 10	TX 11	TX 12 (SW ^a)	TX 13	TX 14 (LD)	15 (EOT/ET ^{b, c, d})
Protocol Activity/Visit	1														
Study Week ^e	-3 to -1	0	2	4	6	12	14	22	30	38	46	54	62	70	78
Study Day	-21 to -1	1	15	29	43	85	99	155	211	267	323	379	435	491	547
Visit Window in Days			±2	±2	±2	±2	±2	±7	±7	±7	±7	±7	±7	±7	+7
Exploratory biomarker samples		X			X		X		X			X			X
Tender (68) and swollen (66) joint counts ⁵	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient's Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient's Assessment of Arthritis Pain		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician's Global Assessment of Arthritis [†]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAQ-DI		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug infusion ^u		X	X		X		X	X	X	X	X	X	X	X	X
Background methotrexate and folic/folinic acid supplementation	X	Continue per Standard of Care													
Assessment of AEs ^{b, d}	X	At each clinical visit													
Assessment of prior/concomitant medications ^{c, d}	X	At each clinical visit													

Source: Section 16.1.1

Abbreviations: Ab = antibody; ADA = Anti-drug antibody; AE = adverse event; anti-CCP = anti-cyclic citrullinated peptide; anti-dsDNA antibody = anti-double-stranded deoxyribonucleic acid antibody; BL = baseline; ECG = electrocardiogram; EOT = end of treatment; FSH = follicle-stimulating hormone; ET = early termination; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; IRR = infusion-related reaction; LD = last dose; IEC = Independent Ethics Committee; IRB = Institutional Review Board; NAb = neutralizing antibody; PE = physical examination;

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RA = rheumatoid arthritis; RF = rheumatoid factor; RNA = ribonucleic acid; SAE = serious adverse event; SW = switch of study drug; TB = tuberculosis; TP1 = Treatment Period 1; TX = treatment administration (study dosing).

- a. Subjects were randomized to PF-06438179 and infliximab-EU treatment arms in a 1:1 ratio prior to the first dosing on Day 1. Subjects initially assigned to the infliximab-EU study arm would be re-randomized in a 1:1 ratio, with 50% of the re-randomized subjects switching to PF-06438179 from Week 30 dosing and the subjects remaining on infliximab-EU switching to PF-06438179 from Week 54 dosing.
- b. AEs were collected from the time of first dose of study treatment until 8 weeks after the last dose of study treatment. Subjects with a new or ongoing AE at Week 78, or at their Early Termination visit would be asked to return for extended follow-up at the investigator's discretion until the AE resolved or stabilized. Reporting of SAEs began at the time of informed consent and continued through and including 8 weeks after last administration of the investigational product. For subjects who discontinued before Week 54, see Footnote d. Additional brief PE could also be performed at the investigator's discretion during the extended AE follow-up, as indicated by signs and symptoms of ongoing AEs.
- c. Medications that were taken after informed consent was obtained but before the first dose of study medication was received were documented as prior medications, with the exception of pre-medication prior to the first infusion of study medication, if any, which would be documented as concomitant medications. Medications taken after the first dose of study drug had been administered were documented as concomitant medications. If a subject discontinued early, concomitant medications were followed for 8 weeks after last dose of study drug. For subjects who discontinued before Week 54, see Footnote d.
- d. For subjects who discontinued dosing before Week 30, but did not withdraw consent, all remaining scheduled study visits in TP1 (up to and including Week 30 Visit) were performed on-site in person and all assessments (with the exception of all remaining study drug infusions and the Week 14 pre-dose drug concentration sample collection) were completed. These subjects would be contacted by telephone to obtain AEs and concomitant medications at Weeks 38, 46 and 54 unless subjects withdrew consent and/or started participation in another study. For subjects who discontinued dosing between Weeks 30 and 54, telephone contact would be made at Weeks 38, 46 and 54 if not conducted on site in person to obtain AEs and concomitant medications unless they withdrew consent and/or started participation in another study.
- e. Visits occurred when scheduled, within the time window indicated in the column headings, with the exception of informed consent which could be obtained earlier than 21 days prior to dosing. On study drug dosing days, assessments including joint counts and questionnaires and sampling were performed prior to dosing unless otherwise stated. Patient reported outcomes questionnaires were administered prior to any other assessments. Additional unscheduled assessments were performed as clinically indicated.
- f. Viral disease screening, including HIV screening (HIV-1 Ab and HIV-2 Ab), hepatitis B screening (HBsAg, HBcAb, HBsAb) and hepatitis C screening (HCVAb). HIV screening (HIV-1 Ab and HIV-2 Ab) was performed on all subjects unless not permitted by local regulations. Testing was performed by the central laboratory unless testing at a local laboratory was required by local regulations. HIV testing was required at the Screening Visit unless it had been performed within 8 weeks prior to the first dose of study drug on Day 1 and results were available. HBsAg, HBcAb, HBsAb and HCVAb testing was required to determine eligibility. Hepatitis testing was performed by the central laboratory. Subjects with positive HBsAg or HBcAb results were not eligible to participate in the study. Subjects with negative HBcAb and HBsAg results but positive HBsAb due to hepatitis B immunization were eligible to participate in the study. Subjects with positive HCVAb were eligible to participate in the study provided confirmatory HCV RNA testing was negative. For re-screen subjects, hepatitis testing was not required at the repeated Screening visit if it had been performed at the central laboratory within 8 weeks prior to the first dose of study drug on Day 1 and the results met eligibility criteria.

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- g. Screening test for female subjects who were amenorrheic for at least 12 consecutive months at the time of study screening with no alternative pathological or physiological cause. The test was used to confirm the subject's post-menopausal status.
- h. TB test was performed using QuantiFERON®-TB Gold In-Tube test. TB test was required at the Screening Visit unless it had been performed within 8 weeks prior to the first dose of study drug on Day 1 and results were available.
- i. Chest radiography was performed at the Screening Visit unless it had been performed within 12 weeks prior to first dose of study drug on Day 1 and results were available.
- j. Complete PE of major body systems included weight and height. An initial complete PE was performed between Screening and Day 1. Additional brief PEs could be performed during the study at the investigator's discretion, as indicated by signs and symptoms of ongoing AEs.
- k. Vital signs included blood pressure, respiratory and pulse rate, and body temperature. Blood pressure was taken from the subject in the supine position after the subject had been resting quietly for at least 5 minutes.
- l. For visits with study dosing, vital signs were taken prior to study drug infusion. Additional vital signs could be taken during infusion per local standard of care guidelines.
- m. Screening body weight was used to calculate dosing for Week 0 (Day 1), Week 2, Week 6, Week 14 and Week 22. Week 30 body weight was used to calculate dosing for Week 30, Week 38 and Week 46. Week 54 body weight was used to calculate dosing for Weeks 54, Week 62 and Week 70.
- n. Pregnancy testing at Screening in female subjects of childbearing potential was performed at the central laboratory by serum hCG test. Pregnancy testing (hCG) after Screening was performed locally using urine samples, with any positive results to be further confirmed by the central laboratory with a serum hCG test. Urine pregnancy testing may have been repeated more frequently during the study if required by IRB/IECs or local regulations, or if potential pregnancy was suspected.
- o. Baseline assessment was not required if Screening assessments had been performed within 7 days prior to first dose of study drug on Day 1 and all results had been received at the site.
- p. Serum samples were collected immediately prior to (within 4 hours) dose administration.
- q. Serum samples could be collected any time during the study visit.
- r. On the days of dose administration for Week 0 (Day 1) and Week 14 (Day 99) only, 2 serum samples were collected; one was collected immediately prior to (within 4 hours) dose administration and the other within 5 min prior to the end of infusion.
- s. All joint count assessments for an individual subject were performed pre-dose by an independent blinded assessor. It was especially important to have the same assessor perform the evaluations at Screening, Baseline, and Week 14 to ensure the integrity of entry criteria and primary endpoint. The same blinded assessor was used to perform the subject's subsequent joint count assessments throughout the study whenever possible.
- t. Physician assessment was performed without knowledge of patient reported outcomes assessments.
- u. Study drug (PF-06438179 or infliximab-EU) was administered intravenously over a period of no less than 2 hours using a calibrated infusion pump. Pre-medication was allowed. All subjects were observed for at least 1 to 2 hours post-infusion for acute IRRs. Infusion rate could be slowed in order to decrease the risk of IRRs especially if IRRs had occurred previously.

Source Module 5.3.5.1 CSR B5371002, Table 1, Page 31

Population

Inclusion Criteria (key)

- Male or female subjects aged 18 years or older at the time of informed consent.
- Diagnosis of RA based on 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA for at least a 4-month duration.
- Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA.
- Moderately to severely active RA disease as defined by the following criteria:
 - 6 tender joints (of 68 assessed) and
 - 6 swollen joints (of 66 assessed) and
 - High-sensitive C-reactive protein (hs-CRP) ≥ 10 mg/L (≥ 1 mg/dL).
- Stable dose of oral or parenteral methotrexate of 10 to 25 mg/week. Subjects who could not tolerate 10 to 25 mg/week methotrexate could take a lower dose of as low as 7.5 mg/week. In geographic regions where specified by local guidance or standard of care, a stable dose of as low as 6 mg/week was allowed.
- Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 6 months after the last dose of assigned treatment.

A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

Female subjects who are not of childbearing potential must meet at least 1 of the following criteria:

- a. Achieved postmenopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum FSH level in the laboratory's reference range for postmenopausal females.
- b. Have undergone a documented hysterectomy and/or bilateral oophorectomy.
- c. Have medically confirmed ovarian failure.

All other female subjects (including females with tubal ligations and females that do NOT have a documented hysterectomy or bilateral oophorectomy) will be considered to be of childbearing potential.

- If receiving an oral corticosteroid, subjects must be on a stable dose of ≤ 10 mg/day of prednisone (or equivalent) for 4 weeks prior to the first dose of study drug, without any intramuscular (IM) or intra-articular (IA) corticosteroids within the 4 weeks prior to the first dose of study drug.
- If receiving a NSAID/Cox-2 inhibitor, subject must be on a stable dose of only one NSAID/Cox-2 inhibitor drug for 4 weeks prior to the first dose of study drug at a dosage less than or equal to the maximum recommended dose in the product information. In addition, a cardiovascular dose of aspirin (≤ 325 mg/day) is permitted. Topical NSAIDs (in addition to one NSAID/Cox-2 inhibitor drug) are allowed, prior to and during the study. Topical NSAIDs should not be used within 24 hours prior to joint assessments.

Exclusion Criteria (key)

- Pregnant females and breastfeeding females; males and females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 6 months after last dose of investigational product. Females must not breastfeed for at least 6 months after last dose of investigational product.
- Clinically significant laboratory abnormalities at Screening, including but not limited to inadequate bone marrow, liver, renal and immune system functions.
- Evidence or history of moderate or severe heart failure (NYHA class III/IV, NYHA classification of congestive heart failure) and subjects who are contraindicated for treatment with infliximab in accordance with the approved local label.

- Evidence of current or recent history of uncontrolled, clinically significant infectious, hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease.
- Evidence or history of seizures, or nervous system demyelinating diseases (including multiple sclerosis, optic neuritis, Guillain-Barré syndrome).
- Evidence or history of a malignancy within the past 5 years with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ with no evidence of recurrence.
- History of any lymphoproliferative disorder (eg, Epstein Barr Virus (EBV) related lymphoproliferative disorder, lymphoma, leukemia).
- History of recurrent (more than one episode) limited herpes zoster or disseminated (a single episode) herpes zoster or herpes simplex. History of disseminated or recurrent infection of EBV or human papilloma virus (HPV) (a single, limited episode in the past is not exclusionary).
- Infection requiring hospitalization or parenteral antimicrobial therapy judged clinically significant by the investigator within 6 months prior to first dose of study drug.
- History of an infected joint prosthesis at any time.
- History of recurrent inflammatory joint disease other than RA (e.g., post infectious arthritis, gout, etc.) or history of any other autoimmune rheumatic diseases (e.g., vasculopathies, spondyloarthropathies, etc.) other than Sjogren's syndrome.
- Evidence of untreated or inadequately treated latent, or inadequately treated or active infection with tuberculosis (TB) as defined by one or more of the following:
 - a. Positive TB test at Screening (QuantiFERON®-TB Gold In-Tube Test).

Note: If a false positive TB result is suspected by the investigator at Screening (e.g., when the screening chest radiography result is negative for TB and workup for non-pulmonary TB is negative, although the Screening QuantiFERON®-TB is positive), the subject should be referred to a TB specialist, pulmonologist or infectious disease specialist for further evaluation before initiating study treatment. Prior to enrolling a subject who is suspected of having a false positive QuantiFERON®-TB test result, the investigator must discuss the case with the Medical Monitor.
 - b. History of either untreated or inadequately treated latent or active TB. Subjects previously treated for latent TB infection must have completed a successful course of treatment in accordance with local guidelines. Subjects detected with latent TB infection at Screening may be rescreened and randomized after having completed successful course of treatment in accordance with local guidelines. Subjects currently receiving treatment for active or latent TB are excluded.
- Chest radiography with evidence of active TB, fungal infections, or other clinically significant abnormalities taken at Screening or within 12 weeks prior to first dose of study drug on Day 1.
- Any current or prior treatment for the following DMARDs within the relevant washout period.
- Current or prior treatment with infliximab or lymphocyte depleting therapies (e.g., Rituximab, Campath). Prior exposure to biologic therapy for RA (with the exception of

up to 2 doses of one biologic therapy for RA, including anti-TNF therapies other than infliximab). For prior exposure to a biologic therapy for RA, a washout period of at least 12 weeks or 5 half-lives (whichever is longer) is required prior to the first dose of study drug.

- Known or Screen test positive human immunodeficiency virus (HIV). Positive for hepatitis B virus (HBV), or hepatitis C virus (HCV) at Screening. Subjects with positive hepatitis C antibody (HCVAb) and negative confirmatory HCV riboneucleic acid (RNA) results at Screening will be eligible to participate in the study.
- Screening 12-lead ECG that demonstrates clinically relevant abnormalities which may affect subject safety or interpretation of study results.
- History of allergic or hypersensitivity reaction to active or inactive components of the study drug or any murine, chimeric or human proteins.
- Exposure to any live vaccines within 4 weeks prior to administration of the first dose of study drug or lack of willingness to avoid exposure to any live vaccines during the trial and for at least 3 months after the last dose of study drug.
- Participation in other studies involving investigational drug(s) (Phase 1-4) within at least 4 weeks or 5 half-lives from last dose, whichever is longer, before the current study begins and/or during study participation.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

Prohibited Medications

- Any live attenuated vaccines
- Cytotoxic drugs
- New Biologic DMARDs (e.g., abatacept, tocilizumab, TNF inhibitors)
- New non-Biologic DMARDs (e.g., penicillamine)
- Other investigational drugs or investigational biologics
- B-cell depleting therapy
- Plasma exchange therapy
- IV immunoglobulin (IVIG)
- IM or IV corticosteroids (unless required for subject safety including management of adverse drug reactions or infusion related reactions)

Permitted Medications

Subjects could receive the following concomitant medications during the study under restricted conditions as specified below:

1. Subjects taking one non-steroidal anti-inflammatory drug (NSAID), including COX-2 inhibitors must have been on a stable dosage for at least 4 weeks prior to first dose of study treatment and remained on a stable dosage throughout the first 54 weeks of the study treatment course unless treatment adjustment is needed to protect a subject's safety. Topical NSAIDs (in addition to one NSAID/Cox-2 inhibitor drug) were allowed, prior to and during the study. Topical NSAIDs were not to be used within 24 hours prior to joint assessments.

Subjects could additionally be receiving low dose aspirin (≤ 325 mg per day).

2. Subjects that were taking low dose oral corticosteroids (≤ 10 mg prednisone or equivalent per day) must have been on a stable dosage for at least 4 weeks prior to first dose of study treatment and must have remained on a stable dosage throughout the first 54 weeks of the study treatment course unless treatment adjustment was needed to protect a subject's safety.

Intra-articular (IA) corticosteroids were allowed as rescue therapy.

Tapering and discontinuation of corticosteroids was allowed after Week 54, at the discretion of the investigator.

3. Daily doses of opioids (tramadol, codeine, hydrocodone, oxycodone and propoxyphene) and acetaminophen/paracetamol must have been stable for at least 2 weeks prior to first study dose and must have remained on a stable dosage throughout the first 54 weeks of the study treatment course unless treatment adjustment was needed to protect a subject's safety or required as rescue therapy.

Management of Infusion Related Reactions

Remicade infusion related reactions (IRRs) were managed by the investigator as clinically indicated and according to the institutional policies. IRRs could be treated with normal saline and different medications (e.g., acetaminophen/paracetamol, NSAIDs, antihistamines, epinephrine, hydrocortisone / methylprednisolone) as considered necessary by the investigator. Emergency equipment including artificial airway was available.

If IRRs occurred previously, the investigator could slow the infusion rate to decrease the risk of IRRs.

The infusion could be interrupted (stop then restart gradually) for mild reactions at the discretion of the investigator and according to the institutional guidelines. If a subject developed what the

investigator felt was a typical mild infusion reaction, steps were taken to ensure subject comfort (e.g., NSAIDs, antihistamines, changing rate of infusion) at the discretion of the investigator, for the remaining drug infusion duration to ensure subject safety.

In the event of a severe infusion reaction, the infusion was stopped immediately and permanently, and urgent treatment was provided.

Rescue Therapy

1. Acetaminophen/paracetamol dosed at the locally approved recommended dose and/or an opioid not exceeding the maximum allowed daily dose were allowed as rescue medication for no more than 10 consecutive days. If a subject was already taking stable background doses of acetaminophen/paracetamol, s/he could have increased the dose up to the locally approved recommended dose for up to 10 consecutive days for rescue purposes. Acetaminophen/paracetamol was not permitted as part of combination products such as over-the-counter “cold remedies” or in combination with opioids if the total acetaminophen/paracetamol dose exceeded the locally approved recommended dose. Subjects who required rescue for more than 10 consecutive days were discontinued from receiving further treatment. In addition, subjects were not to be dosed with rescue therapy during the 24 hours prior to a study visit. However, baseline stable use acetaminophen/paracetamol or opioids was NOT to be discontinued in advance of study visits.
2. IA corticosteroids could not be administered within 4 weeks prior to first study dose and was not be administered before the Week 14 assessment is completed. However, IA injections of corticosteroids were allowed as rescue therapy at and after Week 14 dosing in accordance with the local label in this study.

Following restrictions will apply when the rescue injections are performed:

Rescue injections were always to be performed following the joint assessment.

- IA corticosteroids could have been administered in up to 2 joints (total) in a cumulative dose of ≤ 40 mg methylprednisolone or its equivalent during the study. IA corticosteroid injections should have been avoided within 4 weeks before a study visit. Injected joints were considered as active joints (tender/painful and swollen joint count) for the remainder of the study and the subject’s last observation was carried forward.
- IM and IV corticosteroids were NOT allowed unless required for subject safety including management of adverse drug reactions or IRRs.
- Arthrocentesis (without injection of IA medication) was allowed. Arthrocentesis (with injection of IA medication) was allowed, but was counted toward the 2 joints (total), and the joint(s) having arthrocentesis (with injection of IA medication) was considered as active joints (tender/painful and swollen joint count) for the remainder of the study and the subject’s last observation was carried forward.

Removal of Subjects from Therapy or Assessment

Subjects could withdraw from the study at any time at their own request or could be withdrawn at any time at the discretion of the investigator or Sponsor for safety, behavioral, or administrative reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for discontinuation from study treatment could include, but were not limited to:

- Inadequate response to study treatment (in the judgment of the investigator).
- Unacceptable AE (e.g., severe hypersensitivity reaction, serious infection, serious cardiac arrhythmia).
- Subjects who required rescue therapy for more than 10 consecutive days.
- Subject noncompliance.
- Subject choice to withdraw from treatment (follow-up permitted by subject).
- Subject choice to withdraw from study participation (cessation of follow-up).
- Subject lost to follow-up.

Pursuant to specific requests by regulatory authorities, if a subject did not return for a scheduled visit, every effort was made to contact the subject. The investigator was requested to attempt to contact the subject twice. After 2 attempts, site staff could send a registered letter requesting the subject to return for scheduled visits. If no response was received from the subject, the subject was considered lost to follow-up. All attempts to contact the subject and information received during contact attempts were documented in the subject's medical record. In any circumstance, every effort was made to document subject outcome, if possible. The investigator was to inquire about the reason for withdrawal, to request the subject to return for a final visit, if applicable, and to follow-up with the subject regarding any unresolved AEs.

Treatment

In a full course of study treatment, a study subject would receive a total of 11 infusions of study drug, including 5 infusions in Treatment Period 1, 3 infusions in Treatment Period 2, and 3 infusions in Treatment Period 3.

All subjects started their treatment with a uniform dose regimen, which is an intravenous (IV) infusion at a dose of 3 mg/kg at Weeks 0, 2, and 6, followed by a maintenance regimen of every 8 weeks. The dose will remain consistent for a minimum of 3 doses (up to Week 14). A one-time dose escalation for subjects who have not experienced a minimal response may begin at or after the scheduled Week 14 study visit, with a dose increase to 5 mg/kg every 8 weeks. Subjects who fail to achieve a minimal response by Week 30 (including dose escalation) will be discontinued from further study treatment.

Therefore, the earliest possible time point when a subject would be withdrawn for lack of efficacy is Week 30 (Week 14 + 16 weeks).

Subjects were required to continue their stable background regimen of oral or parenteral methotrexate (MTX) (10 to 25 mg/week; or as low as 7.5 mg/week for intolerant subjects) throughout the study. In geographic regions where specified by local guidance, subjects could take doses of MTX as low as 6 mg/week in case of intolerance to higher doses. Subjects were also required to receive a stable background dose of oral folic/folinic acid supplementation throughout the study. Subjects could also continue stable background therapy with sulfasalazine and/or an anti-malarial throughout the study.

Treatment Groups

Table 8. Treatment groups: Study B5371002			
Substance	PF-06438179	US-licensed Remicade	EU-approved Remicade
Pharmaceutical Form	Lyophilized Powder for Infusion		
Dose (mg)	Induction: 3 mg/kg IV Weeks 0, 2 and 6 Maintenance: 3 mg/kg IV Q8 Weeks		
Route of Administration	Intravenous (IV)		
The dose remained consistent for a minimum of 3 doses (up to Week 14). A one-time dose escalation for subjects who did not experienced a minimal improvement may begin at the scheduled Week 14 study visit, with a dose increase to 5 mg/kg every 8 weeks. Continuation of study treatment in subjects who did not show a minimal improvement after receiving two doses of study treatment at the escalated (5 mg/kg) dose was carefully considered by the Investigators. The earliest timepoint when a subject should be considered for discontinuation of treatment due to lack of efficacy would be Week 30 (Week 14 Visit + 16 weeks).			
Source: Module 5.3.5.1: Study B5371002 Protocol, Page 37			

Efficacy Endpoints

Primary Efficacy Endpoint (TP1)

The primary efficacy endpoint was the proportion of subjects achieving a 20% or greater improvement in ACR clinical response (ACR20) at Week 14.

Secondary Efficacy Endpoints (TP1)

- ACR20 response rates at time points of Weeks 2, 4, 6, 12, 22, and 30.
- ACR50 and ACR70 response rates at Week 14 and other protocol-defined time points up to Week 30.
- Change from baseline in individual components of the ACR response criteria (including Health Assessment Questionnaire Disability Index [HAQ-DI]) at Week 14 and other protocol-defined time points up to Week 30.
- Change from baseline in disease activity measured by DAS28-CRP at Week 14 and other protocol-defined time points up to Week 30.

- Proportion of subjects with response (no, moderate or good response) defined according to the EULAR response criteria, at Week 14 and other protocol defined-time points up to Week 30.
- Proportion of subjects with a DAS remission (DAS <2.6) at Weeks 14 and other protocol-defined time points up to Week 30.
- Proportion of subjects with ACR/EULAR remission at Weeks 14 and other protocol-defined time points up to Week 30.

As the primary endpoint was measured at Week 14, there was no primary endpoint assessment during treatment period 2. Secondary endpoints collected during TP2 were nearly identical to those measured during TP2 and consisted of the following;

- Categorical and continuous measures of clinical efficacy, including ACR20 (other than Week 14), ACR50, ACR70, change in DAS28-CRP (Disease Activity Score-28 4 components based on CRP), DAS remission (≤ 2.6), EULAR (European League Against Rheumatism) response, ACR/EULAR remission, and change in HAQ-DI.
- Safety measures characterized by type, incidence, severity, timing, seriousness and relatedness of adverse events and laboratory abnormalities.
- Change from baseline in individual components of ACR response.
- Incidence and titers of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) in response to infliximab-Pfizer and infliximab-EU.
- Serum drug concentrations.

ACR Assessments

The ACR definition for improvement in RA is calculated as a percent improvement from baseline (Day 1) in number of tender and swollen joints and percent improvement in 3 of the 5 other ACR-core set measures: patient's and physician's global assessment of arthritis, patient's assessment of arthritis pain (PAAP), patient's assessment of disability (using HAQ-DI), and an acute-phase reactant (in this study, hs-CRP).

Tender/Painful Joint Count (68)

Sixty-eight (68) joints were assessed by an independent blinded joint assessor to determine the number of joints that were considered tender or painful. For consistency, a single assessor to perform all evaluations across the study for an individual subject was preferred. It was especially important that the same assessor evaluated the subject at Screening, baseline, and Week 14 to ensure integrity of the eligibility criteria and the ACR clinical response primary endpoint. The independent blinded assessors had at least 6 months experience performing joint exams. The response to pressure/motion on each joint was assessed using the following scale: Present/Absent/Not Done/Not Applicable (used for artificial or missing joints). Artificial or missing joints were not assessed.

The 68 joints assessed were:

- Upper Body: temporomandibular, sternoclavicular, acromioclavicular.
- Upper Extremity: shoulder, elbow, wrist (included radiocarpal, carpal and carpometacarpal considered as one unit), metacarpophalangeals (MCP I, II, III, IV, V), thumb interphalangeal (IP), proximal interphalangeals (PIP II, III, IV, V), distal interphalangeals (DIP II, III, IV, V).
- Lower Extremity: hip, knee, ankle, tarsus (included subtalar, transverse tarsal and tarsometatarsal considered as 1 unit), metatarsophalangeals (MTP I, II, III, IV, V), great toe interphalangeal (IP), proximal and distal interphalangeals combined (PIP and DIP II, III, IV, V).

Swollen Joint Count (66)

The blinded joint assessor also assessed joints for swelling using the following scale: Present/Absent/Not Done/Not Applicable (used for artificial or missing joints).

Sixty-six (66) joints were assessed for swelling, the same as those listed above for tenderness/pain, except that the right and left hip joints were not included in the swollen joint count. Again 'Not Applicable' was used for artificial (replaced) or missing (fused or amputated) joints.

A limited number of IA joint injections with corticosteroids or hyaluronate were allowed on study. Injections were only to be performed following the performance of a joint assessment and not prior. Once injected, joints were considered as having their pre-injection status for the remainder of the study. Therefore, the joint was no longer assessed and the subject's last observation was carried forward.

Patient's Assessment of Arthritis Pain (PAAP)

Subjects assessed the severity of their arthritis pain using a 100 mm visual analogue scale (VAS) by placing a mark on the scale between 0 (no pain) and 100 (most severe pain), which corresponded to the magnitude of their pain.

Patient's Global Assessment of Arthritis (PGA)

Subjects answered the following question, "Considering all the ways your arthritis affects you, how are you feeling today?" The subject's response was recorded using a 100 mm VAS.

Physician's Global Assessment of Arthritis (PGAA)

The investigator assessed how the subject's overall arthritis appeared at the time of the visit. This was an evaluation based on the subject's disease signs, functional capacity and physical examination, and was independent of (blind to) the PGA and PAAP. The investigator's response was recorded using a 100 mm VAS. Physician assessment was performed without knowledge of patient reported outcomes assessments.

High-Sensitivity C-Reactive Protein (hs-CRP)

Serum samples for hs-CRP assessment were collected at the visits specified in the protocol and analyzed by the central laboratory.

Health Assessment Questionnaire-Disability Index (HAQ-DI)

The HAQ-DI assessed the degree of difficulty a subject had experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities. Each activity category consisted of 2-3 items. For each question in the questionnaire, the level of difficulty was scored from 0 to 3 with 0 representing “no difficulty,” 1 as “some difficulty,” 2 as “much difficulty,” and 3 as “unable to do.” Any activity that required assistance from another individual or required the use of an assistive device adjusted to a minimum score of 2 to represent a more limited functional status. This questionnaire was completed by the subject prior to any procedures being performed at the visit, if possible.

DAS Assessments

The DAS assessment is a continuous composite measure derived using differential weighting given to each component. Assessments of DAS28-CRP on study subjects during the study period were performed as described in the protocol.

The components of the DAS28-CRP assessment included:

- Tender/Painful Joint Count (28)
- Swollen Joint Count (28)
- hs-CRP
- PGA (0 – 100 mm VAS)

Tender/Painful Joint Count (28)

The 28 joints evaluated for DAS included the following: shoulders, elbows, wrists, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), and knees. This count was calculated by the Sponsor from the 68 joint counts.

Swollen Joint Count (28)

This measurement included the following joints: shoulders, elbows, wrists, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), and knees. This count was calculated by the Sponsor from the 66 joint counts.

Additional Clinical Response Assessments

Other secondary clinical endpoints, including the proportion of subjects achieving EULAR response (Table 9), DAS remission (DAS <2.6), and ACR/EULAR remission, as well as change from baseline of HAQ-DI, were also assessed at the study visits as indicated in the protocol to further evaluate clinical responses to study treatment.

Table 9. EULAR Response Criteria

DAS28 Improvement Present DAS28	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	good response	moderate response	no response
>3.2 and ≤5.1	moderate response	moderate response	no response
>5.1	moderate response	no response	no response

Abbreviations: DAS = Disease Activity Score; EULAR = European League Against Rheumatism.
 Source: Module 5.3.5.1: CSR Study B5371002, Table 3, Page 54

Subjects were considered to be in ACR/EULAR remission when either:

- Scores on the tender joint count, swollen joint count, hs-CRP (mg/dL), and subject global assessment (0-10 scale) were all ≤1 (Boolean Method).

Or:

- The score on the Simplified Disease Activity Index (SDAI) was ≤3.3.

The SDAI was calculated using the following formula:

Sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), PGA (0–10 scale), physician global assessment (0–10 scale), and hs-CRP (mg/dL).

Both the Boolean method and the SDAI methods of meeting ACR/EULAR remission were calculated, and proportion of subjects who met either criterion was summarized.

Pharmacokinetic Assessments

The PK (secondary) endpoint was serum drug concentrations.

Pharmacokinetic Sampling and Handling

Blood samples for measurement of serum drug concentrations were collected immediately (within 4 hours) prior to dose administration at Weeks 0, 2, 6, 14, 22, 30, 38, 54, and 62; within 5 minutes prior to the end of infusion at Weeks 0 and 14; and anytime during study visits at Weeks 4 and 78 (EOT).

Pharmacodynamic Evaluations

The PD (secondary) endpoint was the serum hs-CRP concentration.

Immunogenicity Evaluations

The immunogenicity (secondary) endpoints were the number and proportion of subjects who had at least 1 sample that tested positive for antidrug antibodies (ADA) and neutralizing antibodies (NAb; in ADA positive subjects only), and titers of ADA and NAb in response to PF-06438179 and EU approved Remicade.

Blood samples for measurement of serum ADA and NAb were collected immediately (within 4 hours) prior to dose administration at Weeks 0, 2, 6, 14, 30, 38, 54, and 62; and anytime during study visit at Week 78 (EOT).

Safety Evaluations

Safety (secondary) endpoints included safety outcomes that were characterized by type, incidence, severity, timing with respect to Study Day 1, duration, seriousness and relatedness of AEs and laboratory abnormalities.

Adverse Events

An AE was defined as any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event did not need necessarily have a causal relationship with the treatment or usage. All observed or volunteered AEs, regardless of treatment arm or suspected causal relationship to the investigational products were required to be reported.

For all reported AEs, the investigator pursued and obtained information adequate both to determine the outcome of the AE and to assess whether it met the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information was obtained by the investigator to determine the causality of the AE. The investigator was required to assess causality. Follow-up by the investigator could be required until the event or its sequelae resolved or stabilized at a level acceptable to the investigator, and the Sponsor concurred with that assessment.

Serious Adverse Events

An SAE⁴ was any untoward medical occurrence at any dose that:

- Resulted in death;
- Was life-threatening (immediate risk of death);
- Required inpatient hospitalization or prolongation of existing hospitalization;
- Resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Resulted in congenital anomaly/birth defect.

Protocol-Specified Serious Adverse Events

Unless the investigator believed that there was a causal relationship between study drug and an SAE specified below, these events were not to be urgently reported by the investigator to Pfizer as SAEs. These events were anticipated to occur commonly in a population with RA. However, these events were still captured as SAEs in the CRF.

⁴ 21 CFR 312.32 (a)

Protocol-specified SAEs that were not normally required to be reported in an expedited manner:

- Arthritis
- Arthralgia
- Joint effusion
- Joint range of motion decrease
- Nerve entrapment
- Pleuritis due to RA
- Rheumatoid nodule
- Temporomandibular joint disorder
- Tendon inflammation due to RA

Potential Cases of Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin that met the criteria outlined below in the absence of other causes of liver injury were to be considered potential cases of drug-induced liver injury (potential Hy's Law cases) and were to be always considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depended on the subject's individual baseline values and underlying conditions. Subjects who presented with the following laboratory abnormalities were to be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently presented with AST or ALT $\geq 3 \times$ ULN concurrent with a total bilirubin $\geq 2 \times$ ULN with no evidence of hemolysis and an alkaline phosphatase $\leq 2 \times$ ULN or not available.

Or

- For subjects with preexisting ALT or, AST or total bilirubin values above the ULN, the following threshold values were to be used in the definition mentioned above:
 - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT $\geq 2 \times$ the baseline values and $\geq 3 \times$ ULN, or $\geq 8 \times$ ULN (whichever was smaller).

Concurrent with

- For subjects with pre-existing values of total bilirubin above the normal range: total bilirubin increased by $1 \times$ the ULN or $\geq 3 \times$ the ULN (whichever was smaller).

All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, were to be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases were to be reported as SAEs.

Laboratory Evaluations

Blood and urine samples for laboratory tests (Table 10) were collected at the time points specified in Table 7.

Table 10. Laboratory Tests

Laboratory Test	Parameters Included
Hematology	Hemoglobin, platelet count, RBC count and morphology, WBC count, absolute differential counts – neutrophils, lymphocytes, monocytes, eosinophils, basophils.
Chemistry	ALT, AST, alkaline phosphatase, blood urea nitrogen, creatinine, glucose, calcium, corrected calcium, sodium, potassium, bicarbonate, chloride, total protein, albumin, total bilirubin, direct bilirubin.
Urine	Urine test by dipstick - pH, glucose, protein, blood, ketones, leukocyte esterase Urine microscopy only if dip stick positive for blood or protein or clinically indicated.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; RBC = red blood cell; WBC = white blood cell.

Source: Module 5.3.5.1: CSR Study B5371002, Table 5, Page 61

Unscheduled clinical labs were allowed to be obtained at any time during the study to assess any perceived safety concerns. Hematology and chemistry laboratory samples were analyzed by the central laboratory. Each subject's liver enzymes were routinely tested and monitored for methotrexate induced liver injury.

Vital Signs

Body temperature, blood pressure and respiratory and pulse rate were measured as described in the protocol, and in the event of an infusion reaction.

Blood pressure was measured in the subject's arm and recorded to the nearest mm Hg. The same arm and position was to be used throughout the study, using an appropriate cuff size. All blood pressure readings were measured in the supine position after resting for at least 5 minutes. When the timing of these measurements coincided with blood collection, the blood pressure and heart rate were to be obtained first. For visits with study dosing, vital signs were to be measured prior to PF-06438179 or EU approved Remicade infusion.

Physical Examination

A standard complete physical examination was performed between Screening and Day 1, 1 year (Week 54), and the end of study treatment, as described in the protocol. Additional brief physical examinations could be performed during the study at the investigator's discretion, as indicated by signs and symptoms of ongoing AEs.

The following parameters and body systems were examined during the complete physical examinations and any abnormalities described: weight, height, general appearance, skin (including presence of rash), head, eyes, ears, nose, and throat (HEENT), lungs (including auscultation), heart (including auscultation for presence of murmurs, gallops, rubs), extremity exam for the presence of peripheral edema, abdominal (including palpation and auscultation), neurologic (including mental status, station, gait, reflexes, motor and sensory function, coordination), musculoskeletal and lymph nodes.

Chest Radiography

A chest radiography was performed at Screening unless it had been performed within 12 weeks prior to first dose of study drug on Day 1 and results were available. The chest radiography was performed according to local health authority guidance. To be considered eligible for the study, the screening radiograph had to be negative for signs of active TB infection, fungal infection, or any other clinically significant abnormalities.

Electrocardiogram

Twelve-lead ECGs were performed after the subject had rested quietly for at least 10 minutes at study visits as described in the protocol. EOT ECG was compared to screening ECG and any clinically significant changes were recorded as AEs and evaluated further, as clinically warranted.

QuantiFERON-TB Gold In-Tube Test

QuantiFERON-TB Gold In-Tube testing was performed for all subjects at Screening (unless it had been performed within 8 weeks prior to the first dose of study drug on Day 1 and results were available), Week 30 visit, and Week 54 visit (Table 1).

In the case of an indeterminate result, a repeat test could be permitted for the purpose of determining eligibility of subjects to enroll in this study at the discretion of the Sponsor's Medical Monitor.

If a false positive QuantiFERON-TB result was suspected by the investigator at Screening (eg, when the screening chest radiography result was negative for TB and workup for non-pulmonary TB was negative, although the screening QuantiFERON-TB was positive), the subject was to be referred to a TB specialist, pulmonologist or infectious disease specialist for further evaluation before initiating study treatment. Prior to enrolling a subject who was suspected of having a false positive QuantiFERON-TB test result, the investigator was required to discuss the case with the medical monitor.

After the initiation of study treatment, study subjects were evaluated for TB at Week 30 and Week 54 by QuantiFERON-TB testing. If a subject initially had a negative QuantiFERON-TB test and was subsequently found to have a positive result at either Week 30 or Week 54 after initiating study treatment, the subject was to be evaluated by a TB specialist, pulmonologist or infectious disease specialist before continuing the study treatment. If latent or active TB was confirmed (eg, not a false positive test), the subject was to be permanently discontinued from

study treatment due to the AE. The subject was to be managed for TB infection following local standard of care and be followed by the investigator for safety.

Viral Disease Screening

HBsAg, HBcAb, HBsAb and HCVAb testing was required at Screening to determine eligibility. Hepatitis testing was performed by the central laboratory. Subjects with positive HCVAb were reflex tested for HCV RNA and were eligible to participate if HCV RNA results were negative. Subjects with positive HBsAg or HBcAb results were not eligible to participate in the study. Subjects with negative HBcAb and HBsAg results but positive HBsAb due to hepatitis B immunization were eligible to participate in the study.

HIV (HIV-1 antibody [Ab] and HIV-2 Ab) testing was also required to demonstrate eligibility unless not permitted by local regulations. HIV testing was performed by the central laboratory unless testing at a local laboratory was required per local regulations. HIV testing was completed at Screening unless testing had been performed within 8 weeks before study dosing on Day 1 and results were available.

Treatment Compliance

Study treatment was administered under the supervision of the investigator and delegated site personnel. Compliance and non-compliance of study subjects were monitored by study personnel at the site by using the source documents and the eCRFs. The site study pharmacist or designee was responsible for drug preparation, the maintenance of accurate and complete dispensing and accountability forms showing the receipt and dispensation of study drug. The pharmacist was responsible for performing accountability and reconciliation of the investigational products.

Statistical Plan

Analysis of Efficacy

All efficacy endpoints were summarized for the ITT population using descriptive statistics. The ITT population was defined as all subjects who were randomized to study treatment.

Analysis of Primary Efficacy Endpoint

The primary efficacy parameter was the clinical response according to the ACR definition of 20% improvement, ACR20. The proportion of subjects achieving ACR20 response at Week 14 was analyzed by calculating a point estimate with 95% and 90% CIs for the difference between the 2 treatment arms.

Two exact methods were used to calculate CIs for the difference in ACR20 response rate at Week 14 between the 2 treatment arms. One was the score statistic method based on Farrington-Manning score statistic, and the other was the unconditional approach, which eliminates nuisance parameters by maximizing the p-value over all possible values of the nuisance parameters. The CI calculated by the score statistic method was used for the inference of equivalence. The CIs for the primary efficacy endpoint calculated by the 2 methods were compared to each other for a

sensitivity evaluation. The analyses were carried out using SAS PROC FREQ (SAS/STAT 9.3).

(b) (4)

. The FDA endorsed the alternative approach where equivalence would be declared if the 2-sided 90% CI fell within the asymmetric equivalence margin (-12%, 15%).

The ITT was the primary analysis population for ACR20 at Week 14. The primary analysis for ACR20 was performed with the missing data imputed using a non-responder imputation method.

To account for a stratification factor (region), a sensitivity analysis was performed on the primary endpoint, utilizing a binomial model (SAS PROC GENMOD with identity link function) with treatment arm as a fixed effect and geographic region as a covariate. The “identity link function” is an option in the model that allows the difference in ACR20 response rates between the 2 arms and its confidence interval to be estimated. This analysis used all observed data at Week 14 in the ITT population, and no imputation was applied for missing ACR20 data at Week 14 for this analysis.

Descriptive statistics including number of subjects (n), frequency and percentage (%) were presented for ACR20 response at Week 14 in both ITT population.

Analysis of Secondary Efficacy Endpoints

Descriptive statistics were presented for all secondary efficacy endpoints for the ITT population. Point estimates for the difference in ACR50 and ACR70 response rates between PF-06438179 and infliximab-EU at all protocol-defined time points for TP1 and TP2 were summarized. Figures of changes from baseline value by visit were presented for some of the secondary efficacy endpoints including joint counts, DAS-CRP, hs-CRP, PAAP, PGA, PGAA and HAQ-DI in the ITT population.

6 Review of Efficacy

Efficacy Summary

The efficacy of PF-06438179 compared to EU-approved Remicade (with extrapolation to US-licensed Remicade) was assessed in Study B5371002, the comparative clinical study, comparing PF-06438179 with EU-approved Remicade in patients with RA. Efficacy was not assessed in the PK-similarity study, B5371001, conducted in healthy subjects. The FDA evaluation of efficacy focused on the single, randomized, double-blind controlled study B5371002 in moderately to severely active RA who have had an inadequate response to methotrexate therapy. The primary efficacy assessment was obtained at Week 14 and descriptive efficacy assessments were provided through Week 54, which included patients who underwent a single transition from EU-approved Remicade to PF-06438179.

Study B5371002 consisted of three treatment periods: Treatment Period 1 (TP1) began with the first dose of study drug on Week 0 (Day 1) and ended with the completion of Week 30 pre-dose assessments; Treatment Period 2 (TP2) began with dosing on Week 30 when subjects initially assigned to the EU approved Remicade arm were re-randomized in a 1:1 ratio to switch to PF-06438179 or to remain on EU approved Remicade and all subjects initially assigned to PF06438179 remained on PF06438179 through Week 54; finally, Treatment Period 3 (TP3) began with the Week 54 dosing, when all subjects remaining on EU-approved Remicade were switched to PF-06438179 and received open-label PF-06438179 treatment for an additional 24 weeks with the last study drug dosing on Week 70 and the end of treatment visit on Week 78.

Baseline demographics in study B5371002 were fairly balanced across treatment groups and generally representative of the population in whom RA is known to occur. The mean age ranged from 52-54 years, with a majority being white (73-81%) females (78-83%). A majority of the patients in this comparative clinical study were enrolled from outside of the United States.

Study B5371002 met its primary objective of demonstrating that the proportion of patients achieving ACR20 response at Week 14 was similar between the PF06438179 and EU approved Remicade treatment groups [(n=198, 61%) and (n=207, 64%), respectively]. The 90% CI for the estimate of treatment difference (-2.39) was contained within the prespecified asymmetric similarity margin of -12% to 15% (90% CI: -8.75, 4.02). In light of the scientifically justified bridge to EU-approved Remicade, these results support the conclusion of no clinically meaningful differences between PF06438179 and U.S. licensed Remicade in RA.

Analysis of secondary efficacy endpoints in Study B5371002 including ACR20, ACR50, ACR70 responses and disease activity score (DAS28-CRP) at various time points through Week 54, showed similar results between PF06438179 and EU-approved Remicade treatment groups.

The transition-extension period of Study B5371002 had a single transition from EU-approved Remicade to PF06438179 at Week 30 and was supportive of the primary endpoint. ACR20 response rates over time up to Week 54 were comparable between the different treatment arms. Efficacy endpoint analysis demonstrated consistent efficacy up to Week 54 in each treatment group, PF06438179 maintenance, EU-approved Remicade maintenance and EU approved Remicade to PF06438179 transition group.

6.1 Indication

PF-06438179 is a proposed biosimilar to US-licensed Remicade and includes the same proposed indications as the reference product, which include the following:

- Rheumatoid arthritis (RA)
Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. To be administered in conjunction with methotrexate (MTX) at doses of 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks; for patients who have an incomplete

response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks.

- Ankylosing spondylitis (AS)
Reducing signs and symptoms in patients with active ankylosing spondylitis. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.
- 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. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks with or without MTX.
- 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. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.
- Adult Crohn's disease (CD)
 - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely Crohn's 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.
 - Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue.
- Pediatric Crohn's disease (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. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.
- Adult 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. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

- Pediatric Ulcerative colitis (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. Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.⁵

6.1.1 Methods

In the context of a biosimilar development program, the objective of the clinical development program of a proposed biosimilar is to help resolve any residual uncertainties that arise after a robust analytical similarity is established between the proposed biosimilar and the reference product. As such, the clinical development program of PF-06438179 was designed to assess comparative PK between PF-06438179, EU approved Remicade and US licensed Remicade in Study B5371001 and the safety and efficacy of PF-06438179 compared to EU approved Remicade in the comparative clinical study (B5371002).

To demonstrate that there were no clinically meaningful differences between PF-06438179 and US-licensed Remicade, the applicant chose the indication of RA in the pivotal comparative clinical study (B5371002), as RA has been well-studied among the anti-TNF indications. In addition, the use of infliximab has been well-characterized including PK profiles, safety and efficacy in the RA population. The Agency agreed with the Applicant's rationale that the study population is a sensitive population to use in the assessment of no clinically meaningful differences in the context of a proposed biosimilar development.

The focus of this efficacy review is derived from Studies B5371001 and B5371002. The primary efficacy endpoint was assessed at week 14. All other assessments are presented by treatment period (TP1 and TP2).

The assessment of PF-06438179 was conducted in the Intent-to-Treat (ITT) Population unless otherwise specified. The ITT population was defined as all subjects who are randomized to study treatment.

⁵ We note that Janssen Biotech maintains Orphan Drug Exclusivity for Pediatric UC until September 2018.

6.1.2 Demographics

The demographics for the study population in study B5371001 are displayed in Table 11.

Table 11. Demographics- Per Protocol Analysis Set B5371001			
	PF-06438179 (N=41)	EU Approved Remicade (N=45)	US Licensed Remicade (N=44)
Female n (%)	2 (4.9)	2 (4.4)	5 (11.4)
Mean age (SD)	34.4 (10.0)	30.6 (9.4)	33.8 (9.4)
Race, n (%)			
White	12 (29.3)	18 (40.0)	18 (40.9)
Black	29 (70.7)	26 (57.8)	26 (59.1)
Other	0	1 (2.2)	0
Mean BMI kg/m ² (SD)	26.5 (3.3)	25.4 (3.2)	26.6 (2.9)
US site (%)	100	100	100
Per protocol analysis set (PK evaluable set): The per protocol analysis set includes all randomized subjects who receive the full dose of the assigned study medication and who do not have major protocol deviations. Major deviations include failure to satisfy major entry criteria or use of other medication or treatments during the study other than those as defined/allowed in this protocol.			
Source: Module 5.3.3.1: CSR Study B5371001, Table 13, Page 52			

In Study B5371001, baseline demographics were fairly balanced across treatment groups. The mean age ranged from 31-34 years, with a majority being black (58-71%) males (87-96%). This comparative PK study was conducted fully in the United States.

Table 12. Demographics- ITT Population B5371002			
Treatment Period 1			
	PF-06438179 (N=324)	EU Approved Remicade (N=326)	
Female n (%)	258 (79.6)	264 (81.0)	
Mean age (SD)	52.8 (13.3)	52.8 (12.9)	
Race, n (%)			
White	257 (79.3)	247 (75.8)	
Black	5 (1.5)	9 (2.8)	
Asian	46 (14.2)	45 (13.8)	
Other	15 (4.6)	25 (7.7)	
Un-specified	1 (0.3)	0	
Mean BMI kg/m2 (SD)	27.2 (6.4)	27.7 (7.0)	
US site n (%)	38 (11.8)	44 (13.6)	
Treatment Period 2 Transition			
	PF-06438179/ PF-06438179 (N=280)	EU Approved Remicade/ EU Approved Remicade (N=143)	EU Approved Remicade/ PF-06438179 (N=143)
Female n (%)	221 (78.9)	111 (77.6)	118 (82.5)
Mean age (SD)	52.8 (12.9)	53.8 (12.7)	51.6 (12.9)
Race, n (%)			
White	227 (81.1)	104 (72.7)	109 (76.2)
Black	3 (1.1)	4 (2.8)	4 (2.8)
Asian	38 (13.6)	23 (16.1)	20 (14.0)
Other	12 (4.3)	12 (8.4)	10 (7.0)
Mean BMI kg/m2 (SD)	27.3 (6.5)	27.0 (6.6)	28.0 (7.2)

Source: Module 5.3.5.1: CSR Study B5371002, Table 13, Page 86, CSR Study B5371002 WK54, Table 9, Page 60

In Study B5371002, baseline demographics were fairly balanced across treatment groups. The mean age ranged from 52-54 years, with a majority being white (73-81%) females (78-83%). A majority of the patients in this comparative clinical study were enrolled from outside of the United States.

As the comparative PK study, B5371001, was conducted in healthy volunteers, no baseline rheumatoid arthritis disease characteristics are provided for this study population.

The baseline disease characteristics for the study population in Study B5371002 are displayed in Table 13 for TP1 and Table 14 for TP2.

Table 13. Baseline Disease Characteristics- ITT Population B5371002-TP1		
	PF-06438179 (N=324)	EU Approved Remicade (N=326)
HAQ-DI, Mean (SD)	1.6 (0.6)	1.6 (0.7)
PGAA, Mean (SD)	65.4 (16.2)	64.2 (16.8)
PGA , Mean (SD)	65.4 (20.7)	63.9 (23.0)
Swollen Joint Count (0-66), Mean (SD)	16.1 (9.4)	16.3 (8.7)
Tender Joint Count , Mean (SD)	24.7 (13.9)	25.7 (12.9)
Duration of RA (years), Mean (SD)	7.3 (8.6)	6.4 (6.7)
Duration of Methotrexate used, n (%)		
<6 months	52 (16.0)	58 (17.8)
≥6 months to <1 year	78 (24.1)	83 (25.5)
≥1 year to <3 years	86 (26.5)	93 (28.5)
≥3 years	107 (33.0)	92 (28.2)
Methotrexate Dose (mg/week), Mean (SD)	14.2 (4.5)	14.4 (4.5)
Hs-CRP (mg/mL), Mean (SD)	25.8 (24.3)	25.3 (28.4)
RF or anti-CCP antibody positive, n (%)	249 (76.9)	267 (81.9)
Replaced and/or fused joint, n (%)	23 (7.1)	35 (10.7)
Corticosteroids use, n (%)	178 (54.9)	192 (58.9)
<p>This table reflects subject data that were collected at Screening or Study Day 1 prior to the first study drug infusion. Abbreviations: RA = rheumatoid arthritis; SD = standard deviation; TP1 = Treatment Period 1; TP2 = Treatment Period 2, PGA = Patient's Global Assessment of Arthritis; PGAA = Physician's Global Assessment of Arthritis, hs-CRP = high sensitivity C-reactive protein, HAQ-DI = Health Assessment Questionnaire - Disability Index, RF = rheumatoid factor, anti-CCP = anti-cyclic citrullinated peptide</p>		
<p>Source: Module 5.3.5.1: CSR Study B5371002, Table 14, Page 87</p>		

The rheumatoid arthritis (RA) characteristics were fairly balanced for TP1. Patients reported a mean duration of RA of 6-7 years, a mean weekly dose of methotrexate dose of 14 mg, and an hs-CRP of 25-26 mg/mL.

Table 14. Baseline Disease Characteristics- ITT Population B5371002- TP2			
	PF-06438179/ PF-06438179 (N=280)	EU Approved Remicade/ EU Approved Remicade (N=143)	EU Approved Remicade/ PF-06438179 (N=143)
HAQ-DI Mean (SD)	1.6 (0.7)	1.5 (0.7)	1.7 (0.7)
PGAA Mean (SD)	65.7 (16.1)	63.8 (16.1)	64.5 (17.4)
PGA Mean (SD)	65.0 (21.1)	61.0 (23.4)	66.9 (22.6)
Swollen Joint Count (0- 66) Mean (SD)	16.2 (9.5)	15.7 (8.2)	16.5 (9.2)
Tender Joint Count Mean (SD)	25.0 (13.9)	25.3 (12.7)	26.0 (13.3)
Duration of RA (years) Mean (SD)	7.5 (8.8)	6.7 (7.0)	6.0 (6.2)
Duration of Methotrexate n(%)			
<6 months	45 (16.1)	24 (16.8)	26 (18.2)
≥6 months to <1 year	69 (24.6)	34 (23.8)	40 (28.0)
≥1 year to <3 years	75 (26.8)	39 (27.3)	40 (28.0)
≥3 years	91 (32.5)	46 (32.2)	37 (25.9)
Methotrexate Dose (mg/week), Mean (SD)	14.0 (4.2)	14.0 (4.8)	14.5 (4.3)
hs-CRP (mg/mL) Mean (SD)	25.7 (23.6)	24.6 (22.8)	26.6 (33.8)
RF or anti-CCP antibody positive, n (%)	215 (76.8)	111 (77.6)	121 (84.6)
Replaced and/or fused joint, n (%)	18 (6.4)	12 (8.4)	16 (11.2)
Corticosteroids use, n (%)	156 (55.7)	84 (58.7)	81 (56.6)
This table reflects subject data that were collected at Screening or Study Day 1 prior to the first study drug infusion. Abbreviations: RA = rheumatoid arthritis; SD = standard deviation; TP1 = Treatment Period 1; TP2 = Treatment Period 2, PGA = Patient's Global Assessment of Arthritis; PGAA = Physician's Global Assessment of Arthritis, hs-CRP = high sensitivity C-reactive protein, HAQ-DI = Health Assessment Questionnaire - Disability Index, RF = rheumatoid factor, anti-CCP = anti-cyclic citrullinated peptide			
Source: Module 5.3.5.1: CSR Study B5371002 WK54, Table 10, Page 61			

The rheumatoid arthritis (RA) characteristics were also fairly balanced for TP2. Patients reported a mean duration of RA of 6-8 years, a mean weekly dose of methotrexate dose of 14-14.5 mg, and an hs-CRP of 25-27 mg/mL.

6.1.3 Subject Disposition

Subject disposition for Study B5371001 is described in Table 15. Information regarding subject discontinuation is described in Table 16.

Table 15. Subject Disposition- Full Analysis Set B5371001			
Number (%) of Subjects	PF-06438179	EU Approved Remicade	US Licensed Remicade
Randomized to study treatment	52	50	49
Discontinued prior to study treatment	3 (5.8%)	2 (4.0%)	0
Treated	49 (94.2%)	48 (96.0%)	49 (100%)
Completed ¹	37 (71.2%)	43 (86.0%)	39 (79.6%)
Discontinued prior to Day 85	12 (23.1%)	5 (10.0%)	10 (20.4%)
Discontinued after Day 85	0	0	0
Analyzed for pharmacokinetics			
Per-protocol set	41 (78.8%)	45 (90.0%)	44 (89.8%)
Analyzed for safety			
Adverse events	49 (94.2%)	48 (96.0%)	49 (100%)
Laboratory data	49 (94.2%)	48 (96.0%)	49 (100%)

¹ Included subjects who completed Day 85 and exited the study and who completed Day 85 and safety follow-up.
 Full analysis set: The full analysis set includes all randomized subjects. This is equivalent to the ITT (intent-to-treat) population.

Source: Module 5.3.3.1: CSR Study B5371001, Table 9, Page 49

A majority of patients completed the comparative PK study (71-86%) and provided data for safety (94-100%) and PK analysis (79-90%). The most common reason for discontinuation after treatment was that the subject was no longer willing to participate in study. Discontinuation prior to Day 85 was slightly more frequent in PF-06438179 (23.1%) compared to EU approved Remicade (10.0%) or US licensed Remicade (20.4%).

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Table 16. Subject Discontinuations- Full Analysis Set B5371001			
Number (%) of Subjects	PF-06438179	EU Approved Remicade	US Licensed Remicade
Randomized to study treatment	52	50	49
Subject discontinued	15	7	10
Discontinued prior to study treatment	3	2	0
No longer willing to participate in study	1	0	0
Chest X-ray abnormality	1	0	0
Insomnia	1	0	0
Abnormal telemetry monitoring	0	1	0
Telemetry malfunction	0	1	0
Treated: discontinued prior to Day 85	12	5	10
No longer willing to participate in study	6	1	2
Lost to follow-up	2	3	3
Drug abuse/positive drug screen	1	1	2
Investigator decision	1	0	0
Employment related relocation	1	0	2
Family emergency/family emergency requiring relocation	1	0	1
Treated: discontinued after Day 85	0	0	0

Full analysis set: The full analysis set includes all randomized subjects. This is equivalent to the ITT (intent-to-treat) population.

Source: Module 5.3.3.1: CSR Study B5371001, Table 10, Page 49

Subject disposition for study B5371002 is described in Table 17.

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Table 17. Subject Disposition- ITT Population B5371002			
Treatment Period 1			
Number (%) of Subjects	PF-06438179	EU Approved Remicade	
Screened n=1603			
Randomized to study treatment	324	326	
Randomized but not treated	1 (0.3) ^a	0	
Treated	323 (99.7)	326 (100.0)	
Completed TP1	280 (86.4)	286 (87.7)	
Discontinued from treatment and continued the study	8 (2.5)	14 (4.3)	
Discontinued from study	35 (10.8)	26 (8.0)	
Treatment Period 2 Transition			
	PF-06438179/ PF-06438179 (N=280)	EU Approved Remicade/ EU Approved Remicade (N=143)	EU Approved Remicade/ PF-06438179 (N=143)
Treated during TP2	280 (100.0)	143 (100.0)	143 (100.0)
Completed TP2	254 (90.7)	126 (88.1)	126 (88.1)
Discontinued form treatment and remained in the study	0	1 (0.7)	1 (0.7)
Discontinued from study	26 (9.3)	16 (11.2)	16 (11.2)
a. One (1) subject identification number and randomization number was assigned in error (1 subject was screened and randomized by 2 different study site personnel), and no data were collected for the subject's second randomization ((b) (6) TP1 = Treatment Period 1, TP2 = Treatment Period 2.			
Source: Module 5.3.5.1: CSR Study B5371002, Table 6, Page 77, CSR Study B5371002 WK54, Table 3, Page 54			

Most patients completed TP1 (86-88%) and TP2 (88-91%) and the number of patients who discontinued from the study was also fairly balanced.

Information regarding subject disposition is described in Table 18 for TP1 and Table 19 for TP2.

Table 18. Subject Discontinuations- Safety Population B5371002- TP1		
Number (%) of Subjects	PF-06438179 (N=323)	EU Approved Remicade (N=326)
Discontinued from study	35 (10.8)	26 (8.0)
Subject died	2 (0.6)	1 (0.3)
Insufficient clinical response ^a	0	2 (0.6)
Lost to follow-up	0	1 (0.3)
No longer willing to participate in study	25 (7.7)	18 (5.5)
Protocol violation	3 (0.9)	0
Adverse event	5 (1.5)	4 (1.2)
Related to study drug	4 (1.2)	2 (0.6)
Not related to study drug	1 (0.3)	2 (0.6)

a. Collected on the Case Report Form (CRF) and defined at the investigator's discretion. TP1 = Treatment Period 1
 Safety Population: The safety population is defined as all subjects who are randomized and receive at least one dose of study treatment, analyzed by actual treatment received.

Source: Module 5.3.5.1: CSR Study B5371002, Table 8, Page 78

The most common reason for premature discontinuation from the study during TP1 was that the subject was no longer willing to participate [(n=25, 7.7% PF-06438179), (n=18, 5.5% EU Approved Remicade)].

Table 19. Subject Discontinuations- Safety Population B5371002- TP2			
	PF-06438179/ PF-06438179 (N=280)	EU Approved Remicade/ EU Approved Remicade (N=143)	EU Approved Remicade/ PF-06438179 (N=143)
Discontinued from study	26 (9.3)	16 (11.2)	16 (11.2)
Subject died	1 (0.4)	0	0
Insufficient clinical response ^a	4 (1.4)	3 (2.1)	1 (0.7)
Lost to follow-up	1 (0.4)	1 (0.7)	0
No longer willing to participate in study	8 (2.9)	8 (5.6)	10 (7.0)
Non-compliance with study treatment	1 (0.4)	0	0
Adverse event	10 (3.6)	4 (2.8)	4 (2.8)
Related to study drug	7 (2.5)	3 (2.1)	4 (2.8)
Not related to study drug	3 (1.1)	1 (0.7)	0
Other	1 (0.4)	0	1 (0.7)

a. Collected on the Case Report Form (CRF) and defined at the investigator's discretion. TP2 = Treatment Period 2.
 Safety Population: The safety population is defined as all subjects who are randomized and receive at least one dose of study treatment, analyzed by actual treatment received.

Source: Module 5.3.5.1: CSR Study B5371002 WK54, Table 5, Page 55

The most common reason for premature discontinuation from the study in TP2 was due to adverse events [(n=10, 3.6% PF-06438179/PF-06438179), (n=4, 2.8% EU Approved Remicade/EU Approved Remicade), (n=4, 2.8% EU Approved Remicade/PF-06438179)].

6.1.4 Analysis of Primary Endpoint(s)

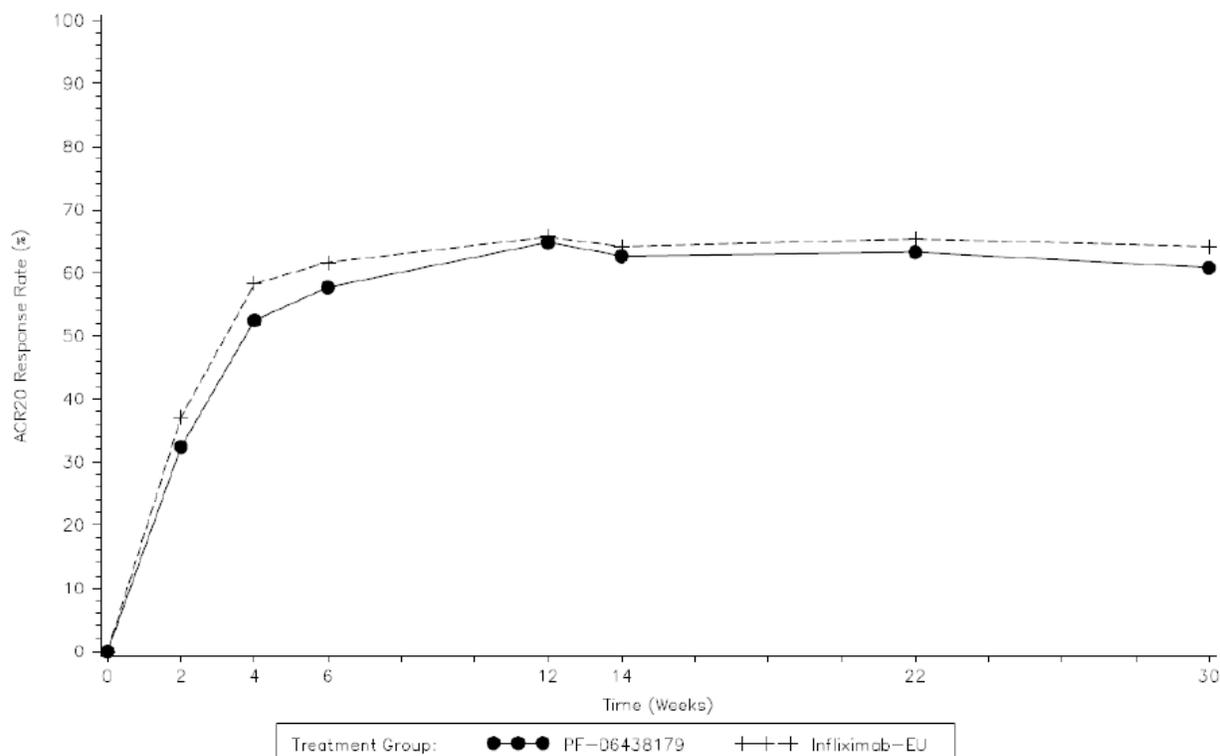
A summary of the results from the comparative PK study (B5371001) are discussed in the clinical pharmacology review.

The primary objective of Study B5371002 was to demonstrated therapeutic equivalence between PF-06438179 and EU approved Remicade as measured by ACR20 response rate at Week 14.

Table 20. ACR20 Response at Week 14- ITT Population B5371002		
PF-06438179 (N=324) n(%)	EU Approved Remicade (N=326) n(%)	Difference in ACR20 Response Rate (PF-06438179 – EU Approved Remicade) Point Estimate (90% CI)
198 (61.1)	207 (63.5)	-2.39 (-8.75, 4.02)
EU = European Union; ITT = Intent-to-Treat; n = number of subjects; N = number of subjects randomized; TP1 = Treatment Period 1; CI = confidence interval Analysis performed using the score statistic method exact binomial approach for ACR20 response rate at Week 14 with non-responder imputation for missing data. The 90% CI is part of the asymmetric margin criterion. Source: Module 5.3.5.1: CSR Study B5371002, Table 17, Page 91		

As described in Table 20, in the ITT population, 198 (61.1%) subjects in the PF-06438179 arm and 207 (63.5%) subjects in the EU approved Remicade arm achieved an ACR20 response at Week 14 with a treatment difference of -2.39% in Week 14 ACR 20 response rate for PF-06438179 as compared to EU approved Remicade. The 2-sided 90% CI of the treatment difference was entirely contained within the asymmetric margin of (-12% to 15%), demonstrating therapeutic equivalence between PF-06438179 and EU approved Remicade treatments.

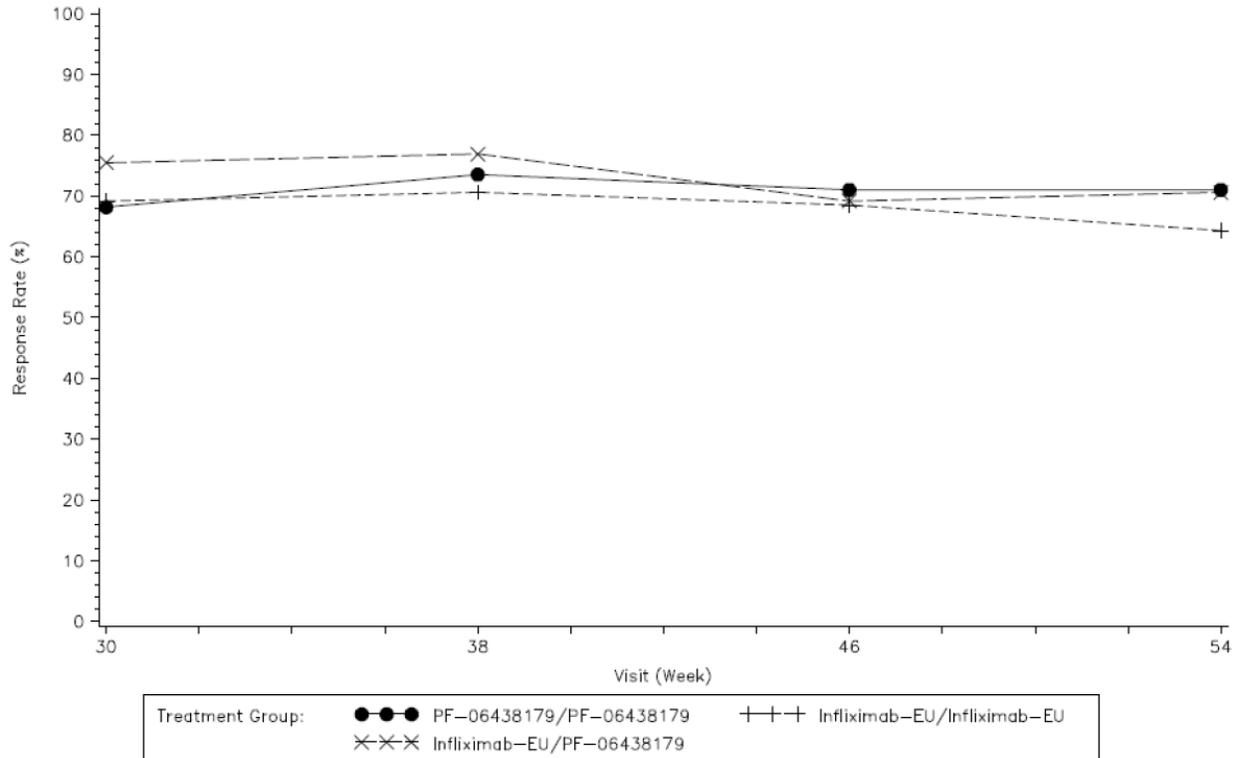
Figure 4. ACR20 Response Rate by Visit, ITT Population B5371002– TP1



ITT = Intent-to-Treat, TP1 = Treatment Period 1, Infliximab EU= EU approved Remicade
 Source: Module 5.3.5.1: CSR Study B5371002, Figure 4, Page 96

Evaluation of ACR20 measurements by visit for both TP1 (Figure 4) and TP2 (Figure 5) demonstrates that the ACR20 response rates were similar between the PF-06438179 and EU approved Remicade treatment arms throughout the treatment period. These figures also demonstrate that the ACR20 treatment effect was maintained over time, through Week 54.

Figure 5. ACR20 Response Rate by Visit, ITT Population B5371002– TP2



ITT = Intent-to-Treat, TP2 = Treatment Period 2, Infliximab EU= EU approved Remicade
 Source: Module 5.3.5.1: CSR Study B5371002 Supplemental Study Report Week 54, Figure 2, Page 65

6.1.5 Analysis of Key Secondary Endpoints(s)

ACR20 Response Rate by Visit

Table 21. Descriptive Summary of ACR20 Response Rate by Visit, ITT Population B5371002- TP1				
Visit	ACR20 Response	PF-06438179 (N = 324) n (%)	EU Approved Remicade (N = 326) n (%)	Difference in ACR20 Response Rate (PF-06438179 - EU Approved Remicade)
Week 2	Yes	105 (32.4)	121 (37.1)	-4.71
	No	214 (66.1)	203 (62.3)	
	Missing	5 (1.5)	2 (0.6)	
Week 4	Yes	170 (52.5)	190 (58.3)	-5.81
	No	147 (45.4)	131 (40.2)	
	Missing	7 (2.2)	5 (1.5)	
Week 6	Yes	187 (57.7)	201 (61.7)	-3.94
	No	126 (38.9)	118 (36.2)	
	Missing	11 (3.4)	7 (2.2)	
Week 12	Yes	210 (64.8)	214 (65.6)	-0.83
	No	101 (31.2)	104 (31.9)	
	Missing	13 (4.0)	8 (2.5)	
Week 14	Yes	203 (62.7)	209 (64.1)	-1.46
	No	108 (33.3)	107 (32.8)	
	Missing	13 (4.0)	10 (3.1)	
Week 22	Yes	205 (63.3)	213 (65.3)	-2.07
	No	96 (29.6)	98 (30.1)	
	Missing	23 (7.1)	15 (4.6)	
Week 30	Yes	197 (60.8)	209 (64.1)	-3.31
	No	97 (29.9)	89 (27.3)	
	Missing	30 (9.3)	28 (8.6)	

Abbreviations: EU = European Union; ITT = Intent-to-Treat; n = number of subjects; N = number of subjects randomized; TP1 = Treatment Period 1.

One (1) subject identification number and randomization number was assigned in error (1 subject was screened and randomized by 2 different study site personnel), and no data were collected for the subject's second randomization ((b) (6))

Source: Module 5.3.5.1, CSR Study B5371002, Table 21, Page 95

As shown in Table 21, ACR20 response rates at Weeks 2, 4, 6, 12, 14, 22 and 30 in the ITT population were similar between the PF-06438179 and EU approved Remicade treatment arms at all time points studied.

Table 22. Descriptive Summary of ACR20 Response Rate by Visit, ITT Population B5371002- TP2				
Visit	ACR20 Response	PF-06438179/ PF-06438179 (N = 280) n (%)	EU Approved Remicade/ EU Approved Remicade (N = 143) n (%)	EU Approved Remicade/ PF-06438179 (N=143) n (%)
Week 30	Yes	191 (68.2)	99 (69.2)	108 (75.5)
	No	89 (31.8)	44 (30.8)	35 (24.5)
Week 38	Yes	206 (73.6)	101 (70.6)	110 (76.9)
	No	71 (25.4)	40 (28.0)	31 (21.7)
	Missing	3 (1.1)	2 (1.4)	2 (1.4)
Week 46	Yes	199 (71.1)	98 (68.5)	99 (69.2)
	No	70 (25.0)	40 (28.0)	34 (23.8)
	Missing	11 (3.9)	5 (3.5)	10 (7.0)
Week 54	Yes	199 (71.1)	92 (64.3)	101 (70.6)
	No	60 (21.4)	38 (26.6)	28 (19.6)
	Missing	21 (7.5)	13 (9.1)	14 (9.8)

Abbreviations: EU = European Union; ITT = Intent-to-Treat; n = number of subjects; N = number of subjects randomized; TP2 = Treatment Period 2.
 One (1) subject identification number and randomization number was assigned in error (1 subject was screened and randomized by 2 different study site personnel), and no data were collected for the subject's second randomization ((b) (6))

Source: Module 5.3.5.1, CSR Study B5371002 Supplemental Study Report Week 54, Table 12, Page 65

Similar results were obtained for TP2 and are described above in Table 22. It is notable that similar efficacy was maintained through Week 54 in the subjects who were transitioned from EU-approved Remicade to PF-06438179 at Week 30.

ACR50 Response Rate by Visit

A selection of the ACR50 response rate data by visit is provided below for TP1 in Table 23 and for TP2 in Table 24. A full spread of the data collected for each time point is displayed graphically for TP1 in Figure 6 and TP2 in Figure 7.

Clinical Review
 Erika Torjusen, M.D., MHS.
 351(k) BLA 761072
 PF-06438179, a proposed biosimilar to US-licensed Remicade

Table 23. Descriptive Summary of ACR50 Response Rate by Visit, ITT Population B5371002- TP1				
Visit	ACR50 Response	PF-06438179 (N = 324) n (%)	EU Approved Remicade (N = 326) n (%)	Difference in ACR50 Response Rate (PF-06438179 - EU Approved Remicade)
Week 2	Yes	24 (7.4)	24 (7.4)	0.05
	No	295 (91.1)	300 (92.0)	
	Missing	5 (1.5)	2 (0.6)	
Week 14	Yes	116 (35.8)	108 (33.1)	2.67
	No	195 (60.2)	208 (63.8)	
	Missing	13 (4.0)	10 (3.1)	
Week 30	Yes	125 (38.6)	132 (40.5)	-1.91
	No	169 (52.2)	166 (50.9)	
	Missing	30 (9.3)	28 (8.6)	

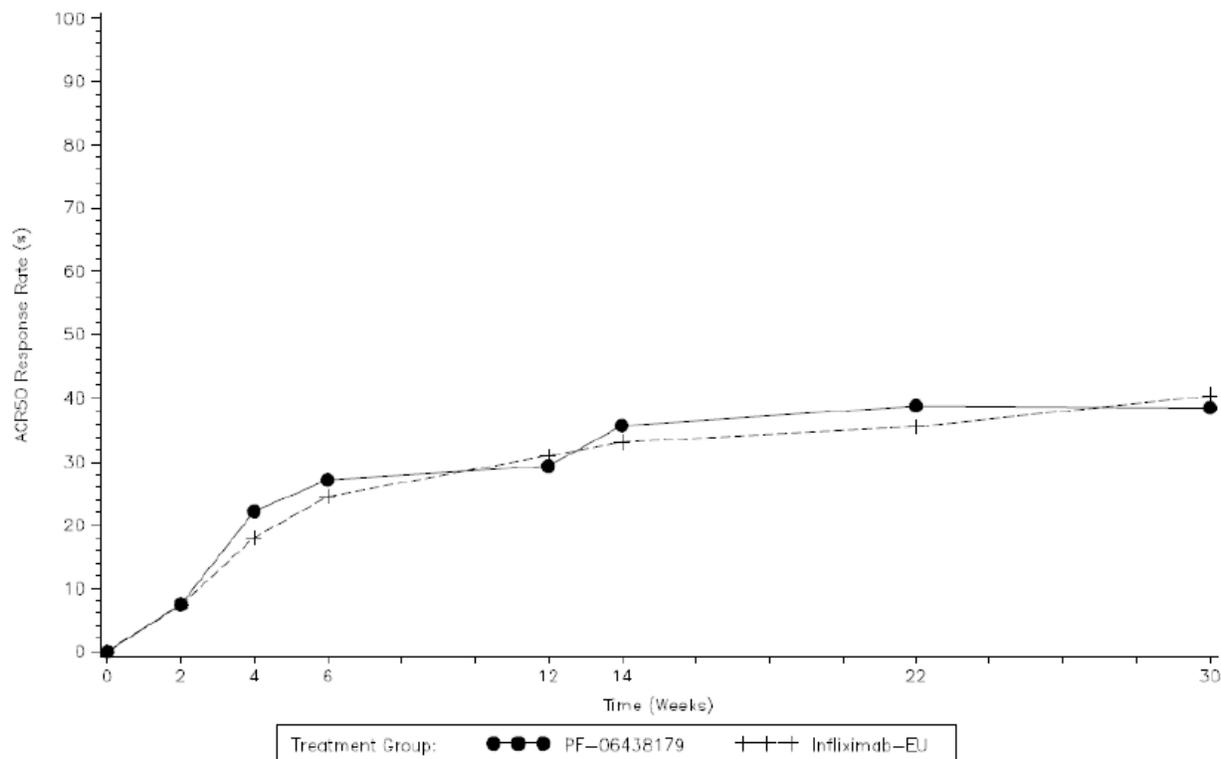
Abbreviations: EU = European Union; ITT = Intent-to-Treat; n = number of subjects; N = number of subjects randomized; TP1 = Treatment Period 1.

One (1) subject identification number and randomization number was assigned in error (1 subject was screened and randomized by 2 different study site personnel), and no data were collected for the subject's second randomization ((b) (6))

Source: Module 5.3.5.1, CSR Study B5371002, Table 25, Page 100

The response rates were generally similar between the PF-06438179 and EU approved Remicade arms at all study visits with the treatment difference ranging from -1.91% to 2.67%, for the time points described in Table 23 for TP1.

Figure 6. ACR50 Response by Visit, ITT Population B5371002– TP1



ITT = Intent-to-Treat, TP1 = Treatment Period 1, Infliximab EU= EU approved Remicade
 Source: Module 5.3.5.1, CSR Study B5371002, Figure 5, Page 101

Table 24. Descriptive Summary of ACR50 Response Rate by Visit, ITT Population B5371002- TP2

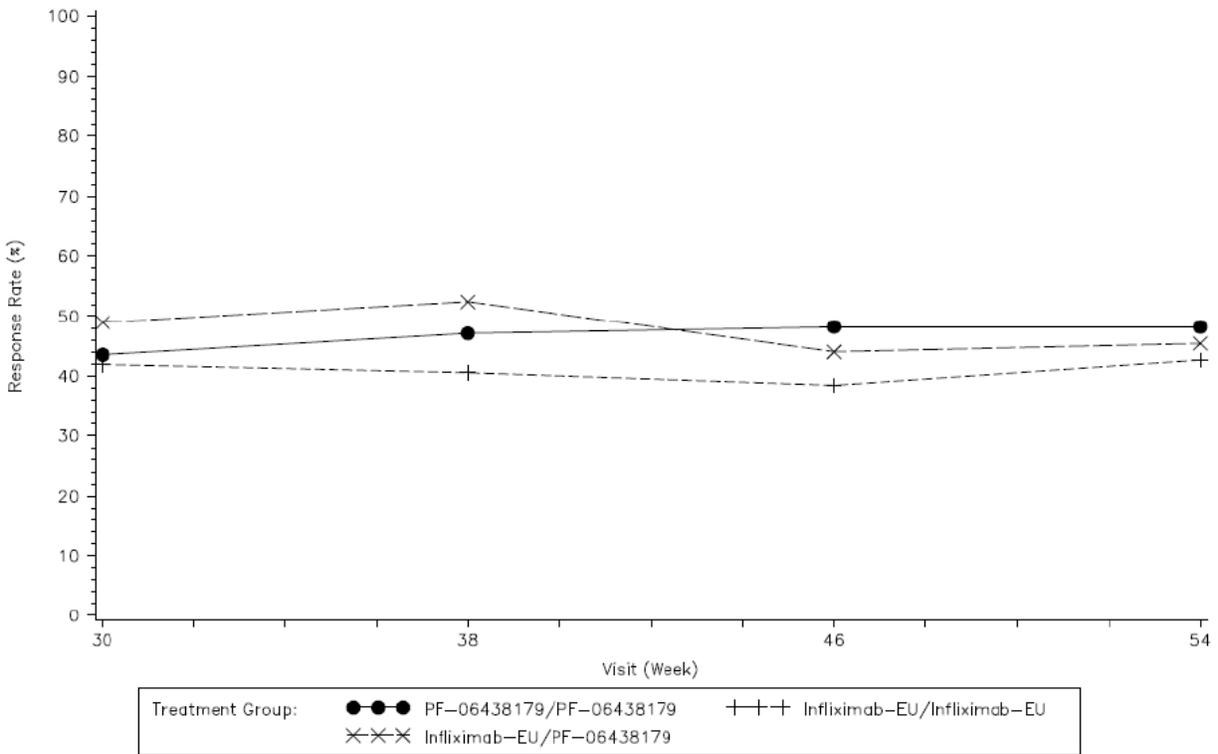
Visit	ACR50 Response	PF-06438179/ PF-06438179 (N = 280) n (%)	EU Approved Remicade/ EU Approved Remicade (N = 143) n (%)	EU Approved Remicade/ PF-06438179 (N=143) n (%)
Week 30	Yes	122 (43.6)	60 (42.0)	70 (49.0)
	No	158 (56.4)	83 (58.0)	73 (51.1)
Week 54	Yes	135 (48.2)	61 (42.7)	65 (45.5)
	No	124 (44.3)	69 (48.3)	64 (44.8)
	Missing	21 (7.5)	13 (9.1)	14 (9.8)

Abbreviations: EU = European Union; ITT = Intent-to-Treat; n = number of subjects; N = number of subjects randomized; TP2 = Treatment Period 2.
 One (1) subject identification number and randomization number was assigned in error (1 subject was screened and randomized by 2 different study site personnel), and no data were collected for the subject's second randomization ((b) (6))

Source: Module 5.3.5.1, CSR Study B5371002 Supplemental Study Report Week 54, Table 13, Page 66

The response rates for TP2 were generally similar between the three treatment arms (PF-06438179/ PF-06438179, EU Approved Remicade/EU Approved Remicade and EU Approved Remicade/ PF-06438179), as described in Table 24 and Figure 7.

Figure 7. ACR50 Response Rate by Visit, ITT Population B5371002– TP2

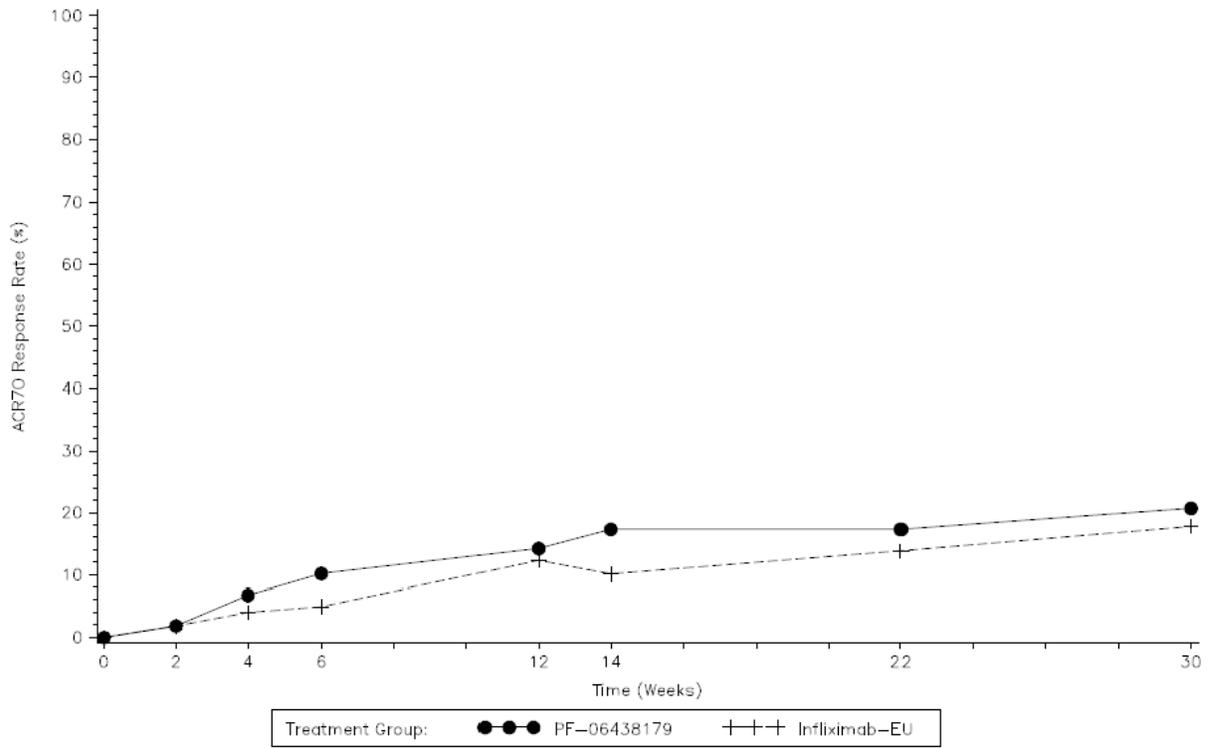


ITT = Intent-to-Treat, TP2 = Treatment Period 2, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002 Supplemental Study Report Week 54, Figure3, Page 67

ACR70 Response Rate by Visit

ACR70 response rates at Weeks 2, 4, 6, 12, 14, 22 and 30 are plotted in Figure 8 for the ITT population. In general, ACR70 response rates were similar between the PF-06438179 and EU Approved Remicade arms at all study visits.

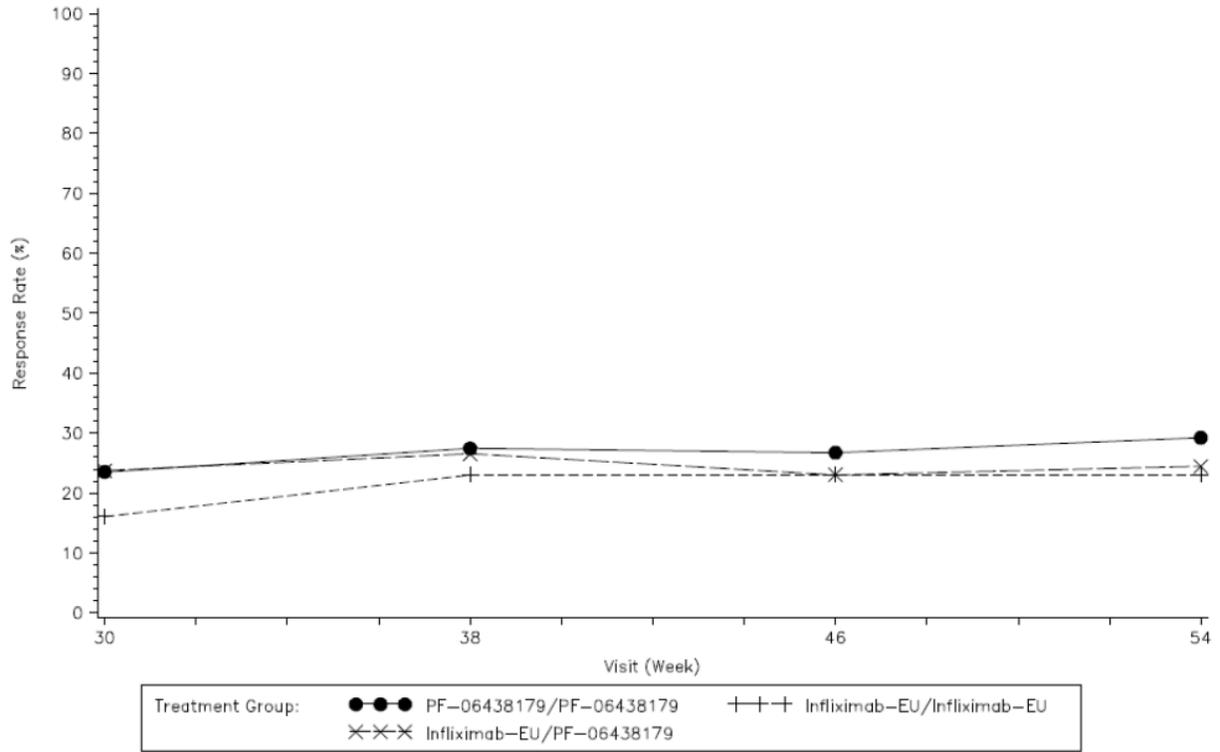
Figure 8. ACR70 Response Rate by Visit, ITT Population B5371002– TP1



ITT = Intent-to-Treat, TP1 = Treatment Period 1, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002, Figure 6, Page 103

ACR70 response rates at Weeks 30, 38, 46 and 54 from study baseline are plotted in Figure 9 for the ITT population. Similar to TP1, the overall ACR70 response rates were comparable among the 3 treatment groups over TP2.

Figure 9. ACR70 Response Rate by Visit, ITT Population B5371002– TP2



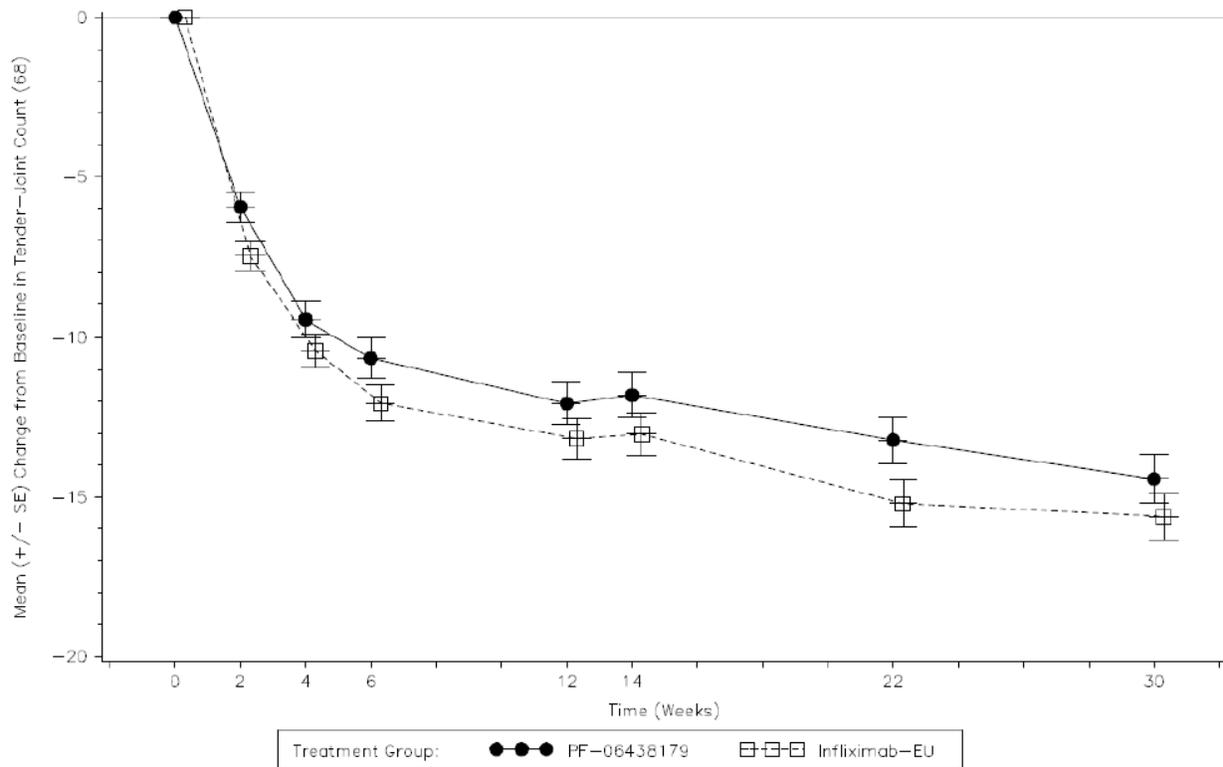
ITT = Intent-to-Treat, TP2 = Treatment Period 2, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002 Supplemental Study Report Week 54, Figure4, Page 69

6.1.6 Other Endpoints

Tender/Painful Joint Count (68)

As seen in Figure 10, mean change from baseline in tender joint count was similar between the 2 arms at each study visit up to Week 30. Results obtained at Week 54 were generally consistent with these findings.

Figure 10. Mean Change From Baseline in Tender Joint Count (68) by Visit, ITT Population B5371002 – TP1

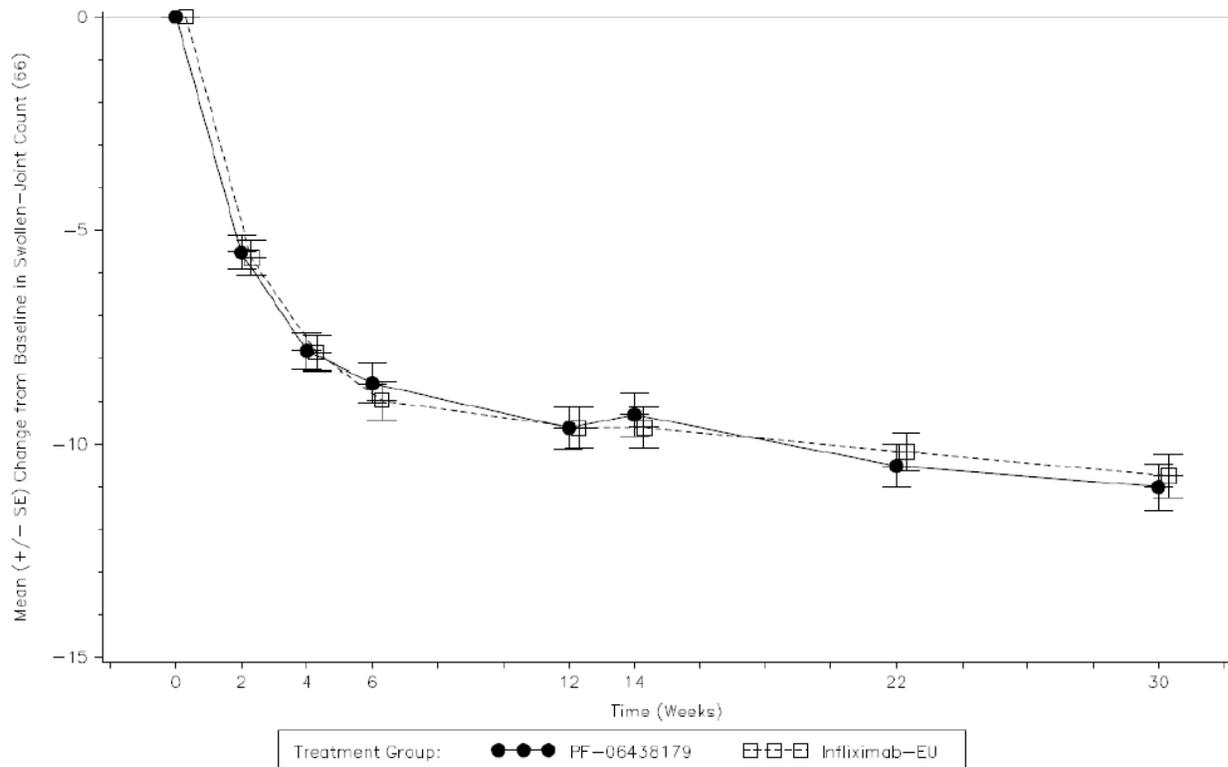


ITT = Intent-to-Treat, TP1 = Treatment Period 1, SE= standard error, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002, Figure 7, Page 104

Swollen Joint Count (66)

As seen in Figure 11, mean change from baseline in swollen joint count was similar between the 2 treatment arms at each study visit up to Week 30. Results obtained at Week 54 were generally consistent with these findings.

Figure 11. Mean Change From Baseline in Swollen Joint Count (66) by Visit, ITT Population B5371002– TP1

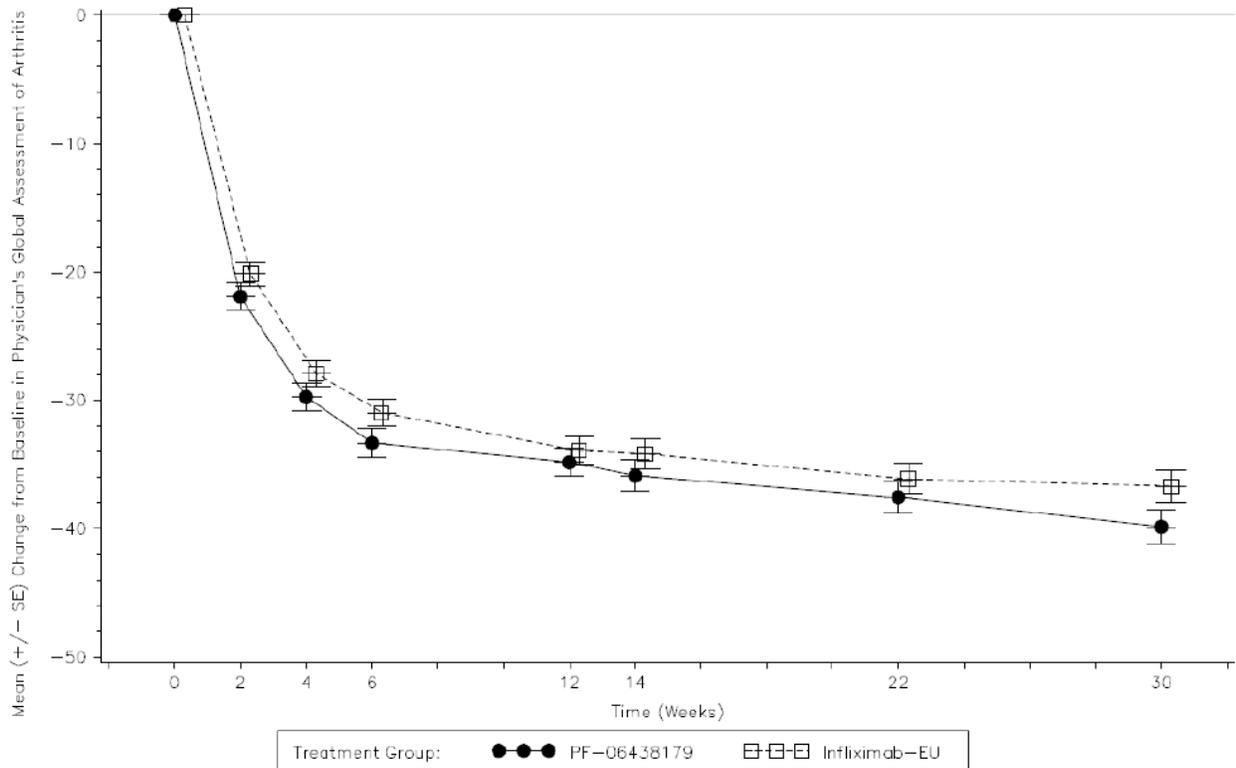


ITT = Intent-to-Treat, TP1 = Treatment Period 1, SE= standard error, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002, Figure 8, Page 105

Physician’s Global Assessment of Arthritis (PGAA)

As seen in Figure 12, the mean change from baseline in PGAA was similar between the 2 treatment arms at each study visit up to Week 30. Results obtained at Week 54 were generally consistent with these findings.

Figure 12. Mean Change From Baseline in Physician’s Global Assessment of Arthritis by Visit, ITT Population B5371002– TP1

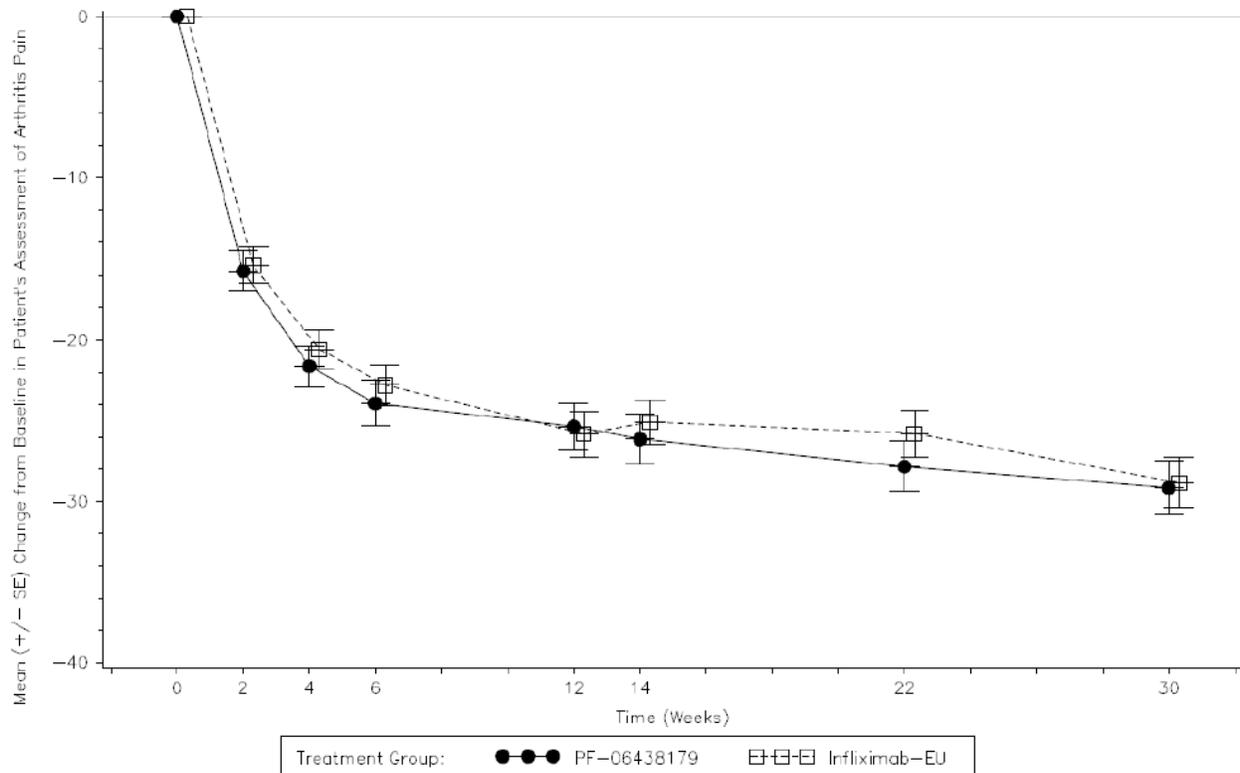


ITT = Intent-to-Treat, TP1 = Treatment Period 1, SE= standard error, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002, Figure 9, Page 106

Patient’s Assessment of Arthritis Pain (PAAP)

As seen in Figure 13, the mean change from baseline in PAAP was similar between the two treatment arms at each study visit up to Week 30. Results obtained at Week 54 were generally consistent with these findings.

Figure 13. Mean Change From Baseline in Patient’s Assessment of Arthritis Pain (PAAP) by Visit, ITT Population B5371002– TP1

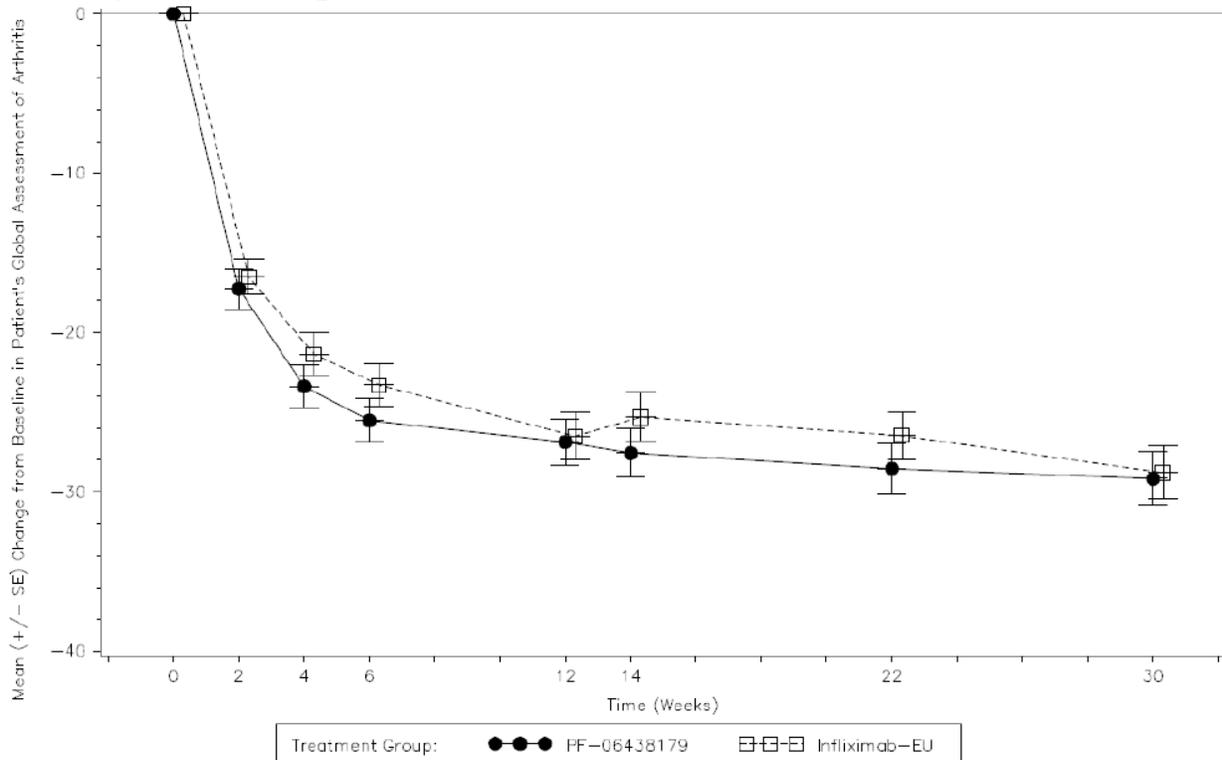


ITT = Intent-to-Treat, TP1 = Treatment Period 1, SE= standard error, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002, Figure 10, Page 107

Patient’s Global Assessment of Arthritis (PGA)

As seen in Figure 14, the mean change from baseline in PGA was similar between the 2 treatment arms at each study visit up to Week 30. Results obtained at Week 54 were generally consistent with these findings.

Figure 14. Mean Change From Baseline in Patient’s Global Assessment of Arthritis (PGA) by Visit, ITT Population B5371002– TP1

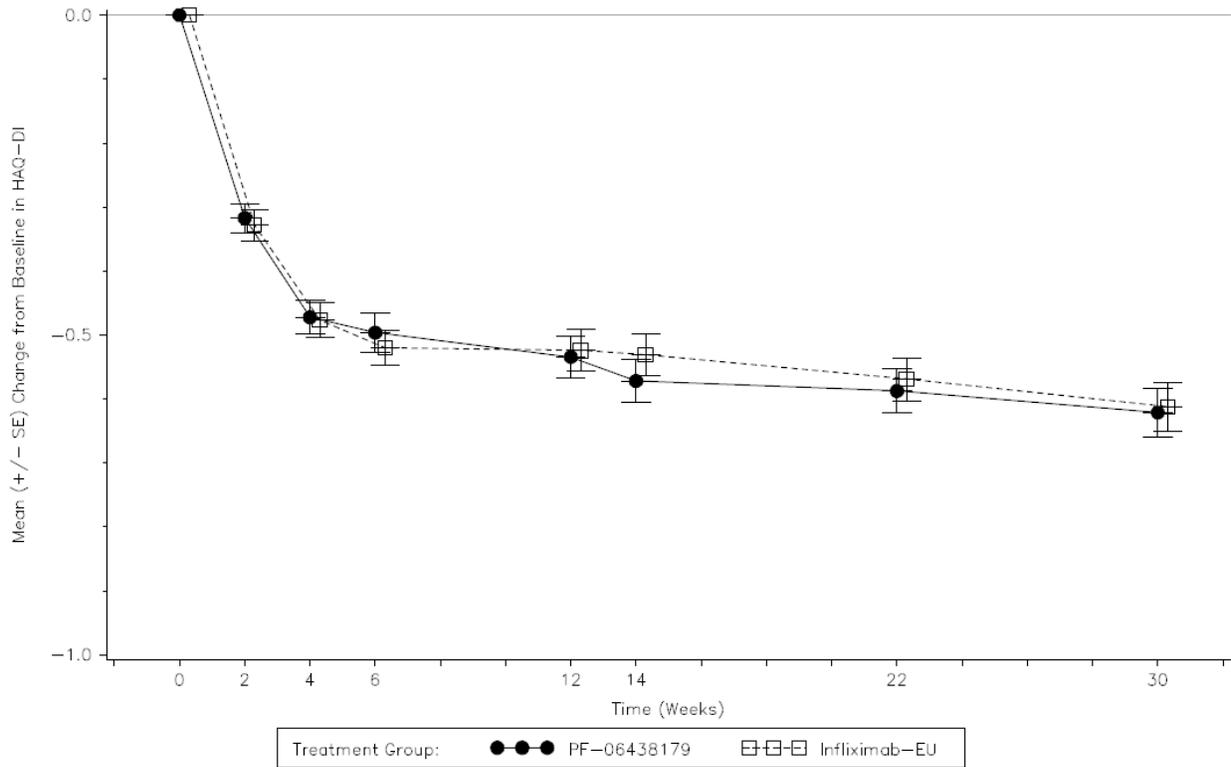


ITT = Intent-to-Treat, TP1 = Treatment Period 1, SE= standard error, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002, Figure 11, Page 108

Health Assessment Questionnaire-Disability Index (HAQ-DI)

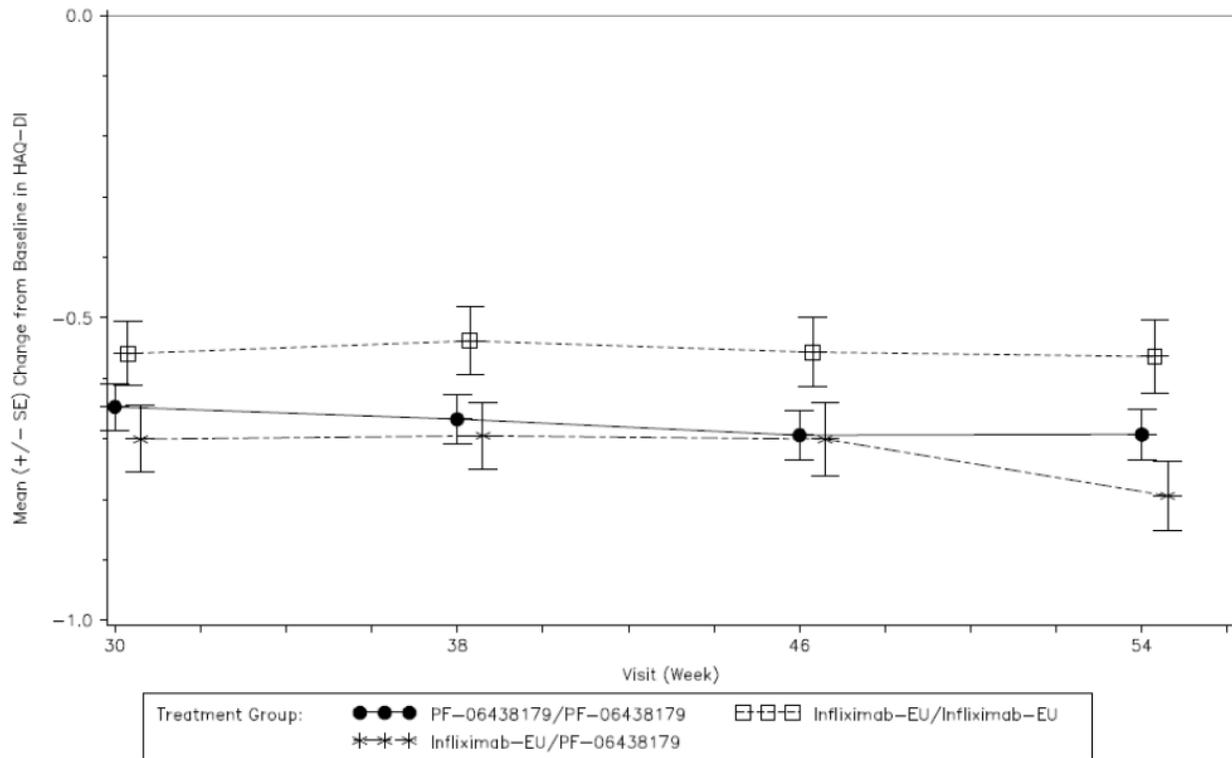
As seen in Figure 15, the mean changes from baseline in HAQ-DI were similar between the 2 treatment arms at each study visit up to Week 30. Slightly larger differences between treatment groups were noted through Week 54, however, as the number of patients in the treatment groups after Week 30 were reduced and many of the confidence intervals overlapped, these differences were not considered to be clinically meaningful (Figure 16).

Figure 15. Mean Change From Baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI) by Visit, ITT Population B5371002– TP1



ITT = Intent-to-Treat, TP1 = Treatment Period 1, SE= standard error, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002, Figure 12, Page 109

Figure 16. Mean Change Baseline in Health Assessment Questionnaire -Disability Index (HAQ-DI) by Visit, ITT Population B5371002–TP2

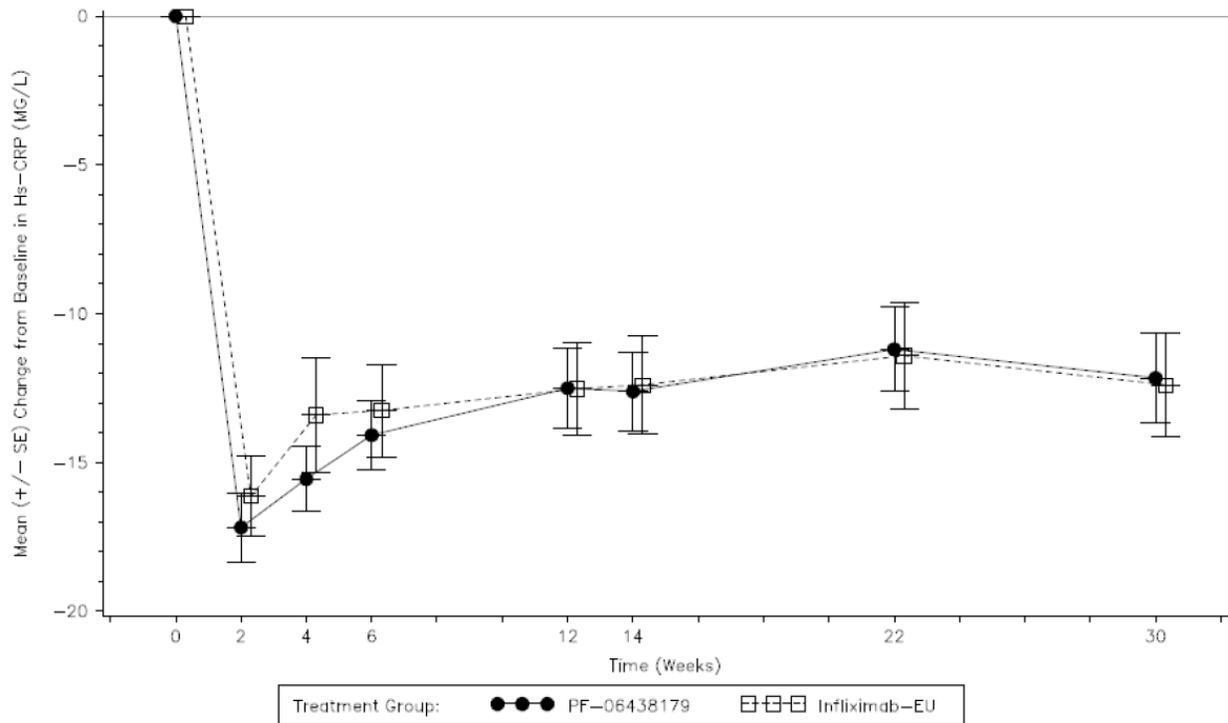


ITT = Intent-to-Treat, TP2 = Treatment Period 2, SE= standard error, Infliximab EU= EU approved Remicade
 Source: Module 5.3.5.1, CSR Study B5371002 Supplemental Report Week 54, Figure 5, Page 72

hs-CRP

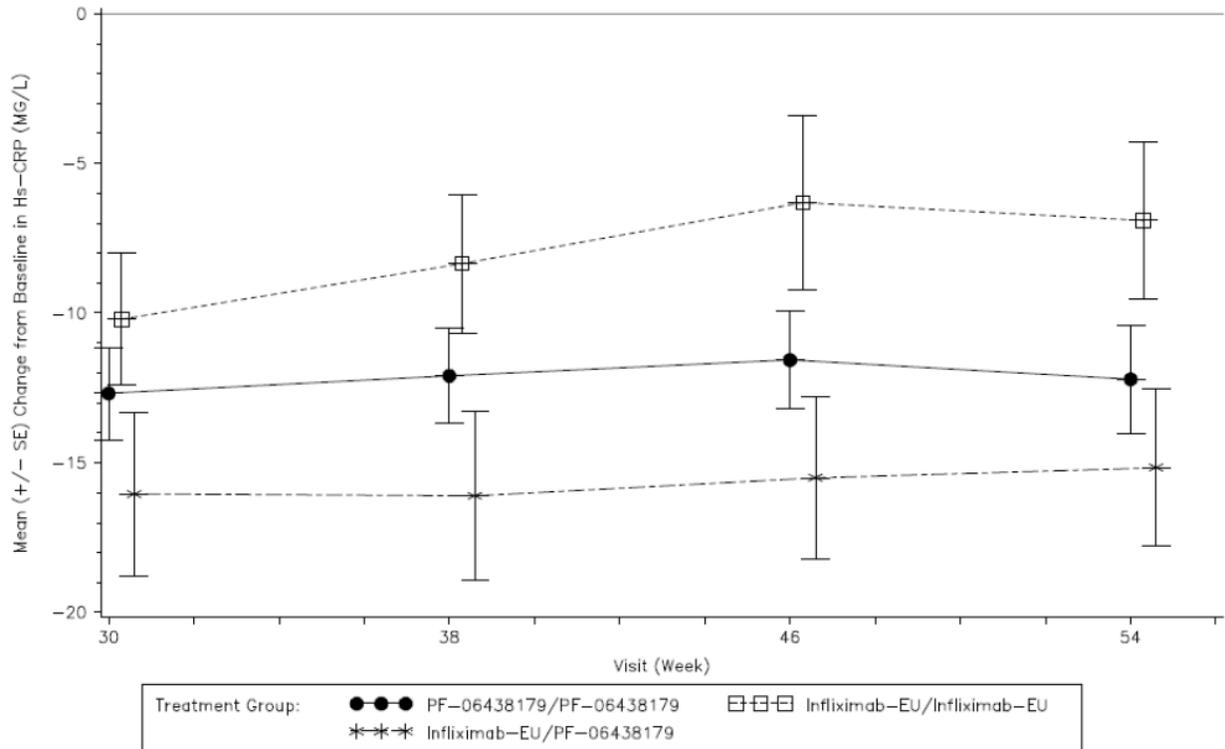
As seen in Figure 17, change from baseline in hs-CRP levels was similar between both treatment arms at each study visit up to Week 30. Slightly larger differences between treatment groups were noted through Week 54, however, as the number of patients in the treatment groups after Week 30 were reduced and many of the confidence intervals overlapped, these differences were not considered to be clinically meaningful (Figure 18).

Figure 17. Mean Change From Baseline in High Sensitivity C-Reactive Protein (hs-CRP) by Visit, ITT Population B5371002– TP1



ITT = Intent-to-Treat, TP1 = Treatment Period 1, SE= standard error, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002, Figure 13, Page 110

Figure 18. Mean Change From Study Baseline in High Sensitivity C-Reactive Protein (hs-CRP) by Visit, ITT Population B5371002– TP2

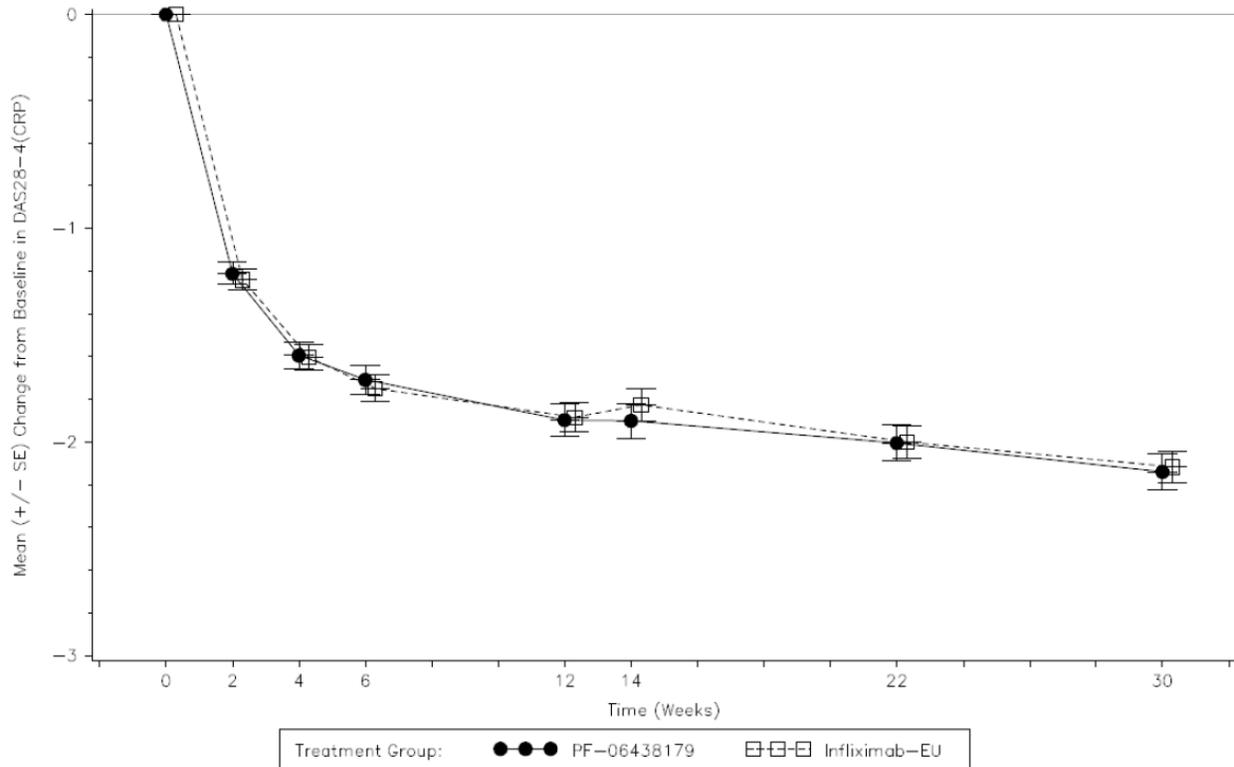


ITT = Intent-to-Treat, TP2 = Treatment Period 2, SE= standard error, Infliximab EU= EU approved Remicade
 Source: Module 5.3.5.1, CSR Study B5371002 Supplemental Report Week 54, Figure 7, Page 74

DAS28-CRP Response

As seen in Figure 19, change from baseline in DAS28-CRP up to Week 30 was similar between the two treatment arms. Results obtained at Week 54 were generally consistent with these findings.

Figure 19. Mean Change From Baseline in DAS28-CRP by Visit, ITT Population B5371002 – TP1



ITT = Intent-to-Treat, TP1 = Treatment Period 1, SE= standard error, Infliximab EU= EU approved Remicade
Source: Module 5.3.5.1, CSR Study B5371002, Figure 14, Page 111

European League Against Rheumatism (EULAR) Response, Disease Activity Score (DAS) Remission and ACR/EULAR Remission

Treatment responses through week 30 were similar between the two treatment arms with slight differences noted between the three treatment groups through week 54.

6.1.7 Subpopulations

The final statistical review was pending at the time of this review. For further details regarding subpopulations, refer to the statistical review by William Koh, PhD.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

Clinical Review
Erika Torjusen, M.D., MHS.
351(k) BLA 761072
PF-06438179, a proposed biosimilar to US-licensed Remicade

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The comparative clinical study (B5371002) demonstrated that an ACR20 response was achieved at Week 14 and this effect was maintained through Week 30 in TP1 (Figure 6) and through Week 54 in TP2 (Figure 7), as discussed in 6.1.4 Analysis of Primary Endpoint(s) and 6.1.5 Analysis of Key Secondary Endpoints(s).

For further details, refer to the statistical review by William Koh, PhD.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The safety of PF-06438179 compared to EU approved Remicade (with extrapolation to US-licensed Remicade) was assessed in Study B5371002, the comparative clinical study, comparing PF-06438179 with EU-approved Remicade in patients with RA as well as the single dose, healthy subject, comparative PK study, B5371001. Safety assessments in these 2 studies included adverse events (AEs), physical examinations, vital signs, ECGs, clinical laboratory testing and immunogenicity assessments. Study B5371001 was a single dose study and provided information regarding short term exposure to PF-06438179. Study B5371002 provided information regarding longer term exposure to PF-06438179, up to 54 weeks, as well as data for patients who underwent a single transition from EU-approved Remicade to PF-06438179.

The comparative clinical study (B5371002) safety database included 323 patients randomized to PF-06438179 and 326 patients randomized to EU-Remicade during treatment period 1 (TP1) and 280 patients randomized to PF-06438179/PF-06438179, 143 patients randomized to EU-approved Remicade/EU-approved Remicade and 143 patients randomized to EU-Remicade/PF-06438179 during treatment period 2 (TP2). The single dose comparative PK study (B5371001) safety database included 49 healthy volunteers randomized to PF-06438179, 48 subjects randomized to EU-Remicade and 49 subjects randomized to US-Remicade.

A majority of patients completed the comparative clinical study (B5371002); TP1 (86-88%) and TP2 (88-91%). Similar findings were noted for the comparative PK study (B5371001), with 71-86% completing the study and 94-100% of subjects providing data for safety analysis. Death was a rare occurrence in Study B5371002, with two events occurring in the PF-06438179 treatment arm and one occurring in the EU Approved Remicade treatment arm during TP1 and one death occurring during TP2 in the PF-06438179 treatment arm. In addition, one patient who received EU Approved Remicade, experienced an SAE during TP1 which resulted in a fatal outcome outside of TP1 and after the June 29, 2016 data cut off. There were no deaths reported in the comparative PK study, B5371001.

The overall occurrence of treatment emergent serious adverse events (TESAEs) was low. TESAEs for TP1 were fairly balanced between the treatment groups with a slight increase in overall adverse events in EU Approved Remicade (n=20, 6.1%), compared to PF-06438179 (n=16, 5%). The system organ class (SOC) with the highest percentage of subjects with TESAEs was Infections and Infestations and these events were more common in the EU Approved Remicade treatment arm (n=9, 2.8%) as compared to the PF-06438179 treatment arm (n=6, 1.9%). Similar findings were noted during TP2, with a slightly higher number of events occurring in the EU Approved Remicade/EU Approved Remicade treatment arm (n=11, 7.7%) compared to both the PF-06438179/PF-06438179 (n=13, 4.6%) and EU Approved Remicade/PF-06438179 treatment arms (n=4, 2.8%). The SOCs with the highest percentage of subjects with TESAEs were Infections and Infestations [PF-06438179/PF-06438179 (n=3, 1.1%)], EU Approved Remicade/EU Approved Remicade (n=2, 1.4%), and EU Approved Remicade /PF-06438179 (n=1, 0.7%)], and Injury, Poisoning and Procedural Complications [PF-06438179/PF-06438179 (n=3, 1.1%), EU Approved Remicade/EU Approved Remicade (n=2, 1.4%) and EU Approved Remicade /PF-06438179 (n=1, 0.7%)]. During the comparative PK study (B5371001), there 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. In general, the numbers of patients experiencing individual TESAEs were small, without meaningful imbalances noted.

Adverse events of special interest (AESI) were identified by the Applicant based upon known experiences with biologic products which included; IRR, hypersensitivity, infections (including TB and pneumonia), and malignancy (including lymphoma). During TP1 of the comparative clinical study (B5371002), events occurring within the infection SOC were the most commonly reported events across both treatment arms [(n=87, 26.9%) in PF-06438179 treatment arm and (n=73, 22.4%) in the EU Approved Remicade arm]. Similar findings were reported in TP2 with

IRRs being reported slightly more frequently in the EU Approved Remicade/ EU Approved Remicade treatment arm (n=12, 8.4%) compared to subjects in the PF-06438179/PF-06438179 (n=9, 3.2%) and EU Approved Remicade/PF-06438179 (n=6, 4.2%) treatment arms. Infusion related reactions, hypersensitivity events and anaphylaxis were generally balanced between the treatment groups, with a slight increase in IRRs noted in the EU Approved Remicade/ EU Approved Remicade treatment arm during TP2. It is notable that IRRs and hypersensitivity events did not increase following transition from EU approved Remicade to PF-06438179. During the comparative PK study, no IRRs were reported. Overall, the differences noted were small and not considered to be clinically meaningful in the overall assessment of similarity of safety.

Adverse events were generally balanced across the groups in the comparative clinical study, B5371002. During TP1, events were most frequently reported in the Infections and Infestations SOC [(n=86, 26.6%) in the PF-06438179 treatment arm and (n=72, 22.1%) in the EU approved Remicade treatment arm]. The most frequently reported adverse events by preferred term (PT), were IRR [(n=19, 5.9%) in subjects on PF-06438179 and (n=21, 6.4%) in subjects on EU approved Remicade] and ALT increased [(n=19, 5.9%) in subjects on PF-06438179 and (n=15, 4.6%) of subjects on EU approved Remicade]. Similar results were noted during TP2 with the SOC with the highest percentage of subjects with TEAEs being Infections and Infestations [(n=45, 16.1%) of subjects on PF-06438179/PF-06438179, (n=21, 14.7%) of subjects on EU Approved Remicade/EU Approved Remicade, and (n=19, 13.3%) of subjects on EU Approved Remicade /PF-06438179). The most frequently reported PTs during TP2 were IRR [(n=9, 3.2% subjects on PF-06438179/PF-06438179), (n=12, 8.4% subjects on EU approved Remicade/EU approved Remicade), and (n=6, 4.2% subjects on EU approved Remicade/PF-06438179)] and nasopharyngitis [(n=9, 3.2% subjects on PF-06438179/PF-06438179), (n=5, 3.5% subjects on EU approved Remicade/EU approved Remicade), and (n=2, 1.4% subjects on EU approved Remicade/PF-06438179)]. Review of the adverse event data did not reveal any new safety signals or significant imbalances.

The safety database is adequate to assess the comparative safety of PF-06438179. In summary, the safety data for PF-06438179 did not reveal any new safety concerns. Adverse events were few and generally consistent with those observed with similar approved TNF inhibitor biologic products. In addition, transitioning of non-treatment naïve patients, i.e., patients previously treated with EU approved -Remicade, to PF-06438179 did not result in an increase in clinically significant adverse reactions.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data were derived from the comparative clinical study, B5371002. Study B5371002 was a multi-national, randomized, double-blind, 2-arm, parallel group study which consisted of three treatment periods. Upon completion of screening, 650 subjects were randomized (1:1 ratio) to TP1 into two treatment arms to receive either PF-06438179 or EU approved Remicade. Upon completion of TP1 at Week 30, 566 subjects were re-randomized

into TP2. TP2 began with the dosing at Week 30, when subjects initially assigned to the EU approved Remicade study arm were re-randomized in a 1:1 ratio, with 50% of the EU approved Remicade arm switching to PF-06438179 and the other 50% remaining on EU approved Remicade. All subjects initially assigned PF-06438179 remained blindly assigned to continue on PF-06438179. Treatment continued in TP2 for another 24 weeks and ended with the completion of the Week 54 pre-dose assessments. TP2 provided additional safety and immunogenicity information 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. TP3 is currently ongoing and began with the Week 54 dosing, when all subjects remaining on EU approved Remicade were switched to PF-06438179. All subjects continued to receive open-label PF-06438179 treatment for an additional 24 weeks, with last study drug dosing scheduled at Week 70, and the end of treatment (EOT) visit at Week 78 (8 weeks after dosing at Week 70).

Supportive safety and immunogenicity information was also provided from the single dose PK study in healthy subjects (Study B5371001).

The assessment of similarity, as it pertains to the safety profile for PF-06438179 as compared to EU approved Remicade, was performed in the safety population, unless otherwise specified. The safety population was defined as all subjects who were randomized and received at least one dose of study treatment. The safety population was also used for the anti-drug antibody (ADA) and neutralizing antibody (Nab) analyses.

7.1.2 Categorization of Adverse Events

AEs were presented using the most current version of MedDRA available at the time of the data base lock for each study, MedDRA version 19.0 in the comparative clinical study (B5371002) and MedDRA 16.1 in the comparative PK study (B5371001).

AEs were recorded from the time the subject received the study treatment through last subject visit. For both studies, the severity of AEs was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 whenever possible. AEs in terms of TEAEs; treatment-related AEs; and SAEs were summarized by SOC and preferred term (PT) according to MedDRA terminology. A TEAE was defined as any AE that occurred after the beginning of the study treatment or any pre-existing AE that worsened after the beginning of the study treatment.

The Pfizer standard 3-tier AEs reporting was employed in Study B5371002: Adverse events of Special Interest (Tier-1 events) were identified by the medical team on an ongoing basis and the final list of events was determined before database lock: infections (including pneumonia and TB), malignancies, IRRs and hypersensitivity. Frequency and percentage of subjects within each treatment arm, risk difference (RD), 95% CI on RD were provided for each event. Events that occurred in $\geq 5\%$ subjects in at least 1 treatment arm were considered Tier-2 events. The frequency and percentage of subjects, RD and 95% CI of RD were provided for each Tier-2 event. Tier-3 events were all other events that were neither Tier-1 nor Tier-2. Only frequency

and percentage of subjects were provided. The AE summary tables were generated for all TEAEs and then for those that were related to the study treatment.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No combined or integrated analyses across studies B5371001 and B5371002 were planned or performed due to the different study design, including different treated populations and different dose levels.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent of exposure for the comparative clinical study B5371002 and comparative PK study B5371001 is described below in the subsequent tables.

Table 25. Extent of exposure to PF-06438179- Full Analysis Set B5371001			
	PF-06438179 (N = 52)	EU Approved Remicade (N =50)	US-licensed Remicade (N =49)
Single Dose Study			
Not Treated n (%)	3 (6)	2 (4)	0
Treated n (%)			
Complete Dose	49 (94)	48 (96)	49 (100)
Incomplete Dose	0	0	0
Full analysis set: The full analysis set includes all randomized subjects. This is equivalent to the ITT (intent-to-treat) population.			
Source: Module 5.3.3.1, CSR B5371001, Table 14.4.1.2, Page 301.			

As seen in Table 25, 94-100% of the subjects were treated and received a single dose of PF-06438179, EU Approved Remicade and US-licensed Remicade, respectively. The exposure in this single dose PK study conducted in healthy volunteers provided additional supportive safety information to the evaluation of PF-06438179 in patients with RA.

Table 26. Extent of exposure to PF-06438179- Safety Population B5371002-TP1		
	PF-06438179 (N = 323) n(%)	EU Approved Remicade (N = 326) n(%)
Duration of exposure		
Median (range) week	22.1 (0-27)	22.1 (0-26)
Median (range) day	155.0 (1-190)	155.0 (1-181)
Duration of exposure categories		
Week 0/ <= 1 day	4 (1.2)	2 (0.6)
Week 0-5/ 2-42 days	10 (3.1)	8 (2.5)
Week 6-13/ 43-98 days	11 (3.4)	3 (0.9)
Week 14-29/ 99-210 days	298 (92.3)	313 (96.0)
Based on the treatment received in TP1. Duration of treatment was calculated from date of first infusion to date of last infusion plus 1. Abbreviations: EU = European Union; n = number of subjects; N = number of subjects in the safety analysis set; TP1 = Treatment Period 1.		
Source: Module 5.3.5.1, CSR B5371002, Table 34, Page 127.		

As shown in Table 26, 92% of subjects in the PF-06438179 arm and 96% of the subjects in the EU Approved Remicade arm were in the exposure category Week 14-29.

Table 27. Extent of exposure to PF-06438179- Safety Population B5371002-TP2			
	PF-06438179/ PF-06438179 (N = 280)	EU Approved Remicade/ EU Approved Remicade (N =143)	EU Approved Remicade/ PF-06438179 (N =143)
Duration of exposure			
Median, weeks (range)	16.1 (0-18)	16.1 (0-21)	16.1 (0-20)
Median, days (range)	113.0 (1-127)	113.0 (1-148)	113.0 (1-142)
Duration of treatment was calculated from the date of the first study drug infusion in TP2 to date of the final infusion plus 1. Abbreviations: N = number of subjects in the TP2 safety population; TP2 = Treatment Period 2.			
Source: Module 5.3.5.1, CSR B5371002 Supplemental Study Report Week 54, Table 22, Page 94.			

The median exposure in TP2 was 16 weeks in all three treatment arms, as shown above in Table 27. The extent of exposure in the safety database was adequate to perform the safety evaluation for PF-06438179 in patients with RA.

7.2.2 Explorations for Dose Response

In this BLA, the dose and dosing regimen of PF-06438179 is identical to the reference product, US-Remicade. As such, dose-exploration studies were not required.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

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7.2.4 Routine Clinical Testing

The routine clinical testing in the development program for PF-06438179 included: hematology, blood chemistry and urinalysis, ECGs, chest radiography and quantiFERON TB testing.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

PF-06438179 is a proposed biosimilar to the reference product, US-Remicade, a TNF inhibitor. The safety profile of PF-06438179 was assessed in the context of known adverse event profile of US-Remicade, other DMARDs and biologics.

7.3 Major Safety Results

7.3.1 Deaths

Deaths for TP1 are summarized in Table 28. Deaths for TP2 are summarized in Table 29.

Table 28. Deaths- Safety Population B5371002-TP1		
Preferred Term	PF-06438179 (N = 323) n	EU Approved Remicade (N = 326) n
Deaths	2	1
Shock- Multi-Organ Dysfunction	0	1
Acute Myocardial Infarction	2	0
Note: 4 subjects experienced SAEs during TP1 that led to fatal outcomes, with 1 death occurring outside of TP1 and after the June 29, 2016 data cutoff date. A brief summary is provided in the text below. Source: Module 5.3.5.1, CSR B5371002, Table 14.3.2.1, Page 449, Page 147.		

Death was a rare occurrence, with two events occurring in the PF-06438179 treatment arm and one in occurring in the EU Approved Remicade treatment arm (Table 28).

In addition, one patient who received EU Approved Remicade experienced an SAE during TP1 which resulted in a fatal outcome outside of TP1, and after the June 29, 2016 data cut-off. Thirteen days after the last study drug administration, the subject was hospitalized with a diagnosis of community-acquired pneumonia of the right lower lobe. The subject later experienced chronic pyelonephritis (Grade 3), chronic kidney disease (Grade 3), arterial hypertension (Grade 1) and heart failure (Grade 1). Due to the subject's condition, EU Approved Remicade was permanently discontinued. On Study Day 235, the subject died due to

progression of pneumonia. As this death occurred outside of the treatment period and after the data cut-off date, this event was not captured in the table above.

Table 29. Deaths- Safety Population B5371002-TP2			
	PF-06438179/ PF-06438179 (N = 280)	EU Approved Remicade/ EU Approved Remicade (N =143)	EU Approved Remicade/ PF-06438179 (N =143)
Deaths	1	0	0
Sudden Cardiac Death	1	0	0

Source: Module 5.3.5.1, CSR B5371002 Supplemental Study Report Week 54, Table 14.3.2.1, Page 347, Page 121.

As displayed in Table 29, there was one death (sudden cardiac death) reported during TP2, in the PF-06438179 treatment arm. While there was a higher frequency of deaths in the PF-06438179 treatment arm, the overall number of events was extremely small and therefore this difference (n=1) was not felt to be clinically significant.

There were no deaths reported in the comparative PK study, B5371001.

7.3.2 Nonfatal Serious Adverse Events

An overview of treatment emergent serious adverse events (TESAEs) for TP1 is provided in Table 30. Results for TP2 are described in Table 31.

Table 30. All-Causality Treatment-Emergent SAEs- Safety Population B5371002-TP1		
SOC and Preferred Term	PF-06438179 (N = 323) n(%)	EU Approved Remicade (N = 326) n(%)
Any AEs	16 (5.0)	20 (6.1)
Cardiac Disorders	4 (1.2)	3 (0.9)
Acute Myocardial Infarction	2 (0.6)	0
Angina Unstable	1 (0.3)	0
Atrial fibrillation	0	2 (0.6)
Atrial flutter	0	1 (0.3)
Coronary artery disease	0	1 (0.3)
Myocardial infarction	1 (0.3)	0
Eye disorders	0	1 (0.3)
Keratitis	0	1 (0.3)
Gastrointestinal disorders	0	2 (0.6)
Diverticular perforation	0	1 (0.3)
Dyspepsia	0	1 (0.3)
General disorders and administration site conditions	2 (0.6)	2 (0.6)
Chest pain	2 (0.6)	0
Multi-organ disorder	0	1 (0.3)
Systemic inflammatory response syndrome	0	1 (0.3)
Infections and infestations	6 (1.9)	9 (2.8)
Bronchitis	0	1 (0.3)
Cellulitis	1 (0.3)	0
Diverticulitis	0	1 (0.3)
Gastroenteritis norovirus	1 (0.3)	0
Localized infection	1 (0.3)	0
Peritonitis	0	1 (0.3)
Pneumocystis jirovecii pneumonia	1 (0.3)	0
Pneumonia	2 (0.6)	2 (0.6)
Purulent synovitis	0	1 (0.3)
Pyelonephritis acute	1 (0.3)	1 (0.3)
Subcutaneous abscess	0	1 (0.3)
Tuberculosis	0	1 (0.3)
Urinary tract infection	0	1 (0.3)
Injury, poisoning and procedural complications	1 (0.3)	3 (0.9)
Cartilage injury	0	1 (0.3)
Contusion	0	1 (0.3)
Fall	0	1 (0.3)
Hip fracture	0	1 (0.3)
Ligament rupture	0	1 (0.3)
Meniscus injury	0	1 (0.3)
Multiple injuries	0	1 (0.3)
Patella fracture	1 (0.3)	0
Radius fracture	0	1 (0.3)
Sternal fracture	0	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.3)	1 (0.3)
Rheumatoid arthritis	1 (0.3)	1 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.3)

Table 30. All-Causality Treatment-Emergent SAEs- Safety Population B5371002-TP1		
SOC and Preferred Term	PF-06438179 (N = 323) n(%)	EU Approved Remicade (N = 326) n(%)
Colon cancer	0	1 (0.3)
Nervous system disorders	1 (0.3)	0
Transient ischemic attack	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	2 (0.6)	2 (0.6)
Chronic obstructive pulmonary disease	1 (0.3)	0
Interstitial lung disease	1 (0.3)	0
Pleurisy	0	1 (0.3)
Pulmonary embolism	0	1 (0.3)
Vascular disorders	0	2 (0.6)
Shock	0	1 (0.3)
Venous stenosis	0	1 (0.3)

Abbreviations: AE = adverse event; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects included in the safety analysis set; SAE = serious adverse event; SOC = system organ class; TP1 = Treatment Period 1.
 MedDRA version 19.0

Source: Module 5.3.5.1, CSR B5371002, Table 51, Page 149.

As seen in Table 30, the TESAEs for TP1 were fairly balanced between the treatment groups. There was a slight increase in overall adverse events in EU Approved Remicade (6.1%), compared to PF-06438179 (5%). The SOC with the highest percentage of subjects with TESAEs was Infections and Infestations and these events were more common in the EU Approved Remicade treatment arm (2.8%) as compared to the PF-06438179 treatment arm (1.9%). Overall, these differences were small and not considered clinically meaningful. No new safety signal was noted as a result of the TESAE analysis by SOC or preferred terms.

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Table 31. All-Causality Treatment-Emergent SAEs- Safety Population B5371002-TP2			
	PF-06438179/ PF-06438179 (N = 280) n(%)	EU Approved Remicade/ EU Approved Remicade (N =143) n(%)	EU Approved Remicade/ PF-06438179 (N =143) n(%)
Any AEs	13 (4.6)	11 (7.7)	4 (2.8)
Blood and lymphatic system disorders	1 (0.4)	1 (0.7)	0
Anemia	1 (0.4)	0	0
Blood disorder	0	1 (0.7)	0
Cardiac disorders	0	1 (0.7)	0
Myocardial infarction	0	1 (0.7)	0
Gastrointestinal disorders	1 (0.4)	1 (0.7)	0
Enteritis	1 (0.4)	0	0
Hemorrhoids	0	1 (0.7)	0
General disorders and administration site conditions	1 (0.4)	1 (0.7)	0
Pyrexia	0	1 (0.7)	0
Sudden cardiac death ^a	1 (0.4)	0	0
Hepatobiliary disorders	1 (0.4)	0	0
Cholecystitis	1 (0.4)	0	0
Immune system disorders	1 (0.4)	0	0
Anaphylactic reaction	1 (0.4)	0	0
Infections and infestations	3 (1.1)	2 (1.4)	1 (0.7)
Acute sinusitis	1 (0.4)	0	0
Arthritis bacterial	1 (0.4)	0	0
Clostridium difficile infection	1 (0.4)	0	0
Helicobacter infection	1 (0.4)	0	0
Pneumocystis jirovecii pneumonia	0	1 (0.7)	0
Pneumonia	0	1 (0.7)	0
Urinary tract infection	0	0	1 (0.7)
Injury, poisoning and procedural complications	3 (1.1)	2 (1.4)	1 (0.7)
Femur fracture	0	1 (0.7)	0
IRR	1 (0.4)	1 (0.7)	0
Joint injury	1 (0.4)	0	0
Radius fracture	1 (0.4)	0	0
Spinal compression fracture	0	0	1 (0.7)
Investigations	1 (0.4)	1 (0.7)	0
ALT increased	0	1 (0.7)	0
AST increased	0	1 (0.7)	0
Hepatic enzyme increased	1 (0.4)	0	0
Musculoskeletal and connective tissue disorders	1 (0.4)	2 (1.4)	0
Osteoarthritis	1 (0.4)	0	0
RA	0	2 (1.4)	0
Neoplasms benign,	1 (0.4)	1 (0.7)	1 (0.7)

Table 31. All-Causality Treatment-Emergent SAEs- Safety Population B5371002-TP2			
	PF-06438179/ PF-06438179 (N = 280) n(%)	EU Approved Remicade/ EU Approved Remicade (N =143) n(%)	EU Approved Remicade/ PF-06438179 (N =143) n(%)
malignant and unspecified (incl. cysts and polyps)			
Colon cancer	0	1 (0.7)	0
Laryngeal squamous cell carcinoma	1 (0.4)	0	0
Ocular lymphoma	0	0	1 (0.7)
Reproductive system and breast disorders	0	0	1 (0.7)
Genital prolapse	0	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	1 (0.4)	2 (1.4)	0
Dyspnea	0	1 (0.7)	0
Pulmonary embolism	1 (0.4)	0	0
Pulmonary mass	0	1 (0.7)	0
Skin and subcutaneous tissue disorders	0	1 (0.7)	0
Erythema	0	1 (0.7)	0

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects included in the TP2 safety population; RA = rheumatoid arthritis; SAE = serious adverse event; PT = preferred term; SOC = system organ class; TP2 = Treatment Period 2.
 a. The event was updated to Cardiac arrest in SOC Cardiac Disorders following the Week 54 database lock.
 MedDRA version 19.1

Source: Module 5.3.5.1, CSR B5371002 Supplemental Study Report Week 54, Table 37, Page 123.

Similar findings were noted during TP2 (Table 31), with a slightly higher percentage of events occurring in the EU Approved Remicade/EU Approved Remicade treatment arm (7.7%) compared to the PF-06438179/PF-06438179 treatment arm (4.6%) and the EU Approved Remicade/PF-06438179 treatment arm (2.8%). The SOCs with the highest percentage of subjects with TESAEs were Infections and Infestations [PF-06438179/PF-06438179 (1.1%), EU Approved Remicade/EU Approved Remicade (1.4%), and EU Approved Remicade /PF-06438179 (0.7%)], and Injury, Poisoning and Procedural Complications [PF-06438179/PF-06438179 (1.1%), EU Approved Remicade/EU Approved Remicade (1.4%) and EU Approved Remicade /PF-06438179 (0.7%)]. Once again, these differences were small and not considered clinically meaningful.

In the comparative PK study (B5371001), there 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.

7.3.3 Dropouts and/or Discontinuations

Adverse events (AEs) leading to study drug withdrawal during TP1 are listed in Table 32. Similar results are displayed for TP2 in Table 33.

Table 32. All-Causality TESAEs Leading to Permanent Discontinuation- Safety Population B5371002-TP1		
SOC and Preferred Term	PF-06438179 (N = 323) n(%)	EU Approved Remicade (N = 326) n(%)
Blood and lymphatic system disorders	0	2 (0.6)
Leukopenia	0	1 (0.3)
Neutropenia	0	1 (0.3)
Cardiac Disorders	3 (0.9)	2 (0.6)
Acute myocardial infarction	2 (0.6)	0
Angina pectoris	1 (0.3)	0
Cyanosis	1 (0.3)	0
Palpitations	1 (0.3)	1 (0.3)
Tachycardia	0	1 (0.3)
Ear and labyrinth disorders	0	1 (0.3)
Vertigo	0	1 (0.3)
Gastrointestinal disorders	3 (0.9)	2 (0.6)
Diarrhea	1 (0.3)	0
Dyspepsia	0	1 (0.3)
Gastritis	0	1 (0.3)
Nausea	2 (0.6)	0
General disorders and administration site conditions	0	5 (1.5)
Fatigue	0	1 (0.3)
Multi-organ disorder	0	1 (0.3)
Pyrexia	0	2 (0.6)
Systemic inflammatory response syndrome	0	1 (0.3)
Infections and infestations	5 (1.5)	6 (1.8)
Localized infection	1 (0.3)	0
Osteomyelitis	1 (0.3)	0
Pharyngitis	1 (0.3)	0
Pneumonia	1 (0.3)	2 (0.6)
Purulent synovitis	0	1 (0.3)
Pyelonephritis acute	0	1 (0.3)
Subcutaneous abscess	0	1 (0.3)
Tuberculosis	0	1 (0.3)
Latent tuberculosis	1 (0.3)	0
Injury, poisoning and procedural complications	6 (1.9)	6 (1.8)
Infusion-related reaction	6 (1.9)	6 (1.8)
Investigations	1 (0.3)	3 (0.9)
Alanine aminotransferase increased	0	2 (0.6)
Aspartate aminotransferase increased	0	2 (0.6)
Blood pressure decreased	1 (0.3)	0
Mycobacterium tuberculosis complex test positive	0	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.3)	1 (0.3)
Rheumatoid arthritis	1 (0.3)	1 (0.3)

Table 32. All-Causality TESAEs Leading to Permanent Discontinuation- Safety Population B5371002-TP1

SOC and Preferred Term	PF-06438179 (N = 323) n(%)	EU Approved Remicade (N = 326) n(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	1 (0.3)
Colon cancer	1 (0.3)	1 (0.3)
Nervous system disorders	2 (0.6)	0
Dizziness	2 (0.6)	0
Pregnancy, puerperium and perinatal conditions ^a	2 (0.8)	0
Pregnancy	2 (0.8)	0
Respiratory, thoracic and mediastinal disorders	3 (0.9)	7 (2.1)
Asphyxia	0	1 (0.3)
Atelectasis	0	1 (0.3)
Dyspnea	1 (0.3)	3 (0.9)
Interstitial lung disease	1 (0.3)	0
Pleural effusion	0	1 (0.3)
Pulmonary fibrosis	0	1 (0.3)
Respiratory disorder	1 (0.3)	0
Respiratory distress	0	1 (0.3)
Skin and subcutaneous tissue disorders	8 (2.5)	7 (2.1)
Cold sweat	0	1 (0.3)
Dermatitis	0	1 (0.3)
Dermatitis allergic	1 (0.3)	0
Erythema	1 (0.3)	0
Hypersensitivity vasculitis	1 (0.3)	1 (0.3)
Pruritus	0	1 (0.3)
Pustular psoriasis	1 (0.3)	0
Rash	1 (0.3)	2 (0.6)
Rash macular	1 (0.3)	0
Urticaria	2 (0.6)	1 (0.3)
Vascular disorders	1 (0.3)	1 (0.3)
Flushing	1 (0.3)	0
Hyperemia	0	1 (0.3)

Abbreviations: AE = adverse event; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects included in the safety analysis set; SAE = serious adverse event; SOC = system organ class; TP1 = Treatment Period 1. MedDRA version 19.0

a. Percentages of gender specific events were calculated using the corresponding gender count as denominator.

Source: Module 5.3.5.1, CSR B5371002, Table 50, Page 145.

As seen in Table 32, 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]. Overall, adverse events were not a significant cause for patient discontinuation and the differences noted by SOC and PT were small and not considered clinically meaningful.

Table 33. All-Causality TESAEs Leading to Permanent Discontinuation- Safety Population B5371002-TP2			
SOC and Preferred Term	PF-06438179/ PF-06438179 (N = 280) n(%)	EU Approved Remicade/ EU Approved Remicade (N =143) n(%)	EU Approved Remicade/ PF-06438179 (N =143) n(%)
Any AEs	14 (5.0)	10 (7.0)	7 (4.9)
Blood and lymphatic system disorders	1 (0.4)	1 (0.7)	0
Anemia	1 (0.4)	0	0
Blood disorder	0	1 (0.7)	0
Cardiac disorders	0	1 (0.7)	0
Myocardial infarction	0	1 (0.7)	0
Gastrointestinal disorders	1 (0.4)	1 (0.7)	0
Nausea	1 (0.4)	1 (0.7)	0
Vomiting	0	1 (0.7)	0
General disorders and administration site conditions	3 (1.1)	1 (0.7)	0
Chills	2 (0.7)	0	0
Feeling hot	1 (0.4)	0	0
Pyrexia	0	1 (0.7)	0
Sudden cardiac death ^a	1 (0.4)	0	0
Immune system disorders	1 (0.4)	0	0
Anaphylactic reaction	1 (0.4)	0	0
Hypersensitivity	1 (0.4)	0	0
Infections and infestations	2 (0.7)	4 (2.8)	2 (1.4)
Arthritis bacterial	1 (0.4)	0	0
Latent tuberculosis	0	2 (1.4)	2 (1.4)
Pneumocystis jirovecii	0	1 (0.7)	0
Pneumonia	0	1 (0.7)	0
Vaginal infection	1 (0.4)	0	0
Injury, poisoning and procedural complications	6 (2.1)	2 (1.4)	2 (1.4)
IRR	6 (2.1)	2 (1.4)	2 (1.4)
Investigations	0	1 (0.7)	0
ALT increased	0	1 (0.7)	0
AST increased	0	1 (0.7)	0
Hepatitis C antibody positive	0	1 (0.7)	0
Musculoskeletal and connective tissue disorders	2 (0.7)	0	1 (0.7)
Osteoarthritis	1 (0.4)	0	0
RA	1 (0.4)	0	1 (0.7)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.4)	0	1 (0.7)
Laryngeal squamous cell carcinoma	1 (0.4)	0	0
Ocular lymphoma	0	0	1 (0.7)
Respiratory, thoracic and	0	2 (1.4)	1 (0.7)

Table 33. All-Causality TESAEs Leading to Permanent Discontinuation- Safety Population B5371002-TP2			
SOC and Preferred Term	PF-06438179/ PF-06438179 (N = 280) n(%)	EU Approved Remicade/ EU Approved Remicade (N =143) n(%)	EU Approved Remicade/ PF-06438179 (N =143) n(%)
mediastinal disorders			
Dyspnea	0	1 (0.7)	1 (0.7)
Pulmonary mass	0	1 (0.7)	0
Skin and subcutaneous tissue disorders	4 (1.4)	1 (0.7)	3 (2.1)
Erythema	0	1 (0.7)	0
Pruritus	2 (0.7)	0	0
Rash	1 (0.4)	0	1 (0.7)
Rash pruritic	0	0	1 (0.7)
Urticaria	1 (0.4)	0	1 (0.7)
Vascular disorders	2 (0.7)	0	1 (0.7)
Flushing	0	0	1 (0.7)
Hypotension	2 (0.7)	0	0

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects included in the TP2 safety population; RA = rheumatoid arthritis; SAE = serious adverse event; PT = preferred term; SOC = system organ class; TP2 = Treatment Period 2.
 a. The event was updated to Cardiac arrest in SOC Cardiac Disorders following the Week 54 database lock.
 MedDRA version 19.1

Source: Module 5.3.5.1, CSR B5371002 Supplemental Study Report Week 54, Table 36, Page 119.

Similar results were noted for TP2 and are displayed above in Table 33. The SOCs with the highest percentage of subjects with AEs leading to discontinuation were: Injury, Poisoning, and Procedural Complications; Skin and Subcutaneous Tissue Disorders; and Infections and Infestations.

There were no permanent discontinuations due to adverse events reported in the comparative PK study, B5371001.

7.3.4 Significant Adverse Events

Refer to Section 7.3.2 Nonfatal Serious Adverse Events.

7.3.5 Submission Specific Primary Safety Concerns

Table 34. All-Causality TEAEs of Special Interest- Safety Population B5371002-TP1		
Events of Special Interest	PF-06438179 N=323 n(%)	EU Approved Remicade N=326 n(%)
Infusion-related reaction	19 (5.9)	21 (6.4)
Hypersensitivity	44 (13.6)	51 (15.6)
Infections	87 (26.9)	73 (22.4)
Tuberculosis	1 (0.3)	1 (0.3)
(PT) Tuberculosis	0	1 (0.3)
(PT) Latent tuberculosis	1 (0.3)	0
Pneumonia	3 (0.9)	3 (0.9)
(PT) Pneumonia	2 (0.6)	3 (0.9)
(PT) Pneumocystis jirovecii pneumonia	1 (0.3)	0
Neoplasms	1 (0.3)	2 (0.6)
Malignancies (PT Colon cancer)	1 (0.3)	1 (0.3)

Abbreviations: AE = adverse event; EU = European Union; n = number of subjects; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects included in the safety analysis set; PT = MedDRA (version 19.0) preferred term; TEAE = treatment-emergent AE; TP1 = Treatment Period 1.

Source: Module 5.3.5.1, CSR B5371002, Table 42, Page 134.

As seen in Table 34, TEAEs of special interest included infusion related reactions (IRR), hypersensitivity, infections (including TB and pneumonia), and malignancy (including lymphoma). Events occurring within the infection SOC were the most commonly reported events across both treatment arms [(26.9%) PF-06438179 and (22.4%) EU Approved Remicade]. No clinically meaningful differences in the reporting of IRRs, hypersensitivity, overall infections or malignancies were noted between the two treatment arms.

Table 35. All-Causality TEAEs of Special Interest- Safety Population B5371002-TP2			
Events of Special Interest	PF-06438179/ PF-06438179 N=280 n(%)	EU Approved Remicade/ EU Approved Remicade N=143 n(%)	EU Approved Remicade/ PF-06438179 N=143 n(%)
Infusion-related reaction	9 (3.2)	12 (8.4)	6 (4.2)
Hypersensitivity	20 (7.1)	13 (9.1)	10 (7.0)
Infections	46 (16.4)	21 (14.7)	19 (13.3)
Tuberculosis			
(PT) Latent tuberculosis	0	2 (1.4)	2 (1.4) ^a
Pneumonia			
(PT) Pneumonia	0	2 (1.4)	0
(PT) Pneumocystis jirovecii pneumonia	0	1 (0.7)	0
Neoplasms	1 (0.4)	1 (0.7)	2 (1.4)
Malignancies			
(PT) Colon cancer	0	1 (0.7)	0
(PT) Laryngeal squamous cell carcinoma	1 (0.4)	0	0
(PT) Ocular lymphoma	0	0	1 (0.7)

Abbreviations: AE = adverse event; n = number of subjects; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects included in the TP2 safety population; PT = MedDRA (version 19.1) preferred term; RD = risk difference; TEAE = treatment-emergent AE; TP2 = Treatment Period 2.

a. As the subjects had QuantiFERON®-TB test obtained prior to dosing at Week 30, they had been exposed only to infliximab-EU at the time of seroconversion.

Source: Module 5.3.5.1, CSR B5371002 Supplemental Study Report Week 54, Table 29, Page 105.

Similar findings were reported in TP2, as described in Table 35. IRRs were reported slightly more frequently in the EU Approved Remicade/EU Approved Remicade treatment arm (n=12, 8.4%) compared to PF-06438179/PF-06438179 (n=9, 3.2%) and EU Approved Remicade/PF-06438179 (n=6, 4.2%) treatment arms. This imbalance may be, in part, related to the smaller sample size in the EU Approved Remicade/EU Approved Remicade treatment arm (n=143) compared to the PF-06438179/PF-06438179 treatment arm (n=280). Accordingly, a small change in the absolute number of events has a greater effect on the overall percentage of events. In addition, a further assessment of these events by severity and events resulting in discontinuation did not demonstrate clinically meaningful differences, as seen in Table 36 .

Table 36. All-Causality Treatment-Emergent IRRs- Safety Population B5371002-TP2			
	PF-06438179/ PF-06438179 N=280 n(%)	EU Approved Remicade/ EU Approved Remicade N=143 n(%)	EU Approved Remicade/ PF-06438179 N=143 n(%)
Infusion-related reaction	9 (3.2)	12 (8.4)	6 (4.2)
Subjects with SAEs	1 (0.4)	1 (0.7)	0
Subjects with Grade 3 AEs	2 (0.7)	1 (0.7)	1 (0.7)
Subjects with Grade 4 AEs	1 (0.4)	0	0
Subjects with Grade 5 AEs	0	0	0
Subjects discontinued from treatment due to AEs	6 (2.1)	2 (1.4)	2 (1.4)
Subjects discontinued from study due to AEs	5 (1.8)	1 (0.7)	1 (0.7)
Subjects with temporary discontinuation ^a due to AEs	3 (1.1)	7 (4.9)	4 (2.8)

Includes all data collected since the first infusion of study drug in TP2.
 AEs were graded in accordance with National Cancer Institute Common Terminology Criteria for AEs (CTCAE) Version 4.03. Grades 1-5 AEs are defined as mild, moderate, severe, life threatening AEs and death related to AE, respectively.
 MedDRA (version 19.1) coding dictionary was applied.
 Abbreviations: AE = adverse event; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects in the TP2 safety population; SAE = serious adverse event; TP2 = Treatment Period 2.
 a. PF-06438179 or infliximab-EU could be temporarily discontinued due to safety reasons and resumed as described in the protocol

Source: Module 5.3.5.1, CSR B5371002 Supplemental Study Report Week 54, Table 32, Page 112.

There were no IRR reported in the comparative PK study (B5371001).

Anaphylaxis Events According to Sampson et al. (TP1)

In addition to the TEAEs of special interest described above, events of anaphylaxis which specifically met criterion 1 according to Sampson et al.⁶ were also evaluated for TP1. A total of 10 cases were reported for 8 subjects (5 cases in the EU approved Remicade arm and 3 subjects in the PF-06438179 arm). One subject in each arm reported two cases on two separate occasions. Of the 10 reported cases, none were considered as serious (e.g, life-threatening, medically important or requiring hospitalization) by the Investigators, and all were reported with severity grades 1 to 3, with the majority classified as grade 1 to 2. There were no cases reported as an “anaphylactic reaction”, and no subject received epinephrine, fluid resuscitation, adrenergic agonists or vasopressors. There were no reported symptoms of end-organ dysfunction (e.g, shock, incontinence, collapse) in any subject.

⁶ Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006; 117(2):391-97

Study treatment for all 8 subjects was permanently discontinued and all 8 subjects received treatment for all or some of the events reported in the cases, consisting of corticosteroids (methylprednisolone, prednisolone, hydrocortisone, dexamethasone), antihistamines (chloropyramine, ebastine), calcium or a combination of these. In addition, all subjects were anti-drug antibody (ADA) positive at the date of their event.

Overall, anaphylaxis was a rare event and similar across treatment arms.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 37. All-causality TEAEs Occurring in $\geq 3\%$ Subjects – Safety Population B5371002-TP1		
SOC and Preferred Term (MedDRA version 19.0)	PF-06438179 N=323 n(%)	EU Approved Remicade N=326 n(%)
Any AEs	185 (57.3)	176 (54.0)
Blood and lymphatic system disorders	19 (5.9)	18 (5.5)
Anemia	7 (2.2)	10 (3.1)
Gastrointestinal disorders	41 (12.7)	36 (11.0)
Nausea	7 (2.2)	10 (3.1)
General disorders and administration site conditions	22 (6.8)	22 (6.7)
Pyrexia	3 (0.9)	10 (3.1)
Infections and infestations	86 (26.6)	72 (22.1)
Bronchitis	14 (4.3)	6 (1.8)
Nasopharyngitis	14 (4.3)	13 (4.0)
Upper respiratory tract infection	12 (3.7)	13 (4.0)
Injury, poisoning and procedural complications	36 (11.1)	36 (11.0)
Infusion-related reaction	19 (5.9)	21 (6.4)
Investigations	37 (11.5)	26 (8.0)
ALT increased	19 (5.9)	15 (4.6)
AST increased	14 (4.3)	11 (3.4)
Nervous system disorders	17 (5.3)	23 (7.1)
Headache	10 (3.1)	9 (2.8)
Skin and subcutaneous tissue disorders	38 (11.8)	41 (12.6)
Rash	8 (2.5)	10 (3.1)
Vascular disorders	20 (6.2)	23 (7.1)
Hypertension	14 (4.3)	11 (3.4)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects included in the safety analysis set; SOC = system organ class; TEAE = treatment-emergent AE; TP1 = Treatment Period 1.

Source: Module 5.3.5.1, CSR B5371002, Table 38, Page 131

As shown in Table 37, common adverse events occurring in $\geq 3\%$ of subjects by PT were generally balanced between the PF-06438179 and the EU Approved Remicade treatment arms. Events were most frequently reported in the Infections and Infestations SOC [(26.6%) PF-

06438179, (22.1%) EU approved Remicade]. The most frequently reported PTs were IRR [(5.9%) PF-06438179 and (6.4%) EU approved Remicade], ALT increased [(5.9%) PF-06438179 and (4.6%) EU approved Remicade] and nasopharyngitis [(4.3%) PF-06438179 and (4.0%) EU approved Remicade]. In addition, bronchitis events were reported more frequently in the PF-06438179 treatment arm compared to the EU approved Remicade (4.3% and 1.8%, respectively). However, as seen in Table 38, this trend did not persist in TP2 (bronchitis events were fairly balanced across the three treatment arms). No new safety signals were identified by SOC or PT.

Table 38. All-Causality TEAEs ≥1% - Safety Population B5371002-TP2			
SOC and PT (MedDRA version 19.1)	PF-06438179/ PF-06438179 N=280 n(%)	EU Approved Remicade/ EU Approved Remicade N=143 n(%)	EU Approved Remicade/ PF-06438179 N=143 n(%)
Any AEs	103 (36.8)	48 (33.6)	54 (37.8)
Blood and lymphatic system disorders	6 (2.1)	3 (2.1)	4 (2.8)
Anemia	4 (1.4)	2 (1.4)	2 (1.4)
Iron deficiency anemia	1 (0.4)	0	2 (1.4)
Gastrointestinal disorders	8 (2.9)	9 (6.3)	5 (3.5)
Large intestine polyp	0	2 (1.4)	0
Nausea	1 (0.4)	4 (2.8)	1 (0.7)
Vomiting	0	2 (1.4)	2 (1.4)
Infections and infestations	45 (16.1)	21 (14.7)	19 (13.3)
Bronchitis	3 (1.1)	3 (2.1)	2 (1.4)
Gastroenteritis	3 (1.1)	0	0
Latent tuberculosis	0	2 (1.4)	2 (1.4)
Nasopharyngitis	9 (3.2)	5 (3.5)	2 (1.4)
Pharyngitis	2 (0.7)	2 (1.4)	0
Pneumonia	0	2 (1.4)	0
Upper respiratory tract infection	6 (2.1)	2 (1.4)	3 (2.1)
Urinary tract infection	3 (1.1)	2 (1.4)	3 (2.1)
Viral infection	2 (0.7)	0	2 (1.4)
Injury, poisoning and procedural complications	18 (6.4)	16 (11.2)	9 (6.3)
Contusion	0	2 (1.4)	0
Fall	5 (1.8)	0	0
IRR	9 (3.2)	12 (8.4)	6 (4.2)
Investigations	10 (3.6)	4 (2.8)	2 (1.4)
ALT increased	1 (0.4)	2 (1.4)	0
AST increased	2 (0.7)	2 (1.4)	0
Metabolism and Nutrition disorders	3 (1.1)	4 (2.8)	1 (0.7)
Hyperglycemia	0	2 (1.4)	0
Musculoskeletal and connective tissue disorders	26 (9.3)	11 (7.7)	12 (8.4)
Arthralgia	0	1 (0.7)	3 (2.1)
Joint swelling	6 (2.1)	1 (0.7)	1 (0.7)

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Pain in extremity	1 (0.4)	0	2 (1.4)
RA	5 (1.8)	4 (2.8)	3 (2.1)
Spinal pain	1 (0.4)	2 (1.4)	0
Nervous system disorders	5 (1.8)	4 (2.8)	1 (0.7)
Headache	2 (0.7)	2 (1.4)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	6 (2.1)	11 (7.7)	4 (2.8)
Cough	2 (0.7)	2 (1.4)	1 (0.7)
Dyspnea	0	3 (2.1)	1 (0.7)
Skin and subcutaneous tissue disorders	13 (4.6)	7 (4.9)	10 (7.0)
Erythema	0	3 (2.1)	0
Pruritus	2 (0.7)	2 (1.4)	1 (0.7)
Rash	3 (1.1)	0	3 (2.1)
Vascular disorders	9 (3.2)	5 (3.5)	5 (3.5)
Flushing	0	0	3 (2.1)
Hypertension	4 (1.4)	3 (2.1)	2 (1.4)
Hypotension	4 (1.4)	1 (0.7)	0

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects included in the TP2 safety population; RA= rheumatoid arthritis; SOC = system organ class; TEAE = treatment-emergent AE; TP2 = Treatment Period 2.

Source: Module 5.3.5.1, CSR B5371002 Supplemental Study Report Week 54, Table 26, Page 99.

Similar results are displayed for TP2 in Table 38 for TEAS $\geq 1\%$. Once again, events were generally balanced between the PF-06438179/PF-06438179, EU Approved Remicade/EU Approved Remicade and the EU Approved Remicade/PF-06438179 treatment arms and the SOC with the highest percentage of subjects with TEAEs was Infections and Infestations [(16.1%) PF-06438179/PF-06438179, (14.7%) EU Approved Remicade/EU Approved Remicade, and (13.3%) EU Approved Remicade /PF-06438179].

Discussion of the slight imbalance in IRR is discussed for TP2 in section 7.3.5 Submission Specific Primary Safety Concerns.

Table 39. Treatment-Emergent Adverse Events (All Causality) Occurring in ≥5% Safety Population- B5371001			
SOC and PT	PF-06438179 N=49 n(%)	EU Approved Remicade N=48 n(%)	US Licensed Remicade N=49 n(%)
Nervous system disorders	3 (6.1)	3 (6.3)	4 (8.2)
Headache	3 (6.1)	3 (6.3)	4 (8.2)
Blood and lymphatic system disorders	0	3 (6.3)	2 (4.1)
Granulocytopenia	0	3 (6.3)	2 (4.1)
Infections and infestations	3 (6.1)	2 (4.2)	0
Upper respiratory tract infection	3 (6.1)	2 (4.2)	0
Investigations	0	0	3 (6.1)
AST increased	0	0	3 (6.1)
Gastrointestinal disorders	0	3 (6.3)	0
Constipation	0	3 (6.3)	0

Subjects were counted only once per treatment in each row.
 Included all data collected since the first infusion of study drug.
 Abbreviations: AE = adverse event; AST = aspartate aminotransferase; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; US = United States.

Source: Module 5.3.3.1, CSR B5371001, Table 19, Page 62.

As seen in Table 39, the most common AE reported in the comparative PK study, B5371001, was headache, which was experienced by 3 subjects each in the PF-06438179 and EU approved Remicade treatment groups, and 4 subjects in the US licensed Remicade treatment group (6.1%, 6.3% and 8.2%, respectively). Small differences were noted between the treatment groups for other AEs, however, given the small sample size, these differences were not considered to be clinically meaningful.

7.4.2 Laboratory Findings

Overall, review of the clinical laboratory data did not reveal any clinically significant differences.

7.4.3 Vital Signs

Across studies, no clinically meaningful changes in vital sign parameters (weight, temperature, respiratory rate, pulse rate, systolic and diastolic blood pressures) were observed.

7.4.4 Electrocardiograms (ECGs)

Twelve-lead ECGs were performed at baseline and end of treatment. Clinically significant changes were recorded as AEs and evaluated further, as clinically warranted. No new cardiac safety signals were identified among the common adverse events.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies conducted as part of this BLA.

7.4.6 Immunogenicity

Assessment of immunogenicity is generally expected as part of the biosimilar development program. See FDA guidance, “Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product”.

Therefore, an application submitted under section 351(k) of the PHS Act contains, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from “a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.”⁷ Immune responses against therapeutic biological products are a concern because they can negatively impact the drug’s pharmacokinetics, safety, and efficacy. Unwanted immune reactions to therapeutic biological products are mostly caused by antibodies against the drug (antidrug antibodies; ADA). Therefore, immunogenicity assessment for therapeutic biological products focuses on measuring ADA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of ADA (including neutralizing antibodies, NAb) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Infliximab is known to be immunogenic and anti-infliximab antibodies have implications on both safety and efficacy.⁸ Immunogenicity was prospectively evaluated in the PF-06438179 development program; the comparative assessment of immunogenicity was one of the objectives of both the phase 1 comparative PK study (B5371001) in healthy subjects and the phase 3 comparative clinical study (B5371002) in RA patients. The incidence of ADAs (anti-drug antibodies) and Nabs (neutralizing antibodies) were the respective immunogenicity endpoints in these studies. Immunogenicity data will be reviewed in this section. For a discussion of the assays used to evaluate immunogenicity, please refer to OBP Review.

Immunogenicity Results

The determination of anti-drug antibodies (ADA) consisted of multi-tiered approach with sequential screening, confirmation, and characterization using validated assays.

⁷ Section 351(k)(2)(A)(i)(I) of the PHS Act.

⁸ FDA-approved Remicade labeling

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Serum samples were collected at pre-specified time points described in the study protocol to determine the presence of ADA, concurrent with serum samples for PK analysis. Serum samples for measurement of ADA were collected immediately prior to dose administration at Weeks 0, 2, 6, 14, 30, 38, 54, and 62; and anytime during study visit at Week 78 (End of Treatment) and any post-treatment follow-up.

ADA was assessed using validated assays and following a tiered approach of screening, confirmation, and titer determination. Samples confirmed to be positive for ADA were further tested for neutralizing activities using validated Nab assays.

Weeks 0-30 (TP1)

In the comparative clinical study, patients with moderate to severely active RA who have had an inadequate response to methotrexate therapy, 323 subjects were randomized to treatment with PF-06438179 and 326 subjects were randomized to EU approved Remicade, in combination with methotrexate. All subjects began their study treatment with an induction period, followed by a maintenance period. During the induction period subjects were treated with an intravenous infusion of PF-06438179 or EU approved Remicade at a dose of 3 mg/kg on Weeks 0, 2, and 6. This dose remained consistent for all subjects for a minimum of 3 doses (up to Week 14). The maintenance period began at Week 14 and subjects received maintenance PF-06438179 or EU approved Remicade infusions every 8 weeks. The dose was maintained at 3 mg/kg for subjects who achieved a minimum clinical response (20% improvement from baseline in both tender and swollen joint counts), or one-time escalated to 5 mg/kg per infusion for subjects who failed to achieve a minimum clinical response or lost clinical response.

Prior to infusion with study drug, pre-medication, including antihistamines, acetaminophen/paracetamol, and/or corticosteroids, could be administered at the investigator's discretion.

Weeks 30-54 (TP2)

Treatment Period 2 (TP2) began with the dosing on Week 30, when subjects initially assigned to the infliximab-EU study arm were re-randomized in a 1:1 ratio, with 50% of the EU approved Remicade arm switching to PF-06438179 and the other 50% remaining on EU approved Remicade. All subjects initially assigned PF-06438179 remained blindly assigned to continue on PF-06438179. Treatment continued in TP2 for another 24 weeks and ended with the completion of the Week 54 pre-dose assessments.

A summary of Anti-Drug Antibodies (ADA) and Neutralizing Antibodies (Nab) incidence is provided for TP1 in Table 40 and for TP2 in Table 41.

Table 40. Summary of Anti-Drug Antibodies (ADA) and Neutralizing Antibodies (NAb) Incidence – Safety Population B5371002-TP1			
Visit	Criteria	PF-06438179 N=323 n(%)	EU Approved Remicade N=326 n(%)
Week 0 (Baseline)	ADA positive	9 (2.8)	9 (2.8)
	NAb positive ^a	1 (11.1)	1 (11.1)
	NAb negative	8 (88.9)	8 (88.9)
	ADA negative	313 (96.9)	314 (96.3)
	ADA Not done	1 (0.3)	3 (0.9)
Week 2	ADA positive	10 (3.1)	8 (2.5)
	NAb positive ^a	3 (30.0)	3 (37.5)
	NAb negative	7 (70.0)	5 (62.5)
	ADA negative	308 (95.4)	315 (96.6)
	ADA Not done	5 (1.5)	3 (0.9)
Week 6	ADA positive	22 (6.8)	24 (7.4)
	NAb positive ^a	13 (59.1)	19 (79.2)
	NAb negative	8 (36.4)	5 (20.8)
	ADA negative	285 (88.2)	293 (89.9)
	ADA Not done	16 (5.0)	9 (2.8)
Week 14	ADA positive	96 (29.7)	100 (30.7)
	NAb positive ^a	73 (76.0)	78 (78.0)
	NAb negative	23 (24.0)	22 (22.0)
	ADA negative	206 (63.8)	214 (65.6)
	ADA Not done	21 (6.5)	12 (3.7)
Week 30	ADA positive	136 (42.1)	144 (44.2)
	NAb positive ^a	105 (77.2)	120 (83.3)
	NAb negative	31 (22.8)	23 (16.0)
	ADA negative	146 (45.2)	147 (45.1)
	ADA Not done	41 (12.7)	35 (10.7)
Overall	ADA positive	157 (48.6)	167 (51.2)
	NAb positive ^a	124 (79.0)	143 (85.6)
	NAb negative	33 (21.0)	23 (13.8)
	ADA negative	163 (50.5)	158 (48.5)
	ADA Not done	3 (0.9)	1 (0.3)

Not done: Samples were not collected or collected but not analyzed.
 ADA positive and negative test results were defined as ADA titer ≥ 1.30 and < 1.30 , respectively. NAb positive and negative results were defined as NAb titer ≥ 0.70 and < 0.70 , respectively. Overall, a positive subject was defined as having at least 1 post-dose sample tested positive during TP1, regardless of the pre-dose ADA status.
 Abbreviations: EU = European Union; n = number of subjects; N = number of subjects included in the safety analysis set; TP1 = Treatment Period 1.
 a. NAb positive and NAb negative incidences are expressed as percent of ADA positive subjects.

Source: Module 5.3.5.1, CSR B5371002, Table 32, Page 124.

As described in Table 40, the incidences of ADA in PF-06438179 and EU approved Remicade arms were generally similar overall (48.6% vs. 51.2%, respectively) and at each time point during TP1. The proportion of ADA positive subjects at baseline, prior to dosing, was 2.8% for both treatment arms. Of the ADA positive subjects overall, a majority of these subjects also tested positive for Nab [79.0%, PF-06438179 and 85.6% EU approved Remicade]. The

incidence of ADA and NAb were generally balanced between treatment arms over time. The small differences noted were not considered to be clinically significant.

Table 41. Summary of Anti-Drug Antibodies (ADA) and Neutralizing Antibodies (NAb) Incidence – Safety Population B5371002-TP2				
Visit	Criteria	PF-06438179/ PF-06438179 N=280 n(%)	EU Approved Remicade/ EU Approved Remicade N=143 n(%)	EU Approved Remicade/ PF-06438179 N=143 n(%)
Week 30 (N2=566)	ADA positive	132 (47.1)	77 (53.8)	65 (45.5)
	NAb positive	102 (77.3)	65 (84.4)	54 (83.1)
	NAb negative	30 (22.7)	11 (14.3)	11 (16.9)
	NAb Not done	0	1 (1.3)	0
	ADA negative	147 (52.5)	66 (46.2)	78 (54.5)
	ADA Not done	1 (0.4)	0	0
Week 38 (N2=543)	ADA positive	129 (46.1)	77 (53.8)	68 (47.6)
	NAb positive	104 (80.6)	63 (81.8)	52 (76.5)
	NAb negative	24 (18.6)	14 (18.2)	16 (23.5)
	NAb Not done	1 (0.8)	0	0
	ADA negative	143 (51.1)	59 (41.3)	67 (46.9)
	ADA Not done	8 (2.9)	7 (4.9)	8 (5.6)
Week 54 (N2=500)	ADA positive	111 (39.6)	60 (42.0)	67 (46.9)
	NAb positive	85 (76.6)	45 (75.0)	49 (73.1)
	NAb negative	26 (23.4)	15 (25.0)	18 (26.9)
	NAb Not done	0	0	0
	ADA negative	138 (49.3)	65 (45.5)	59 (41.3)
	ADA Not done	31 (11.1)	18 (12.6)	17 (11.9)
EOT/ET (N2=43)	ADA positive	11 (3.9)	9 (6.3)	6 (4.2)
	NAb positive	11 (100.0)	9 (100.0)	3 (50.0)
	NAb negative	0	0	3 (50.0)
	NAb Not done	0	0	0
	ADA negative	6 (2.1)	5 (3.5)	6 (4.2)
	ADA Not done	263 (93.9)	129 (90.2)	131 (91.6)
Overall TP2 (N2=561)	ADA positive	146 (52.1)	86 (60.1)	83 (58.0)
	NAb positive	118 (80.8)	73 (84.9)	65 (78.3)
	NAb negative	28 (19.2)	13 (15.1)	18 (21.7)
	NAb Not done	0	0	0
	ADA negative	133 (47.5)	55 (38.5)	58 (40.6)
	ADA Not done	1 (0.4)	2 (1.4)	2 (1.4)
Overall TP1+TP2 (N2=566)	ADA positive	156 (55.7)	88 (61.5)	89 (62.2)
	NAb positive	127 (81.4)	82 (93.2)	73 (82.0)
	NAb negative	29 (18.6)	6 (6.8)	16 (18.0)
	NAb Not done	0	0	0
	ADA negative	124 (44.3)	55 (38.5)	54 (37.8)
	ADA Not done	0	0	0

NAb positive and NAb negative incidences are expressed as percent of ADA positive subjects.
Overall TP1 + TP2 includes pooled data from TP1 and TP2 for the TP2 safety population; overall TP2 includes data from Week 38, Week 54, EOT/ET and unplanned visits in TP2.
Not done: Samples were not collected or collected but not analyzed.
ADA positive and negative test results were defined as ADA titer ≥ 1.30 and < 1.30 , respectively. NAb positive and negative results were defined as NAb titer ≥ 0.70 and < 0.70 , respectively.
For overall categories, a positive subject was defined as one having at least 1 post-dose sample that tested positive during the specified data collection period.

Abbreviations: ADA = anti-drug antibody; EOT = end of treatment; ET = early termination; n = number of subjects; N1 = number of subjects included in the TP2 safety population; N2 = number of subjects evaluated at each visit; NAb = neutralizing antibody; TP1 = Treatment Period 1; TP2 = Treatment Period 2.

a. ADA/NAb samples were collected pre-dose at study visits.

Source: Module 5.3.5.1, CSR B5371002, Table 19, Page 88.

As described in Table 41, the Week 30 pre-dose incidences of positive ADA test results in the TP2 safety population were 47.1%, 53.8%, and 45.5% in the PF-06438179/PF-06438179, EU Approved Remicade/EU Approved Remicade, and EU Approved Remicade/PF-06438179 treatment arms, respectively. The overall number of subjects with a positive ADA increased over TP2 for all treatment groups. The overall incidence of immunogenicity in TP2 was comparable among the 3 treatment groups: 52.1%, 60.1%, and 58%, in the PF-06438179/PF-06438179, EU Approved Remicade/EU Approved Remicade, and EU Approved Remicade/PF-06438179 treatment arms, respectively. Among the subjects with a positive ADA test during TP2, a majority tested positive for Nab in all three treatment groups: 80.8%, 84.9%, and 78.3%, in the PF-06438179/PF-06438179, EU-Remicade/EU-Remicade, and EU-Remicade/PF-06438179 treatment arms, respectively.

IRRs in ADA Positive Subjects (TP1)

All-causality IRRs that occurred on or after the date a subject first tested positive for ADA, including subjects with a positive baseline pre-dose ADA if the subject remained ADA positive after dosing, are summarized in Table 42.

Table 42. All-Causality Treatment-Emergent Infusion-Related Reactions on or After the Date of Testing Positive for Anti-Drug Antibodies - B5371002-TP1

	PF-06438179 n(%)	EU Approved Remicade n(%)
Subjects with positive post-dose ADA ^a	157	167
Number of AEs	11	14
Subjects with AEs	11 (7.0)	14 (8.4)
Subjects with SAEs	0	0
Subjects with Grade 3 AEs	4 (2.5)	2 (1.2)
Subjects with Grade 4 AEs	0	0
Subjects with Grade 5 AEs	0	0
Subjects discontinued from treatment due to AEs	4 (2.5)	5 (3.0)
Subjects discontinued from study due to AEs	3 (1.9)	3 (1.8)
Subjects with temporary discontinuation ^b due to AEs	3 (1.9)	8 (4.8)

AEs were graded in accordance with National Cancer Institute Common Terminology Criteria for AEs (CTCAE) Version 4.03. Grades 1-5 AEs are defined as mild, moderate, severe, life threatening AEs and death related to AE, respectively.

MedDRA (version 19.0) coding dictionary was applied.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; SAE = serious adverse event; TP1 = Treatment Period 1.

a. A positive subject was defined as having at least 1 post-dose sample tested positive during TP1, regardless of the baseline pre-dose ADA status.

b. PF-06438179 or infliximab-EU could be temporarily discontinued due to safety reasons and resumed as described in the protocol.

Source: Module 5.3.5.1, CSR B5371002, Table 45, Page 140.

IRRs among ADA positive subjects were generally balanced across the two treatment arms [(7.0%, PF-06438179) and (8.4%, EU approved Remicade)]. Grade 3 IRRs were slightly more frequent in the PF-06438179 treatment arm (2.5%) compared to the EU approved Remicade treatment arm (1.2%), however these differences were small. Discontinuations from treatment and temporary discontinuations due to IRR AEs were slightly more frequent in the EU approved Remicade treatment arm as compared to the PF-06438179 treatment arm. Overall, the IRR data does not indicate a new safety signal for PF-06438179.

IRRs in ADA Positive Subjects (TP2)

All-causality IRRs in TP2 that occurred on or after the date a subject first tested positive for ADA are summarized in Table 43.

Table 43. All-Causality Treatment-Emergent Infusion-Related Reactions on or After the Date of Testing Positive for Anti-Drug Antibodies- B5371002-TP2

	PF-06438179/ PF-06438179 N=280 n(%)	EU Approved Remicade/ EU Approved Remicade N=143 n(%)	EU Approved Remicade/ PF-06438179 N=143 n(%)
Subjects with positive post-dose ADA ^a	156	88	89
Number of AEs	9	11	6
Subjects with AEs	9 (5.8)	11 (12.5)	6 (6.7)
ADA positive subset 1 ^b	9 (5.8)	10 (11.4)	6 (6.7)
ADA positive subset 2 ^b	0	1 (1.1)	0
Subjects with SAEs	1 (0.6)	1 (1.1)	0
Subjects with Grade 3 AEs	2 (1.3)	1 (1.1)	1 (1.1)
Subjects with Grade 4 AEs	1 (0.6)	0	0
Subjects with Grade 5 AEs	0	0	0
Subjects discontinued from treatment due to AEs	6 (3.8)	2 (2.3)	2 (2.2)
Subjects discontinued from study due to AEs	5 (3.2)	1 (1.1)	1 (1.1)
Subjects with temporary discontinuation ^c due to AEs	3 (1.9)	7 (8.0)	4 (4.5)

AEs were graded in accordance with National Cancer Institute Common Terminology Criteria for AEs (CTCAE) Version 4.03. Grades 1-5 AEs are defined as mild, moderate, severe, life threatening AEs and death related to AE, respectively.

MedDRA (version 19.1) coding dictionary was applied.

Abbreviations: ADA = Anti-drug antibody; AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects in the TP2 safety population; SAE = serious adverse event; TP2 = Treatment Period 2.

a. A positive subject was defined as having at least 1 post-dose sample tested positive during TP1 or TP2.

b. ADA positive subsets 1 and 2 were defined as subjects with first post-dose positive ADA identified prior to and after re-randomization to TP2, respectively.

c. PF-06438179 or infliximab-EU could be temporarily discontinued due to safety reasons and resumed as described in the protocol.

Source: Module 5.3.5.1, CSR B5371002 Supplemental Study Report Week 54, Table 33, Page 114.

Grade 3 IRRs were fairly balanced across the three treatment groups (1.1% to 1.3%). Most of the IRRs reported during TP2 occurred in patients who developed ADA during TP1. There was one reported Grade 4 IRR, which occurred in the PF-06438179/PF-06438179 treatment arm.

The percentage of subjects experiencing an IRR AE and the percentage of subjects with temporary discontinuation due to an AE was highest in the EU Approved Remicade/EU Approved Remicade treatment arm. While these differences were noted, permanent study discontinuation and \geq Grade 3 adverse events were generally balanced across treatment arms. Some of the other sub categories demonstrated slight imbalances, however, these differences were small, and not clinically meaningful.

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. Once again, a review of the IRR data does not indicate a new safety signal for PF-06438179.

Hypersensitivity AEs in ADA Positive Subjects (TP1)

All-causality treatment-emergent hypersensitivity AEs that occurred on or after the date a subject first tested positive for ADA antibodies, including subjects with a positive baseline pre-dose ADA if the subject remained ADA positive after dosing, are summarized in Table 44.

Table 44. All-Causality Treatment-Emergent Hypersensitivity AEs on or After the Date of Testing Positive for Anti-Drug Antibodies- B5371002-TP1		
	PF-06438179 N=323 n(%)	EU Approved Remicade N=326 n(%)
Subjects with positive post-dose ADA ^a	157	167
Number of AEs	14	25
Subjects with AEs	11 (7.0)	19 (11.4)
Subjects with SAEs	0	0
Subjects with Grade 3 AEs	3 (1.9)	2 (1.2)
Subjects with Grade 4 AEs	0	0
Subjects with Grade 5 AEs	0	0
Subjects discontinued from treatment due to AEs	5 (3.2)	5 (3.0)
Subjects discontinued from study due to AEs	3 (1.9)	2 (1.2)
Subjects with temporary discontinuation ^b due to AEs	2 (1.3)	6 (3.6)

AEs were graded in accordance with National Cancer Institute Common Terminology Criteria for AEs (CTCAE) Version 4.03. Grades 1-5 AEs are defined as mild, moderate, severe, life threatening AEs and death related to AE, respectively.
 MedDRA (version 19.0) coding dictionary was applied.
 Abbreviations: ADA = anti-drug antibody; AE = adverse event; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; SAE = serious adverse event; TP1 = Treatment Period 1.
 a. A positive subject was defined as having at least 1 post-dose sample tested positive during TP1, regardless of the baseline pre-dose ADA status.
 b. PF-06438179 or infliximab-EU could be temporarily discontinued due to safety reasons and resumed as described in the protocol.

Source: Module 5.3.5.1, CSR B5371002, Table 47, Page 142.

The percentage of subjects experiencing hypersensitivity AEs (7% vs. 11.4%) and temporary discontinuation due to hypersensitivity AEs (1.3% vs. 3.6%) was slightly higher in the EU Approved Remicade treatment arm as compared to the PF-06438179 treatment arm. While the percentage of subjects experiencing a Grade 3 AE was slightly higher in the PF-06438179 treatment arm (1.9%) as compared with EU approved Remicade (1.2%), no Grade 4-5 AEs or SAEs were reported. Overall, these differences were small and not considered to be clinically meaningful.

Hypersensitivity AEs in ADA Positive Subjects (TP2)

All-causality treatment-emergent hypersensitivity AEs in TP2 that occurred on or after the date a subject first tested positive for ADA are summarized in Table 45.

Table 45. All-Causality Treatment-Emergent Hypersensitivity on or After the Date of Testing Positive for Anti-Drug Antibodies - B5371002-TP2

	PF-06438179/ PF-06438179 N=280 n(%)	EU Approved Remicade/ EU Approved Remicade N=143 n(%)	EU Approved Remicade/ PF-06438179 N=143 n(%)
Subjects with positive post-dose ADA ^a	156	88	89
Number of AEs	14	17	12
Subjects with AEs	11 (7.1)	13 (14.8)	8 (9.0)
ADA positive subset 1	11 (7.1)	13 (14.8)	8 (9.0)
ADA positive subset 2	0	0	0
Subjects with SAEs	1 (0.6)	1 (1.1)	0
Subjects with Grade 3 AEs	2 (1.3)	1 (1.1)	1 (1.1)
Subjects with Grade 4 AEs	1 (0.6)	0	0
Subjects with Grade 5 AEs	0	0	0
Subjects discontinued from treatment due to AEs	6 (3.8)	1 (1.1)	2 (2.2)
Subjects discontinued from study due to AEs	4 (2.6)	1 (1.1)	1 (1.1)
Subjects with temporary discontinuation ^b due to AEs	3 (1.9)	6 (6.8)	4 (4.5)

AEs were graded in accordance with National Cancer Institute Common Terminology Criteria for AEs (CTCAE) Version 4.03. Grades 1-5 AEs are defined as mild, moderate, severe, life threatening AEs and death related to AE, respectively.

MedDRA (version 19.1) coding dictionary was applied.

Abbreviations: ADA = Anti-drug antibody; AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; N = number of subjects in the TP2 safety population; SAE = serious adverse event; TP2 = Treatment Period 2.

a. A positive subject was defined as having at least 1 post-dose sample tested positive during TP1 or TP2.

b. PF-06438179 or infliximab-EU could be temporarily discontinued due to safety reasons and resumed as described in the protocol

Source: Module 5.3.5.1, CSR B5371002 Supplemental Study Report Week 54, Table 35, Page 117.

The percentage of subjects reporting a hypersensitivity AE was higher in the EU Approved Remicade/EU Approved Remicade treatment arm (14.8%) as compared with PF-06438179/PF-06438179 (7.1%) and EU approved Remicade/PF-06438179 (9.0%) treatment arms. Similar to the findings noted for IRRs in TP2 (Table 43), the percentage of ADA positive subjects experiencing a hypersensitivity AE was greater in TP1 as compared to TP2. One hypersensitivity SAE was reported in both the PF-06438179/PF-06438179 and the EU Approved Remicade/ EU Approved Remicade treatment arms; one subject in the PF-06438179/PF-06438179 treatment arm reported a Grade 4 hypersensitivity AE. The data do not indicate an increase in hypersensitivity events with extended exposure to PF-06438179 during TP2, nor do they indicate a significant increase in hypersensitivity events after switching treatment from EU-Remicade to PF-06438179.

The percentage of subjects experiencing \geq Grade 3 and events leading to permanent discontinuation from the study and or study treatment were fairly balanced across the three

treatment arms. The imbalances noted for milder events were not considered to be clinically meaningful.

While the percentage of hypersensitivity AEs was slightly higher in the EU Approved Remicade/EU Approved Remicade treatment arm, the experience of more severe hypersensitivity events (\geq Grade 3 and events leading to permanent discontinuation from the study and or study treatment) were fairly balanced across the three treatment arms. The imbalances noted for milder events were not considered to be clinically meaningful.

ACR20 Response in ADA Positive Subjects (TP1)

In general, the ACR20 response rate at Weeks 14 was higher in the ADA negative and Nab negative subjects compared to the ADA positive and NAb positive subjects. Importantly, the Week 14 ACR20 responses were similar between the PF-06438179 and EU approved Remicade treatment arms, when analyzed by ADA and Nab status.

- Week 14 ACR20 response rates were 51.0% and 49.5% for the PF-06438179 and EU approved Remicade ADA positive subgroups, respectively, and 69.1% and 71.2% for the PF-06438179 and EU approved Remicade ADA negative subgroups, respectively.
- Week 14 ACR20 response rates were 50.0% and 45.7% for the PF-06438179 and EU approved Remicade NAb positive subgroups, respectively, and 67.5% and 70.5% for the PF-06438179 and EU approved Remicade NAb negative subgroups, respectively.

The Week 30 ACR20 response rate was also similar between the 2 treatment arms regardless of ADA and NAb status (PF-06438179 vs. EU approved Remicade):

- ADA Positive: 58% vs. 56.3%
- ADA Negative: 65% vs. 72.8%
- Nab Positive: 55.7% vs. 54.6%
- Nab Negative: 65.3% vs. 72.4%

Pharmacokinetic and Pharmacodynamic effects in ADA Positive Subjects (TP1)

As expected, the concentrations of serum PF-06438179 and EU approved Remicade were lower in ADA positive subjects compared to ADA negative subjects. However, the serum concentrations of PF-06438179 and EU approved Remicade were similar when analyzed by ADA status.

Pharmacokinetic and Pharmacodynamic effects in ADA Positive Subjects (TP2)

The impact of ADA on PK in ADA positive subjects was generally comparable among the 3 treatment groups. As expected, the serum drug trough concentrations were lower in ADA positive subjects compared to ADA negative subjects.

Study B5371001

The comparative PK study was a double-blind, randomized study to compare the PK and assess the safety of single dose PF-06438179, US licensed Remicade and EU approved Remicade in healthy volunteers.

Subjects were randomized in a 1:1:1 ratio to receive PF-06438179, US licensed Remicade, or EU approved Remicade. All treatments were administered intravenously at a dose of 10 mg/kg over a period of not less than 2 hours using a calibrated infusion pump. In the event that there was an infusion interruption, the entire duration of drug infusion, from the initial start of infusion to the completion of infusion, was required not to exceed 4 hours.

Table 46 summarizes the ADA results by treatment group.

Table 46. Summary of Anti-Drug Antibodies Results by Treatment Groups – Safety Population B5371001			
	PF-06438179 N=49	EU Approved Remicade N=48	US licensed Remicade N=49
ADA at baseline (Day 1 pre-dose)			
Number of Subjects tested positive on Day 1	0	0	0
ADA post dose			
Number (%) of subjects tested positive through Day 57	2/38 ^a (5.3)	0/39 ^a (0)	3/41 ^a (7.3)
Number (%) of subjects tested positive through Day 85	6/37 ^a (16.2)	14/43 ^a (32.6)	11/39 ^a (28.2)
Abbreviations: ADA = anti-drug antibodies; EU = European Union; US = United States. a. Indicated number of subjects who completed the ADA assessment.			
Source: Module 5.3.3.1, CSR B5371001, Table 16, Page 58.			

No subject, across the three treatment groups, tested positive for ADA at baseline. Two (5.3%), 0 (0%), and 3 (7.3%) subjects in the PF-06438179, EU Approved Remicade and US licensed Remicade treatment groups, respectively, had at least 1 sample that tested positive through Day 57, and 6 (16.2%), 14 (32.6%) and 11 (28.2%) subjects, respectively, tested positive for ADA through Day 85. While the Day 57 and Day 85 ADA results for EU Approved Remicade were noticeably different from the other two treatment arms, results from this single dose healthy volunteer study is less generalizable than the comparative clinical study, conducted in RA patients, to the intended target population. More importantly, the small number of subjects in each treatment arm can magnify the small numeric imbalances. Accordingly, these differences noted in the comparative PK study were not felt to be clinically meaningful in the context of the overall assessment of immunogenicity.

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The samples that tested positive for ADA were further tested for NAb. Of the 31 subjects who tested positive for ADA post-dose, a majority (n=26) of these subjects also tested positive for NAb (5/6: PF-06438179, 12/14: EU Approved Remicade treatment group, 9/11: US licensed Remicade treatment group).

Clinical Conclusions about Immunogenicity

As noted above, small numerical differences in ADA formation were seen between PF-06438179, EU Approved Remicade and US licensed Remicade. In evaluating the significance of the imbalance seen I considered the following:

- The immunogenicity impacted PK similarly between the products.
- The differences between the PF-06438179 and EU-approved Remicade in Study B5371002 is small and did not increase differently across treatment groups
- ADA formation impacted safety and efficacy outcomes similarly between PF-06438179 and EU approved Remicade treated patients in Study B5371001
- Importantly, the ADA rates did not increase differentially between patients who underwent a single transition at Week 54 from EU approved Remicade to PF-06438179 as compared with those who continued EU approved Remicade or PF-06438179.

Based on these considerations, the immunogenicity differences observed in PF-06438179 clinical program, do not represent clinically meaningful differences and do not preclude a demonstration of biosimilarity between PF-06438179 and US licensed Remicade.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

See sections 7.3 Major Safety Results and 7.4.1 Common Adverse Events for descriptions of adverse events occurring in TP1 (through week 30) versus TP2 (through week 54).

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

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7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Malignancies, including lymphoma, have been identified as potential risk with US licensed Remicade and other TNF-inhibitors as described in the Warnings and Precautions section of the US licensed Remicade's package insert. The incidence and types of these malignancies is expected for the study population and treatment.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

7.7.1 120 Day Safety Update

The Applicant submitted a supplemental clinical study report on June 13, 2017 for TP2 (through Week 54) to Study B5371002 in the 120-day safety update. The additional data was included in this BLA review and is described in the relevant sections.

7.7.2 Long-Term Safety

The long-term safety was assessed in the review of the data for TP2 (through Week 54) in Study B5371002. Results for TP2 are discussed in the relevant sections throughout this BLA review. Overall, no new safety signal was identified.

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8 Postmarket Experience

The Applicant has not submitted any postmarketing data for PF-06438179. At the time of the 120-day safety update (June 2017), there were no ongoing post marketing studies.

9 Appendices

9.1 Literature Review/References

FDA Guidance: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

FDA Guidance for Industry: “*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.*”

FDA Guidance for Industry “*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.*”

Sampson HA et al., Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium *J Allergy Clin Immunol.* 2006 Feb;117(2):391-7

USPI Remicade (infliximab), October 2015

USPI Renflexis (infliximab-abda), April 2017

9.2 Labeling Recommendations

Labeling review is ongoing at the time of this review. Key considerations include updating the label to consistently reflect the currently approved Remicade and Renflexis labeling.

9.3 Advisory Committee Meeting

As this is a biosimilar to Remicade, the risk-benefit assessment of its use is well-established; in addition, other biosimilar products to Remicade have been approved. Therefore, an advisory committee was neither convened, nor required, for this application.

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/s/

ERIKA N TORJUSEN
11/20/2017

BANU A KARIMI SHAH
11/20/2017