

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761072Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

BLA	761072
Submission Date	02/13/2017
Proposed Brand Name	Ixifi
Nonproprietary Name	infliximab-qbtx
Applicant	Pfizer Inc
Submission Type; Code	351(k); standard review
Formulation; Strength(s)	Lyophilized powder for intravenous infusion; 100 mg/vial
Proposed Indications	Rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), plaque psoriasis (Ps), ulcerative colitis (UC), Crohn’s disease (CD), pediatric CD
Proposed Dosage Regimens	RA: 3-10 mg/kg at 0, 2, 6 weeks, then every 8 weeks. AS: 5 mg/kg at 0, 2, 6 weeks, then every 6 weeks. Ps, PA, UC, CD, Pediatric CD: 5 mg/kg at 0, 2, 6 weeks, then every 8 weeks.
Clinical Pharmacology Reviewer	Manuela L. T. Grimstein, M.Sc., Ph.D.
Clinical Pharmacology Team Leader	Anshu Marathe, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products

TABLE OF CONTENTS

1. Executive Summary	3
1.1 Recommendations	3
1.2 Phase IV Commitments	3
1.3 Summary of Clinical Pharmacology Findings	3
2. Question Based Review.....	4
2.1 General Attributes	4
2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?	4
2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?	5
2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?	6
2.1.4 What are the proposed dosages and routes of administration?	6
2.2 General Clinical Pharmacology	6
2.2.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?	6
2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical	

pharmacology studies?	8
2.2.3 What are the PK characteristics of the drug?	8
2.3 Intrinsic Factors	12
2.3.1 Immunogenicity.....	12
2.4 General Biopharmaceutics.....	17
2.4.1 What is the <i>in vivo</i> relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?	17
2.5 Analytical Section.....	17
2.5.1 What are the analytical methods used to measure PF-06438179 or Remicade in serum?	17
2.5.2 For all moieties measured, is free, bound, or total measured?	20
2.5.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?	20
2.5.4 What is the sample stability under conditions used in the study?	20
2.5.5 What is the result for the re-analysis of the incurred samples?	21
2.5.6 What are the findings from OSIS inspection?.....	21
2.5.7 What bioanalytical methods are used to assess the immunogenicity?	21
3. Labeling Recommendations.....	21

LIST OF TABLES AND FIGURES

Table 1: Summary Results of the Comparison of the Pharmacokinetic Parameters between Test and References Products (Study B5371001)	4
Table 2: Composition of PF-06438179 Drug Product, 100 mg/vial.....	5
Table 3: Proposed Dosage and Routes of Administration for PF-06438179.....	6
Table 4: Listing of Clinical Studies	7
Table 5: Geometric Means, Ratios of Geometric Means and 90% Confidence Intervals for the Comparison of the PK Parameters between Test and References Products (Study B5371001)	9
Table 6: Median (5 th -95 th percentile) Value of Serum Concentrations of PF-06438179 and EU-approved Remicade (Study B5371002).....	11
Table 7: Inter-subject Variability of Infliximab Exposure	11
Table 8: Incidence of Anti-Drug Antibody (ADA) in the Clinical Studies B5371001 and B5371002 by Visit and Treatment Group (PF-06438179, EU-approved Remicade, US-licensed Remicade).....	13
Table 9: Median (5 th -95 th percentile) Value of Serum Concentrations of PF-06438179 and EU-approved Remicade by Anti-Drug Antibody (ADA) Status (Study B5371002)	15
Table 10: Incidence of Neutralizing Antibody (NAb) in the Clinical Studies B5371001 and B5371002 by Visit and Treatment Group (PF-06438179, EU-approved Remicade, US-licensed Remicade).....	16
Table 11: Subgroup Analysis of ACR 20 Response Rate at Week 14 in Patients with RA (Study B5371002).....	17
Table 12: Validation Summary for Remicade and PF-06438179 Analytical PK Method	18
Figure 1: Mean Serum Drug Concentration-time Profiles following a Single 10 mg/kg IV Dose of PF-06438179 (Infliximab-Pfizer), EU-approved Remicade (Infliximab-EU), or US-licensed Remicade (Infliximab-US) in Healthy Subjects (Study B5371001).....	9
Figure 2: Comparison of Anti-Drug Antibody (ADA) Titers versus Time between PF-06438179 and EU-approved Remicade in ADA-positive Subjects.....	14

1. Executive Summary

Pfizer submitted a Biologic License Application (BLA) for PF-06438179, a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds to human tumor necrosis factor alpha (TNF α), under Section 351(k) of the Public Health Service Act (42 U.S.C. 262). The applicant is seeking approval for PF-06438179 as a biosimilar to US-licensed Remicade (BLA 103772) and licensure for the following indications currently approved for US-licensed Remicade: Rheumatoid Arthritis (RA), Crohn's Disease (CD), pediatric CD, Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Psoriatic Arthritis (PA), and Ankylosing Spondylitis (AS). PF-06438179 drug product is supplied as a sterile, white, lyophilized powder for intravenous infusion (100 mg/vial).

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

PK similarity has been demonstrated between PF-06438179 and US-licensed Remicade. The clinical pharmacology results add to the totality of evidence to support a demonstration of biosimilarity of PF-06438179 and US-licensed Remicade.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that PK similarity has been demonstrated between PF-06438179 and US-licensed Remicade, and the PK results support a demonstration of no clinically meaningful differences between PF-06438179 and US-licensed Remicade.

Labeling Recommendations

Please refer to Section 3 – Detailed Labeling Recommendations.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

The clinical development for PF-06438179 included two clinical studies: a pivotal three-way PK similarity study of PF-06438179, EU-approved Remicade and US-licensed Remicade in healthy subjects (Study B5371001), and a comparative efficacy and safety of PF-06438179 and EU-approved Remicade in patients with active RA (Study B5371002).

In Study B5371001, the 90% CIs for the geometric mean ratios (GMR) of PF-06438179 to EU-approved Remicade, PF-06438179 to US-licensed Remicade, and EU-approved Remicade to US-licensed Remicade for the tested PK parameters (i.e., AUC_{inf}, AUC_{0-t}, and C_{max}) were all within the acceptance

interval of 80-125%, as presented in Table 1. These pairwise comparisons met the pre-specified criteria for PK similarity between PF-06438179, US-licensed Remicade and EU-approved Remicade. A scientific PK bridge was therefore established to support the relevance of the data generated using EU-approved Remicade in the comparative clinical efficacy study (B5371002). For details refer to section 2.2.3.

Table 1: Summary Results of the Comparison of the Pharmacokinetic Parameters between Test and References Products (Study B5371001)

Comparison	PK Parameter	Geometric Mean Ratio (%)	90% CI (%)
PF-06438179 vs. US-licensed Remicade	C _{max}	107.05	98.53 - 116.31
	AUC _{0-t}	107.67	98.85 - 117.28
	AUC _{inf}	107.06	97.49 - 117.58
PF-06438179 vs. EU-approved Remicade	C _{max}	110.03	101.32 - 119.49
	AUC _{0-t}	111.98	102.85 - 121.92
	AUC _{inf}	110.49	100.67 - 121.28
EU-approved Remicade vs. US-licensed Remicade	C _{max}	97.29	89.72 - 105.50
	AUC _{0-t}	96.15	88.45 - 104.53
	AUC _{inf}	96.90	88.42 - 106.18

In Study B5371002, serum peak and trough concentrations assessed at treatment period 1 (up to Week 30) were generally comparable between PF-06438179 and EU-approved Remicade treatment groups. The incidence of immunogenicity at Week 30 for PF-06438179 and EU-approved Remicade treatment groups were 42.1% and 44.2% respectively. For details refer to section 2.3.1.

Overall, the submitted clinical pharmacology data support a demonstration of PK similarity among PF-06438179, EU-approved Remicade and US-licensed Remicade.

2. Question Based Review

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

PF-06438179 is being developed as a proposed similar biological product to Remicade® (infliximab).

During the clinical development of PF-06438179, four key regulatory interactions with the Applicant occurred:

1. BPD Type 2 meeting held on December 18, 2013 discussed the proposed comparative efficacy study protocol B5371002;
2. BPD Type 3 meeting held on August 5, 2014 reviewed the adequacy of the functional, structural, and PK similarity data to support the comparative clinical development plan;

3. BPD Type 2 meeting held on July 08, 2016 discussed the extent of clinical data to be included in BLA, as well as CMC/Stability, blinding strategy and proposed statistical analyses for Study B5371002.
4. BPD Type 4 meeting held on November 22, 2016 discussed the format and content of the proposed BLA submission.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

PF-06438179 drug substance is a recombinant chimeric IgG1 kappa monoclonal antibody (mAb) composed of complementarity-determining regions derived from mouse anti-human tumor necrosis factor (TNF) alpha monoclonal antibody and framework, and constant regions derived from human IgG1. PF-06438179 is produced by a recombinant (b) (4) cell culture process. Structurally, PF-06438179 is characterized by two identical heavy (H) chains and two identical light (L) chains, covalently linked with four inter-chain disulfide bonds.

PF-06438179 drug product is formulated as a white, lyophilized powder in dosage strength of 100 mg/vial. The concentration of the drug product is 10 mg/mL after reconstitution with 10 mL of Sterile Water for Injection (SWFI). The formula contains (b) (4) succinate buffer, 2.5% sucrose and 0.005% polysorbate 80 at pH 6. The qualitative and quantitative composition of PF-06438179 Drug Product is listed in Table 2. Prior to use, the lyophilized drug product is reconstituted with SWFI to form a solution that is further diluted with sterile 0.9% sodium chloride for administration by intravenous infusion.

The drug product is supplied in a 15-mL glass vial sealed with a stopper and an aluminum seal with flip-off plastic cap. The drug product contains no preservative and is for single use only.

Table 2: Composition of PF-06438179 Drug Product, 100 mg/vial

Ingredient	Reference to Standard	Function	Unit Formula (mg/vial)
PF-06438179	In-house specification	Active ingredient	100
Disodium succinate hexahydrate	In-house specification	(b) (4)	12.1
Succinic acid	NF		0.6
Sucrose	Ph. Eur., NF, JP		250
Polysorbate 80	Ph. Eur., NF, JP		0.5

(Source: Module 3.2.P.1, Description and composition of the drug product, Table 3.2.P.1-1)

US-licensed Remicade, (Infliximab) is a chimeric IgG1κ monoclonal antibody specific for TNFα. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses. US-licensed Remicade is supplied as a sterile, white, lyophilized powder for intravenous use. Following reconstitution with 10 mL of SWFI, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

PF-06438179 is a recombinant chimeric human IgG1 kappa monoclonal antibody that binds to the human TNF α .

In the US, PF-06438179 is intended to be licensed for seven indications currently approved for US-licensed Remicade. These indications are Rheumatoid Arthritis (RA), Crohn's Disease (CD), pediatric CD, Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Psoriatic Arthritis (PA), and Ankylosing Spondylitis (AS). PF-06438179 is not intended to be licensed for pediatric ulcerative colitis.

2.1.4 What are the proposed dosages and routes of administration?

The proposed dosages and route of administration for the listed indications are identical to those approved for US-licensed Remicade (BLA 103772), as outlined in Table 3 Table 3.

Table 3: Proposed Dosage and Routes of Administration for PF-06438179

Indication	Dosage and Administration
RA	In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.
CD (Adult)	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.
CD (Pediatric), UC, Ps, PA	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.
AS	5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

Abbreviations: AS, ankylosing spondylitis; CD, Crohn's disease; PA, psoriatic arthritis; Ps, plaque psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis

(Source: USPI REMICADE® (infliximab), Revised 10/2015, Janssen Biotech)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The clinical development for PF-06438179 included two completed clinical studies, B5371001 and B5371004, and one clinical study ongoing, study B5371002, as listed in Table 4 below.

Study B5371001 was the pivotal 3-way PK-similarity study comparing PF-06438179, EU-approved Remicade and US-licensed Remicade in healthy subjects. In addition, PK of PF-06438179 and EU-approved Remicade was also assessed in adult patients with RA in Study B5371002. Study B5371004 was a pilot PK/safety study using EU-approved Remicade in healthy subjects to assess the inter-subject PK variability and immunogenicity after a single IV dose of 10 mg/kg. PF-06438179 was not administered in this study.

This clinical pharmacology review primarily focused on the pivotal PK similarity study (B5371001). We also reviewed the PK and immunogenicity in the comparative efficacy study (B5371002).

Table 4: Listing of Clinical Studies

Studies	Objective(s)	Study Design	Treatment Groups /Dosing Regimen	Study Population /No. of Subjects
B5371001 Phase 1 single center	Primary: To evaluate and compare the PK of PF-06438179, EU-approved Remicade and US-licensed Remicade in healthy subjects Secondary: To evaluate the single-dose safety, tolerability, and immunogenicity	Randomized, double-blind, three-arm, parallel-group, single-dose	PF-06438179, EU-approved Remicade or US-licensed Remicade Single-dose of 10 mg/kg IV infusion over a period of not less than 2 hours	Healthy subjects <i>Randomized:</i> PF-06438179=52 US-licensed Remicade =49 EU- approved Remicade =50 <i>Treated:</i> PF-06438179=49 US-licensed Remicade =49 EU-approved Remicade =48
B5371002 Comparative Clinical trial 174 centers	Primary: To compare the efficacy between PF-06438179 and EU-approved Remicade in subjects with moderately to severely active RA who are treated with infliximab in combination with MTX. Secondary: To evaluate the overall safety, tolerability, and immunogenicity of PF-06438179 and EU-approved Remicade. To evaluate the PK and PD response to PF-06438179 and EU-approved Remicade.	Randomized, double-blind, two-arm, parallel-group, multiple dose	PF-06438179, EU-approved Remicade Induction Period: 3 mg/kg IV at Study Weeks 0, 2 and 6. Maintenance Period: 3 mg/kg IV every 8 weeks; one-time escalated to 5 mg/kg per infusion for subjects who failed to achieve a minimum clinical response or lost clinical response.	RA patients <i>Randomized:</i> 650 PF-06438179=323 EU-approved Remicade=326 <i>Treated:</i> PF-06438179= 323 EU-approved Remicade=326
B5371004 Phase 1 single center	Primary: To assess the inter-subject variability in single dose PK of infliximab in healthy subjects Secondary: To assess single dose safety (including immunogenicity) and tolerability	Single-dose, single-arm, open-label, pilot	EU-approved Remicade 10 mg/kg IV infusion over a period of not less than 2 hours	Healthy subjects <i>Assigned to study:</i> 20 <i>Treated:</i> 20 <i>Completed:</i> 20

Abbreviations: IV, intravenous; MTX, methotrexate; RA, rheumatoid arthritis.
(Source: Module 5.2 Tabular Listing of all Clinical Studies)

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

PK (AUC_{inf} , AUC_{0-t} , and C_{max}) was assessed as primary endpoint in the Study B5371001 to evaluate and compare the PK profiles of PF-06438179, EU-approved Remicade and US-licensed Remicade in healthy subjects. Safety, tolerability and immunogenicity were the secondary endpoints. Study B5371002 was the comparative efficacy trial in RA patients. Therefore, the primary efficacy endpoint was the proportion of patients achieving a 20% or greater improvement in the American College of Rheumatology (ACR) clinical response (ACR20 criteria) at Week 14. Safety, immunogenicity and PK at steady-state (C_{max} and C_{trough}) were also evaluated.

2.2.3 What are the PK characteristics of the drug?

2.2.3.1 What are the single dose and multiple dose pharmacokinetic characteristics for PF-06438179?

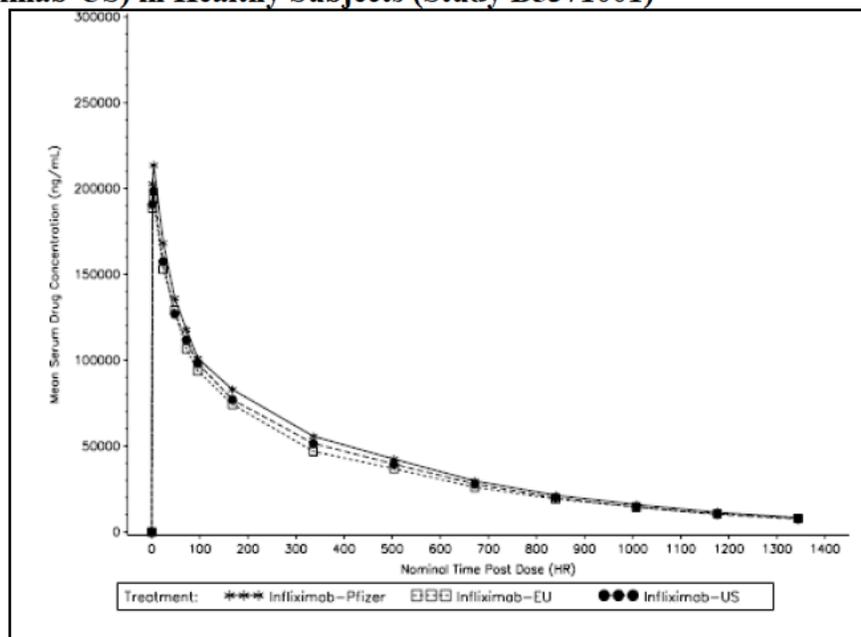
Single-Dose PK

The pivotal PK similarity Study B5371001 was a randomized, double-blind, three-arm, parallel-group, single-dose study in 151 healthy subjects. In each arm of the study, subjects received a single dose 10 mg/kg of either PF-06438179, EU-approved Remicade, or US-licensed Remicade by IV infusion for at least 2 hours. The PK, safety, tolerability, and immunogenicity of PF-06438179, EU-approved Remicade and US-licensed Remicade were assessed.

For the 3-way PK similarity comparisons (PF-06438179 vs. US-licensed Remicade, PF-06438179 vs. EU-approved Remicade and EU-approved Remicade vs. US-licensed Remicade), the 90% CIs for the geometric mean ratios of C_{max} , AUC_{0-t} and AUC_{inf} were all contained within the acceptance range of 80-125% (Table 5).

The mean serum concentration-time profiles of PF-06438179, EU-approved Remicade and US-licensed Remicade treatment groups are presented in Figure 1.

Figure 1: Mean Serum Drug Concentration-time Profiles following a Single 10 mg/kg IV Dose of PF-06438179 (Inflimixab-Pfizer), EU-approved Remicade (Inflimixab-EU), or US-licensed Remicade (Inflimixab-US) in Healthy Subjects (Study B5371001)



(Source: CSR B5371001, Figure 14.4.2.2.3)

Table 5: Geometric Means, Ratios of Geometric Means and 90% Confidence Intervals for the Comparison of the PK Parameters between Test and Reference Products (Study B5371001)

PK Parameters ^a	Geometric Mean ^a			90% CI ^b
	Test	Reference	Ratio T/R (%)	
PF-06438179 (T, n= 41) vs US-licensed Remicade (R, n=44)				
C_{max} (µg/mL)	217.4	203.1	107.05	98.53 - 116.31
AUC_{0-t} (µg.h/mL)	55600	51640	107.67	98.85 - 117.28
AUC_{inf} (µg.h/mL)	59750	55810	107.06	97.49 - 117.58
PF-06438179 (T, n=41) vs EU-approved Remicade (R, n= 45)				
C_{max} (µg/mL)	217.4	197.6	110.03	101.32 - 119.49
AUC_{0-t} (µg.h/mL)	55600	49650	111.98	102.85 - 121.92
AUC_{inf} (µg.h/mL)	59750	54080	110.49	100.67 - 121.28
EU-approved Remicade (T, n=45) vs US-licensed Remicade (R, n= 44)				
C_{max} (µg/mL)	197.6	203.1	97.29	89.72 - 105.50
AUC_{0-t} (µg.h/mL)	49650	51640	96.15	88.45 - 104.53
AUC_{inf} (µg.h/mL)	54080	55810	96.90	88.42 - 106.18

^aData are presented as the geometric means for Test Product and Reference Products based on Least Squares Mean of log-transformed parameter values. ^b90% CI: Lower and upper limits of 90% confidence interval of the geometric mean ratio.

(Source: CSR B5371001, Adapted from Table 14.4.3.3)

Among the 151 subjects randomized in Study B5371001, 146 subjects received the assigned study treatment. Sixteen subjects (8, 3, and 5 in the PF-06438179, EU-approved Remicade, and US-licensed Remicade treatment groups respectively) were excluded from the PK analysis. Of these 16 subjects, 15 subjects were excluded because they discontinued from the study prematurely between Days 2 and 29, and consequently had an incomplete PK profile. The remaining 1 subject was excluded because this subject had an incomplete PK profile resulting from no measurable drug concentrations from Day 29 onward.

Independent PK analyses were conducted by the reviewer with and without data from these subjects. In both the analyses, the 90% CI of the geometric mean ratio of AUC_{inf} , AUC_{0-t} , and C_{max} were all within the PK similarity criteria range of 80-125% for the pairwise comparisons among PF-06438179, EU-approved Remicade, and US-licensed Remicade.

Multiple-Dose PK

The PK of PF-06438179 and EU-approved Remicade was also assessed in the comparative efficacy Study B5371002. This prospective Phase 3 study was designed to compare the efficacy, overall safety and immunogenicity between PF-06438179 and EU-approved Remicade in combination with MTX to treat subjects with moderately to severely active RA who have had an inadequate response to MTX therapy.

Six hundred and fifty male or female RA patients were randomly assigned in a 1:1 ratio to receive either PF-06438179 or EU-approved Remicade study treatment, as described below:

- Induction period: Intravenous infusion (over at least 2 hours) on the first day of each dosing period at a dose of 3 mg/kg on Weeks 0, 2, and 6. The dose remained consistent for all subjects for a minimum of 3 doses (up to Week 14).
- Maintenance period: Beginning at Week 14, the dose was maintained at 3 mg/kg per infusion every 8 weeks.

The primary endpoint of the study was the proportion of subjects achieving a 20% or greater improvement in ACR clinical response at Week 14. Serum drug concentrations were determined prior to dose administration (within 4 hours) at Weeks 0, 2, 6, 14, 22, 30; prior to the end of infusion (within 5 minutes) at Weeks 0 and 14; and anytime during study visits at Weeks 4 and 78 (end-of-study). The values of C_{max} and C_{trough} of PF-06438179 treatment group were generally comparable to those of EU-approved Remicade (Table 6).

Table 6: Median (5th-95th percentile) Value of Serum Concentrations of PF-06438179 and EU-approved Remicade (Study B5371002)

Visit (Week)	PF-06438179		EU-approved Remicade	
	Ctrough (µg/mL) ^a	n	Ctrough (µg/mL) ^a	n
2	16.8 (6.24-28.7)	316	16.1 (6.24-27.3)	323
4	23.5 (4.30-45.8)	308	21.3 (22.6-40.1)	314
6	10.0 (0.1-26.7)	308	9.27 (0-24.2)	315
14	1.49 (0-10.6)	302	1.03 (0-7.643)	310
22	0.576 (0-7.91)	295	0.433 (0-6.22)	303
30	0.413 (0-7.25)	281	0.279 (0-6.01)	290
	Cmax (µg/mL) ^a	n	Cmax (µg/mL) ^a	N
0 (Day 1)	64.2 (31.6-102)	319	62.2 (23.3-95.9)	322
14	71.3 (1.62-151)	297	68.5 (3.37-145)	299

^aData are presented as median value (5th - 95th percentile of the observed data).

(Source: CSR B5371002, Adapted from Table 14.4.3.1.1)

2.2.3.2 What is the variability of the PK parameters in volunteers and patients with the target disease?

In healthy subjects, the inter-subject variability of C_{max} and AUCs evaluated as coefficient of variation (CV) was less than 30% after single dose administration for all three products. In patients with RA, the inter-subject variability of C_{max} concentrations was 52% and 56% for PF-06438179 and EU-approved Remicade, respectively, following multiple dose administration at Week 14 (Table 7).

Table 7: Inter-subject Variability of Infliximab Exposure

Coefficient of Variation (CV) %				
Study B5371001				
Product	Cmax	AUC _{0-t}	AUC _{inf}	Dosage
PF-06438179 (n=41)	20	21	23	10 mg/kg single-dose
US-licensed Remicade (n=44)	24	22	25	10 mg/kg single-dose
EU-approved Remicade (n=45)	23	25	28	10 mg/kg single-dose
Study B5371002				
Product	Cmax at Week 14	Ctrough at Week 14	Dosage	
PF-06438179	52 (n=297)	270 (n=302)	(3 mg/kg at week 0, 2, 6, and q8w thereafter)	
EU-approved Remicade	56 (n=299)	249 (n=310)	(3 mg/kg at week 0, 2, 6, and q8w thereafter)	

(Source: CSR B5371001, Table 14.4.3.1; CSR B5371001, Table 14.4.3.1.1)

2.3 Intrinsic Factors

2.3.1 Immunogenicity

2.3.1.1 How was the immunogenicity assessed and what was the incidence of the formation of the anti-drug antibody?

Immunogenicity samples were analyzed using validated ADA assays based on a tiered approach. Only confirmed anti-drug antibody (ADA) positive samples were then assessed for neutralizing antibodies (NAbs). The measurement of ADA was accomplished using electrochemiluminescence (ECL) method, and measurement of NAb was accomplished using semi-quantitative cell-based assay method. The drug tolerance for the assays was in the range of 1- 5 µg/mL. Refer to the OBP review for detailed information regarding assay validation and analysis of clinical study samples.

In the PK comparative study B5371001, samples were collected on Day 1 (pre-dose), 15, 29, 43, 57, 85 (end-of study) for assessment of immunogenicity. Table 8 summarizes the immunogenicity results by treatment group. Of the total 146 subjects who received the assigned study treatment, 118 and 119 subjects completed immunogenicity assessments through Days 57 (week 8) and 85 (week 12), respectively. No subjects were tested positive for ADA at baseline. A total of 5 (4.2%) and 31 (26.1%) subjects tested positive for ADA through Days 57 and 85, respectively (Table 8). The ADA formation rates for PF-06438179, EU-approved Remicade and US-licensed Remicade in healthy subjects were 16.2%, 32.6%, and 28.2%, respectively. On Day 85, the PF-06438179 treatment group showed a lower incidence of ADA compared to that for the EU-approved Remicade or US-licensed Remicade treatment groups. While small differences in the proportion of subjects with ADA positive response were evident after single dose administration in Study B5371001, it should be noted that assessment of immunogenicity after multiple dose in Study B5371002 is considered clinically more relevant.

In study B5371002, blood samples were collected at baseline and pre-dose at Weeks 2, 6, 14, 30, 38, 54, 62, and 78 for serum ADA and NAb (in ADA positive subjects only) formation and titers in response to PF-06438179 and EU-approved Remicade. The incidences of ADA in PF-06438179 and EU-approved Remicade treatment groups were comparable at each specific time point of measurement during the first 30 weeks of treatment. A total of 157 (48.6%) subjects in the PF-06438179 group and 167 (51.2%) subjects in the EU-approved Remicade were tested positive for ADA during this period (Table 8). The distribution of ADA titers was also comparable between the treatment groups over the 30-weeks treatment period (Figure 2).

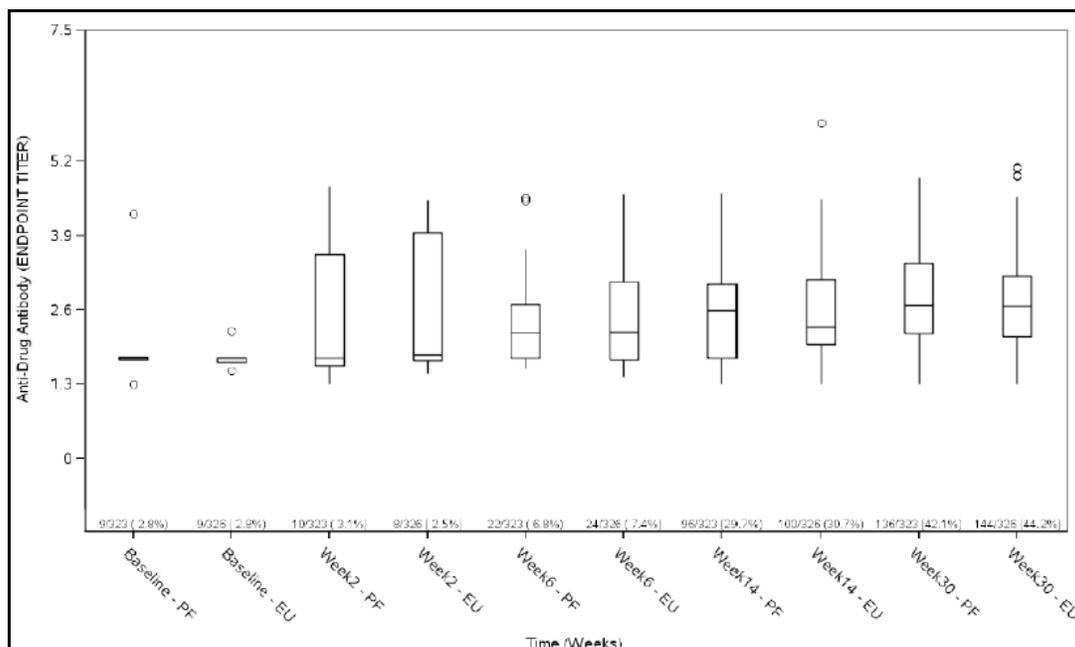
It should be noted that the range of drug tolerance of the ECL method (1-5 µg/mL) overlapped with the range of observed PK concentrations. For the comparative efficacy study (B5371002), the PK concentrations varied between 0.1-60 µg/mL (Table 6). Although, at high concentrations there is a possibility of underestimating the ADA rate, at Week 30 the mean PK concentrations (C_{trough}) were below the lower range of drug tolerance (1 µg/mL). The incidence of immunogenicity for PF-06438179 and EU-approved Remicade was comparable (42.1% and 44.2%, respectively) at Week 30.

Table 8: Incidence of Anti-Drug Antibody (ADA) in the Clinical Studies B5371001 and B5371002 by Visit and Treatment Group (PF-06438179, EU-approved Remicade, US-licensed Remicade)

Visit	Study B5371001 Healthy Subjects (10 mg/kg single dose)			Study B5371002 Patients with RA (3 mg/kg at week 0, 2, 6, and q8w to week 54)	
	PF-06438179 (N=49) ^a	EU- approved Remicade (N=48) ^a	US-licensed Remicade (N=49) ^a	PF-06438179 (N=323) ^a	EU- approved Remicade (N=326) ^a
	Number (%) of subjects tested positive for ADA				
Screening (Baseline/pre-dose)	0	0	0	9/322 (2.8%)	9/323 (2.8%)
Week 2	--	--	--	10/318 (3.1 %)	8/323 (2.5%)
Week 4 (Day 29)	0	0	1/42 ^b (2.4%)	--	--
Week 6 (Day 43)	0	0	1/42 ^b (4.8%)	22/307 (6.8%)	24/317 (7.4%)
Week 8 (Day 57)	2/38 ^b (5.3%)	0 (0%)	3/41 ^b (7.3%)	--	--
Week 12 (Day 85)	6/37 ^b (16.2%)	14/43 ^b (32.6%)	11/39 ^b (28.2%)	--	--
Week 14	--	--	--	96/302 (29.7%)	100/314 (30.7%)
Week 30	--	--	--	136/282 (42.1%)	144/291 (44.2%)
Overall	--	--	--	157/320 (48.6%)	167/325 (51.2%)

^a Number of treated subjects. ^b Number of subjects who completed the anti-drug antibody assessment.
(Source: Adapted from CSR 5371001, Table 14.3.4.5.1; CSR B5371002, Table 14.3.4.5.1)

Figure 2: Comparison of Anti-Drug Antibody (ADA) Titers versus Time between PF-06438179 and EU-approved Remicade in ADA-positive Subjects



PF indicates PF-06438179 and EU indicates EU-approved Remicade. Circles represent outliers. The ADA incidence data at each visit by treatment arm are displayed along the bottom of the figure. (Source: CSR 5371002, Figure 19)

2.3.1.2 Does the immunogenicity affect the PK similarity of the therapeutic protein?

In the PK similarity study B5371001, only 5 subjects tested positive for ADA during the protocol-specified 8-week PK profiling period (Table 8). Therefore, the impact of ADA response on the PK similarity assessment is expected to be limited.

In the comparative efficacy study B5371002, mean serum concentrations of PF-06438179 and EU-approved Remicade appeared to be comparable in each ADA group at each individual time point during the 30-week treatment period (Table 9). It appears that the mean concentrations of serum PF-06438179 and EU-approved Remicade were lower in ADA positive subjects compared to ADA negative subjects. However, the effect of immunogenicity on PK should be interpreted with caution due to the limitations of the immunogenicity assay (refer to section 2.3.1.1).

Table 9: Median (5th-95th percentile) Value of Serum Concentrations of PF-06438179 and EU-approved Remicade by Anti-Drug Antibody (ADA) Status (Study B5371002)

Visit (Week)	ADA-positive Subjects		ADA-negative Subjects	
	PF-06438179	EU-approved Remicade	PF-06438179	EU-approved Remicade
C_{trough} (µg/mL)^a				
2	15.5 (5.68-26.8)	14.2 (5.24-26.1)	18.2 (6.32-28.8)	18.0 (9.08-29.6)
4	17.8 (0.77-37.4)	16.4 (0.256-32.5)	27.9 (10.7-49.2)	26.9 (13.0-41.4)
6	6.16 (0-20.2)	5.1 (0-17.4)	14.0 (3.96-29.9)	12.8 (4.32-26.4)
14	0 (0-4.01)	0 (0-3.43)	3.35 (0.492-15.7)	3.06 (0.197-8.44)
22	0 (0-2.26)	0 (0-1.15)	2.98 (0.206-10.6)	2.49 (0-7.58)
30	0 (0-0.53)	0 (0-0.575)	2.85 (0.386-10.1)	2.39 (0.192-7.58)
C_{max} (µg/mL)^a				
0 (Day 1)	63.8 (35.6-101)	59.3 (1.60-93.2)	65.5 (11.2-102)	66.1 (29.1-101)
14	68.3 (0-157)	62.0 (1.09-118)	75.6 (5.63-129)	75.1 (8.86-159.8)

^aData are presented as median value (5th - 95th percentile).

(Source: CSR B5371002, Adapted from Table 14.4.3.1.1)

2.3.1.3 Do the anti-drug antibodies have neutralizing activities?

In both the PK similarity study (B5371001) and the comparative efficacy study (B5371002), the majority of subjects ADA positive also developed neutralizing antibodies (NAb). In study B5371001, of the 31 subjects who tested positive for ADA post dose, 26 subjects tested positive for Nab (Table 10). In study B5371002, of the ADA positive subjects, 79.0% and 85.6% also tested positive for NAb in the PF-06438179 and EU-approved Remicade treatment groups, respectively (Table 10). The rates of NAb positive subjects appeared to be comparable in study B5371002.

Table 10: Incidence of Neutralizing Antibody (NAb) in the Clinical Studies B5371001 and B5371002 by Visit and Treatment Group (PF-06438179, EU-approved Remicade, US-licensed Remicade)

Visit	Study B5371001 Healthy Subjects (10 mg/kg single dose)			Study B5371002 Patients with RA (3 mg/kg at week 0, 2, 6, and then q8w to week 54)	
	PF-06438179 (N=49) ^a	EU-approved Remicade (N=48) ^a	US-licensed Remicade (N=49) ^a	PF-06438179 (N=323) ^a	EU- approved Remicade (N=326) ^a
	NAb positive /ADA positive (%) ^b				
Screening (Baseline/pre-dose)	0	0	0	1/9 (11.1%)	1/9 (11.1%)
Week 2 (Day 14)	--	--	--	3/10 (30.0%)	3/8 (37.5%)
Week 4 (Day 29)	0	0	1/1 (100%)	--	--
Week 6 (Day 43)	0	0	2/2 (100%)	13/22 (59.1%)	19/24 (79.2%)
Week 8 (Day 57)	2/2 (100%)	0 (0%)	3/3 (100%)	--	--
Week 12 (Day 85)	5/6 (83.3%)	12/14 (85.7%)	9/11 (81.8%)	--	--
Week 14	--	--	--	73/96 (76.0%)	78/100 (78.0%)
Week 30	--	--	--	105/136 (77.2%)	120/144 (83.3%)
Overall	--	--	--	124/157 (79.0%)	143/167 (85.6%)

^a Number of treated subjects. ^b Percentages for NAb incidence are based on the number of subjects who are ADA positive at that visit.

(Source: Adapted from CSR B5371001, Table 14.3.4.5.2; Adapted from CSR B5371002, Table 14.3.4.5.1.1)

2.3.1.4 Does the immunogenicity affect the efficacy comparison of the therapeutic protein?

In the comparative efficacy study B5371002, the ACR20 response rates at Week 14 trended higher in the ADA negative and NAb negative subjects than in the ADA positive and NAb positive subjects (Table 11). The 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. The ACR20 response rates at Week 14 were comparable between the two treatment groups regardless of ADA and NAb status over the 30-week treatment period. Overall, the ADA formation did not significantly affect the comparative efficacy between PF-06438179 and EU-approved Remicade. It should be noted that there is a possibility of underestimation of ADA rate at Week 14 (refer to section 2.3.1.1). However, differential

underestimation of the ADA rate between products is unlikely. Refer to the OBP review for information about the analytical method validation for assessment of immunogenicity. Refer to the Clinical review for further information on the efficacy comparison.

Table 11: Subgroup Analysis of ACR 20 Response Rate at Week 14 in Patients with RA (Study B5371002)

Category	Subgroup	PF-06438179			EU-approved Remicade		
		Total (N) ^a	Events (n) ^b	N/n (%)	Total (N) ^a	Events (n) ^b	N/n (%)
ADA	Positive	100	51	51.0	103	51	49.5
	Negative	220	152	69.1	222	158	71.2
	Not done	3	0	0	1	0	0
Nab	Positive	74	37	50.0	81	37	45.7
	Negative	246	166	67.5	244	172	70.5
	Not done	3	0	0	1	0	0

^aTotal indicates the total number of subjects in each category. ^bEvents indicate the number of ACR20 responders. (Source: Adapted from CSR B5371002, Table 14.2.2.2.3.1)

2.3.1.5 Does the immunogenicity affect the safety comparison of the therapeutic protein?

Overall, the incidence of infusion-related reactions (IRRs) appears comparable between PF-06438179 and EU-approved Remicade in ADA positive subjects. A total of 11 (7.0%) subjects in the PF-06438179 group and 14 (8.4%) subjects in the EU-approved Remicade group reported IRRs; 4 (2.5%) and 2 (1.2%) subjects reported Grade 3 IRRs, respectively. No subjects reported IRR SAEs. Refer to the Clinical review for further details.

2.4 General Biopharmaceutics

2.4.1 What is the *in vivo* relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The PF-06438179 clinical formulation used in the pivotal PK similarity study (B5371001), and in the comparative efficacy study (B5371002) was the same as the proposed to-be-marketed formulation.

2.5 Analytical Section

2.5.1 What are the analytical methods used to measure PF-06438179 or Remicade in serum?

The serum concentrations of PF-06438179, US-licensed Remicade and EU-approved Remicade were quantified using a validated Enzyme Linked ImmunoSorbent Assay (ELISA). A brief description of the ELISA assay: the rh-TNF-alpha was immobilized onto a 96-well microtiter sample plate. All un-adsorbed sites were blocked with the addition of block/diluent buffer. Analytes, diluted 1:100 with block/diluent buffer, were dispensed onto the sample plate and incubated for 1 hour. After washing the plate, a Donkey Anti-Human IgG (H+L)-Peroxidase conjugate was added and incubated for 1 hour. After the final wash step, a tetramethylbenzidine peroxidase substrate solution was added and incubated for 7-15 minutes. The reaction was stopped with a Stop Solution. Color develops in proportion to the

amount of analytes (infliximab or PF-06438179) in the sample. Plates were read on a plate reader with reading capabilities at 450 nm and 620 nm.

PF-06438179, US-license Remicade and EU-approved Remicade concentrations were determined on a standard curve obtained by plotting optical density versus concentration using a four-parameter logistic curve-fitting program. The calibration curve range in human serum was 100 ng/mL - 5,000 ng/mL in 100% matrix. A calibrator outside the validated range of the assay at 50.0 ng/mL in 100% matrix may be included to serve as an anchor point to facilitate curve-fitting.

The validation results are shown in Table 12 and described below:

Matrix effect/selectivity

The potential for variable matrix-related interferences was evaluated for PF-06438179 in independent sources of normal (n=10), disease (n=15), hemolyzed (n=6), and hyperlipidemic (n=6) matrices. No matrix effect in normal and in disease matrix samples was detected. There were no observed effects of hemolysis and lipemia. Selectivity was also established for US-licensed Remicade and EU-approved Remicade in both normal human serum and RA human serum.

Specificity

The specificity of the assay was evaluated by determining the accuracy and precision of US-licensed Remicade and PF-06438179 quantification in the presence of soluble target/endogenous protein and anti-drug antibodies.

The results demonstrated that up to 5,000 pg/mL TNF-alpha did not interfere with the detection of US-licensed Remicade and PF-06438179. Free drug interference was also evaluated by measuring the impact of sTNF-RI and sTNF-RII. The results indicated that up to 100 ng/mL sTNF-RI and up to 100 ng/mL sTNF-RII did not interfere with the detection of US-licensed Remicade.

Anti-drug antibody interference on the quantitation of US-licensed Remicade and PF-06438179 was evaluated using purified polyclonal positive control (Rabbit IgG RA-23008-A.01). The results demonstrated that concentrations up to 4 µg/mL of rabbit IgG RA-23008-A.01 did not interfere with the detection of US-licensed Remicade and PF-06438179 at concentrations of 5 µg/mL, 10 µg/mL and 400 µg/mL; while PF-06438179 concentration of 0.1 µg/mL did not tolerate the positive control at any level.

Table 12: Validation Summary for Remicade and PF-06438179 Analytical PK Method

Analytical Method	
Validation Reports	Title: Validation for the Determination of Infliximab in Human Serum by ELISA (B5379001, (b) (4) validation 178838) Title: The Validation of an ELISA Method for the Determination of PF-06438179 in Human Serum (B5379002, (b) (4) validation 179652)
Reference	M08.J (b) (4) _Infliximab.huse.1 (B5379001) M08.PF-06438179 _Infliximab.huse.1 (B5379002)
Method Description	Matrix Human serum; no anticoagulant
	Primary Antibody Donkey Anti-Human IgG (H+L) Peroxidase-conjugated
	Diluent Solution Blocker™ Casein in PBS/1% BGG

	Detection Method	ELISA with OD quantification; MRD 1:100	
	Sample Volume	10.0 µL at a minimum	
	Calibration Range	50.0 to 5,000 ng/mL	
	ULOQ	5,000 ng/mL	
	LLOQ	100 ng/mL	
Validation Assay Performance			
Analyte	PF-06438179	US-licensed Remicade	EU-approved Remicade
Lots	Z09719 (179652)	CJM76016 (179652) CED32015PV CBS13015P1 (178838) CBS13015P1 (179239)	2RMA68001(179652) 2RMA63401(178838) 2RMA63401(179239)
R2 of Standard Curve		0.99995390	
Lower Limit of quantitation (LLOQ)	100 ng/mL	100 ng/mL	100 ng/mL
LLOQ Mean Intra-run precision (%)	2.78 (n=8)	6.10 (n=7)	5.33 (n=7)
LLOQ Mean Intra-run accuracy (%)	11.5 (n=8)	1.73 (n=7)	0.171 (n=7)
LLOQ Inter-run precision (%)	5.04 (n=24)	9.44 (n=21)	6.74 (n=21)
LLOQ Inter-run accuracy (%)	11.0 (n=24)	2.00 (n=21)	0.00 (n=21)
QC concentrations (ng/mL)	100 (LLOQ), 250 (LQC), 1,000 (MQC), 3,750 (HQC), 5,000 (ULOQ)		
QC Mean Intra-run precision (%)	LQC= 2.14 MQC= 3.73 HQC= 3.35 ULOQ=2.23	LQC= 3.21 MQC= 3.52 HQC=3.77 ULOQ=3.38	LQC= 2.80 MQC= 2.45 HQC=2.68 ULOQ=2.87
QC Mean Intra-run accuracy (%)	LQC= 13.5 MQC= 11.7 HQC=8.19 ULOQ=6.03	LQC= 1.43 MQC= 3.09 HQC=1.80 ULOQ=-0.874	LQC= 2.11 MQC= 0.657 HQC=-1.48 ULOQ=-2.53
QC Inter-run precision (%)	LQC= 4.12 MQC= 4.74 HQC=3.55 ULOQ=3.73	LQC= 3.92 MQC= 3.37 HQC=3.90 ULOQ=4.22	LQC= 3.92 MQC=2.74 HQC=3.09 ULOQ=3.90
QC Inter-run accuracy (%)	LQC= 13.6 MQC=11.7 HQC=8.19 ULOQ=6.04	LQC= 1.60 MQC= 3.10 HQC=1.81 ULOQ=-0.880	LQC= 2.00 MQC= 0.700 HQC=-1.47 ULOQ=-2.54
Total Error (%)	LLOQ=16.0 LQC= 17.7 MQC=16.4 HQC=11.7	LLOQ=11.4 LQC= 5.52 MQC=6.47 HQC=5.71	LLOQ=6.74 LQC= 5.92 MQC=3.44 HQC=4.56

	ULOQ=9.77	ULOQ=5.10	ULOQ=6.44
--	-----------	-----------	-----------

(Source: Adapted from Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies; Reports B5379001 and B5379002)

2.5.2 For all moieties measured, is free, bound, or total measured?

Free drug concentrations were measured in PK samples.

2.5.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The standard curve for PF-06438179, EU-approved Remicade and US-licensed Remicade serum concentration ranged from 100 to 5,000 ng/mL. Quantification was determined from a standard curve by plotting response (fluorescence) versus concentration using a four-parameter logistic curve-fitting program with no weighting.

In study B5371001, several samples required dilution beyond the MRD (1:100) due to concentrations above the upper limit of quantification (ULOQ). These samples were reanalyzed following a 10-, 20- or 150-fold dilution beyond the MRD (overall dilution 1: 1,000; 1: 2,000; or 1: 15,000, respectively) with inclusion of triplicated dilution QC samples (n=3 [6 wells]) in each analytical run. When multiple dilutions on study samples were required within a single analytical run, only dilution QCs identical to the highest dilution factor applied to study samples were included within the run.

2.5.4 What is the sample stability under conditions used in the study?

Pharmacokinetic samples from study B537001 were stored and analyzed within the validated storage stability period and conditions for PF-06438179, US-licensed Remicade and EU-approved Remicade.

Benchtop Stability (ambient temperature)

PF-06438179, US-licensed Remicade and EU-approved Remicade were stable in human serum for 23 hours, 21 hours and 24.7 hours, respectively, at ambient temperature.

Freeze/Thaw Stability

The freeze-thaw stability for PF-06438179 was evaluated at both (b) (4) °C using stability samples subjected to six freeze (b) (4) °C and thaw (ambient temperature) cycles. Results indicated that PF-06438179 was stable in human serum for at least six freeze/thaw cycles. The freeze-thaw stability for US-licensed Remicade and EU-approved Remicade were also demonstrated at (b) (4) °C for four and six freeze/thaw cycles, respectively.

Long-term Storage Stability

The frozen stability for PF-06438179 and US-licensed Remicade was evaluated for 741 days and 740 days, respectively, at both (b) (4) °C. Stability samples for EU-approved Remicade were stored for 668 days at (b) (4) °C and 929 days at (b) (4) °C. Results indicated that PF-06438179, EU-approved Remicade and US-licensed Remicade were stable in human serum for at least 668 days at either temperature (b) (4) °C).

2.5.5 What is the result for the re-analysis of the incurred samples?

Pharmacokinetics samples from the pivotal PK study (B5371001) were re-analyzed for US-licensed Remicade, EU-approved Remicade and PF-06438179 as part of the incurred sample reproducibility assessment. The results of the incurred sample reanalysis met the acceptance criterion demonstrating satisfactory reproducibility of the PK assay throughout the sample analysis period.

2.5.6 What are the findings from OSIS inspection?

The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and bioanalytical sites of the pivotal clinical pharmacology study B5371001. Inspection of the clinical site (Vince & Associates Clinical Research, Inc., Overland Park, KS) was without significant deficiencies (NAI) and OSIS recommended accepting the data for review. Refer to OSIS Memorandum (DARRTS dated 10/27/2017) for further details. OSIS recommended accepting the bioanalytical data without an on-site inspection at the bioanalytical site ((b) (4)) based on their recent satisfactory inspections of this facility without any significant irregularities. Refer to OSIS Memorandum (DARRTS dated 07/14/2017) for further details.

2.5.7 What bioanalytical methods are used to assess the immunogenicity?

Refer to Section 2.3.1.1 and the OBP review for information about the analytical method validation for assessment of immunogenicity.

3. Labeling Recommendations

In comparison to the US-licensed Remicade USPI, the only labeling language changes proposed by the Applicant in Section 12.3 Pharmacokinetics of the PF-06438179 label is the replacement of the term “REMICADE” with “infliximab” (as shown below).

We recommend deletion of (b) (4)).

12.3 Pharmacokinetics

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MANUELA GRIMSTEIN
11/09/2017

ANSHU MARATHE
11/09/2017