

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761118Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

## BIOSIMILAR MULTI-DISCIPLINARY EVALUATION AND REVIEW

|                                                  |                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                          | 351(k) BLA                                                                                                                                                                                                                                                                                                                                      |
| <b>Application Number</b>                        | 761118                                                                                                                                                                                                                                                                                                                                          |
| <b>Submit Date</b>                               | November 16, 2018                                                                                                                                                                                                                                                                                                                               |
| <b>Received Date</b>                             | November 16, 2018                                                                                                                                                                                                                                                                                                                               |
| <b>BsUFA Goal Date</b>                           | November 16, 2019                                                                                                                                                                                                                                                                                                                               |
| <b>Division/Office</b>                           | DPARP/ODE2/OND in collaboration with DDDP and DGIEP                                                                                                                                                                                                                                                                                             |
| <b>Review Completion Date</b>                    | see stamped date                                                                                                                                                                                                                                                                                                                                |
| <b>Product Code Name</b>                         | PF-06410293                                                                                                                                                                                                                                                                                                                                     |
| <b>Proposed Non-Proprietary Name<sup>1</sup></b> | Adalimumab-afzb                                                                                                                                                                                                                                                                                                                                 |
| <b>Proposed Proprietary Name<sup>1</sup></b>     | Abrilada                                                                                                                                                                                                                                                                                                                                        |
| <b>Pharmacologic Class</b>                       | Tumor Necrosis Factor (TNF) blocker                                                                                                                                                                                                                                                                                                             |
| <b>Applicant</b>                                 | Pfizer Inc.                                                                                                                                                                                                                                                                                                                                     |
| <b>Applicant Proposed Indication(s)</b>          | <ol style="list-style-type: none"><li>1. Rheumatoid Arthritis (RA)</li><li>2. Juvenile Idiopathic Arthritis (JIA age <math>\geq 4</math> years)</li><li>3. Psoriatic Arthritis (PsA)</li><li>4. Ankylosing Spondylitis (AS)</li><li>5. Adult Crohn's Disease (CD)</li><li>6. Ulcerative Colitis (UC)</li><li>7. Plaque Psoriasis (Ps)</li></ol> |
| <b>Regulatory Action</b>                         | Approval                                                                                                                                                                                                                                                                                                                                        |

---

<sup>1</sup> The proposed proper and proprietary names are conditionally accepted until such time that the application is approved.

## Table of Contents

|                                                                                                 |    |
|-------------------------------------------------------------------------------------------------|----|
| Reviewers of Biosimilar Multi-Disciplinary Evaluation and Review .....                          | 7  |
| Additional Reviewers of Application .....                                                       | 7  |
| Glossary .....                                                                                  | 9  |
| 1. Executive Summary .....                                                                      | 14 |
| 1.1. Product Introduction .....                                                                 | 14 |
| 1.2. Determination Under Section 351(k)(2)(A)(ii) of the PHS Act .....                          | 15 |
| 1.3. Mechanism of Action, Route of Administration, Dosage Form and Strength Assessment .....    | 15 |
| 1.4. Inspection of Facilities .....                                                             | 16 |
| 1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product .....           | 16 |
| 1.6. Biosimilarity Assessment .....                                                             | 17 |
| 1.7. Conclusions on Licensure .....                                                             | 20 |
| 2. Introduction and Regulatory Background .....                                                 | 21 |
| 2.1. Important Safety Issues with Consideration to US-Humira .....                              | 21 |
| 2.2. Summary of Presubmission Regulatory Activity Related to Submission .....                   | 23 |
| 2.3. Studies and Publicly Available Information Submitted by the Applicant .....                | 24 |
| 3. Clinical Studies: Ethics and Good Clinical Practice .....                                    | 26 |
| 3.1. Submission Quality and Integrity .....                                                     | 26 |
| 3.2. Statistical Analysis of Clinical Data .....                                                | 26 |
| 3.3. Compliance with Good Clinical Practices .....                                              | 26 |
| 3.4. Financial Disclosures .....                                                                | 27 |
| 4. Summary of Conclusions of Other Review Disciplines .....                                     | 28 |
| 4.1. Chemistry, Manufacturing and Controls .....                                                | 28 |
| 4.2. Clinical Microbiology .....                                                                | 28 |
| 4.3. Devices .....                                                                              | 28 |
| 4.4. Office of Study Integrity and Surveillance (OSIS) .....                                    | 30 |
| 4.5. Office of Scientific Investigations (OSI) .....                                            | 30 |
| 5. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations .....                 | 32 |
| 5.1. Nonclinical Executive Summary and Recommendation .....                                     | 32 |
| 5.2. Product Information .....                                                                  | 33 |
| 6. Clinical Pharmacology Evaluation and Recommendations .....                                   | 35 |
| 6.1. Clinical Pharmacology Executive Summary and Recommendation .....                           | 35 |
| 6.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product | 36 |
| 6.3. Human Pharmacokinetics and Pharmacodynamics .....                                          | 37 |

|       |                                                                                                       |     |
|-------|-------------------------------------------------------------------------------------------------------|-----|
| 6.4.  | Clinical Immunogenicity Studies .....                                                                 | 48  |
| 7.    | Statistical and Clinical Evaluation and Recommendations .....                                         | 59  |
| 7.1.  | Statistical and Clinical Executive Summary and Recommendations.....                                   | 59  |
| 7.2.  | Review Strategy .....                                                                                 | 61  |
| 7.3.  | Review of Comparative Clinical Studies with Statistical Endpoints .....                               | 61  |
| 7.4.  | Review of Safety Data .....                                                                           | 88  |
| 7.5.  | Clinical Conclusions on Immunogenicity.....                                                           | 114 |
| 7.6.  | Extrapolation to Support Licensure of Non-Studied Indications .....                                   | 114 |
| 8.    | Labeling Recommendations.....                                                                         | 128 |
| 8.1.  | Nonproprietary Name .....                                                                             | 128 |
| 8.2.  | Proprietary Name.....                                                                                 | 128 |
| 8.3.  | Other Labeling Recommendations .....                                                                  | 128 |
| 9.    | Advisory Committee Meeting and Other External Consultations .....                                     | 129 |
| 10.   | Pediatrics.....                                                                                       | 129 |
| 11.   | Risk Evaluation and Mitigation Strategies (REMS) and Postmarketing Requirements and Commitments ..... | 130 |
| 11.1. | Recommendations for Risk Evaluation and Mitigation Strategies.....                                    | 130 |
| 11.2. | Recommendations for Postmarket Requirements and Commitments .....                                     | 130 |
| 12.   | Division Director/Designated Signatory Comments .....                                                 | 132 |
| 13.   | Appendices.....                                                                                       | 133 |
| 13.1. | References .....                                                                                      | 133 |
| 13.2. | Financial Disclosure.....                                                                             | 133 |
| 13.3. | Office of Clinical Pharmacology Appendices.....                                                       | 136 |
| 13.4. | Nonclinical Pharmacology and Toxicology Appendices .....                                              | 139 |
| 13.5. | Clinical and Statistics Appendices .....                                                              | 157 |

## Table of Tables

|                                                                                                                                                                                                                      |     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Table 1: Summary and Assessment of Biosimilarity .....                                                                                                                                                               | 17  |
| Table 2. PF-06410293 Nonclinical Studies Submitted .....                                                                                                                                                             | 24  |
| Table 3. PF-06410293 Clinical Studies Submitted.....                                                                                                                                                                 | 25  |
| Table 4. Composition of PF-06410293 Drug Products, for injection .....                                                                                                                                               | 34  |
| Table 5. Clinical Pharmacology Major Review Issues and Recommendations .....                                                                                                                                         | 35  |
| Table 6. Summary of statistical analyses for assessment of PK similarity (Study B5381007) .....                                                                                                                      | 36  |
| Table 7. Summary of Statistical Comparisons of PK Exposure Parameters (C <sub>max</sub> , AUC <sub>0-2wk</sub> , AUC <sub>t</sub> , and AUC <sub>inf</sub> ) Between Study Products (Day 1-43, PP Analysis Set)..... | 39  |
| Table 8. Comparison of Study Design Differences Between Studies B5381001 and B5381007 .....                                                                                                                          | 40  |
| Table 9. Summary of PK parameters (Study B5381007).....                                                                                                                                                              | 41  |
| Table 10. Serum PF-06410293 and EU-Humira Concentrations Versus Time by ADA Status, PK Population – Study B5381002 TP1 .....                                                                                         | 42  |
| Table 11. Serum Drug Concentration (ng/mL) Versus Time Summary by ADA Status, TP2 PK Population – TP2 .....                                                                                                          | 44  |
| Table 12. PK comparability assessment - statistical analysis for PF-06410293 PK parameters using PFS and PFP (B5381005).....                                                                                         | 46  |
| Table 13. Immunogenicity results for binding ADA and NAb in Study B5381007 .....                                                                                                                                     | 49  |
| Table 14. Immunogenicity results for binding ADA and NAb in Study B5381001 .....                                                                                                                                     | 49  |
| Table 15. ADA and NAb for ISR/Rash AE and Control Subjects by Visit (Study B5381005) .....                                                                                                                           | 50  |
| Table 16. Summary of ADA and NAb Incidence, Safety Population, TP1 .....                                                                                                                                             | 51  |
| Table 17. Summary of ADA and NAb Incidence, Safety Population, TP 2 (Study B5381002).....                                                                                                                            | 52  |
| Table 18. Summary of PK Parameters in Study B5381007 by the binding ADA Status .....                                                                                                                                 | 54  |
| Table 19 Summary of the Four Historical Randomized Clinical Studies of Adalimumab in Patients with Active RA with Inadequate Response to MTX .....                                                                   | 69  |
| Table 20 Disposition of Patients during TP1, B5381002 .....                                                                                                                                                          | 70  |
| Table 21 Summary of Reasons for Discontinuation from Treatment Prior to Week 26, B5381002 .....                                                                                                                      | 70  |
| Table 22 Summary of Reasons for Discontinuation from Study Prior to Week 26, B5381002 .....                                                                                                                          | 71  |
| Table 23 Reasons for being Excluded from the Per-Protocol Population, B5381002 .....                                                                                                                                 | 72  |
| Table 24 Baseline Characteristics for All Randomized Patients, <sup>a</sup> B5381002 .....                                                                                                                           | 73  |
| Table 25 Baseline Disease Characteristics for all Randomized Patients, <sup>a</sup> B5381002 .....                                                                                                                   | 74  |
| Table 26 Differences in ACR20 Responses at Week 12.....                                                                                                                                                              | 75  |
| Table 27. Regression Analysis of the Change from Baseline in DAS28(CRP) Based on all Patients Regardless of Adherence to Study Treatment and PP Dataset .....                                                        | 80  |
| Table 28. Comparison of Key Characteristics of Historical Randomized, Placebo-Controlled Clinical Trials of Adalimumab <sup>1</sup> in RA and Comparative Clinical Study B5381002.....                               | 82  |
| Table 29. Extent of exposure during TP1 in B5381002.....                                                                                                                                                             | 90  |
| Table 30. Demographics in three comparative PK studies .....                                                                                                                                                         | 91  |
| Table 31. Overall AE profile during the TP1 in Safety Population in Study B5381002 .....                                                                                                                             | 94  |
| Table 32. Overall AE profile during the TP2 in Safety Population in Study B5381002 .....                                                                                                                             | 95  |
| Table 33. All-causality Serious Adverse Events (SAEs) reported during TP1 in Study B5381002 .....                                                                                                                    | 97  |
| Table 34. All-causality Serious Adverse Events during TP2 in Study B5381002 .....                                                                                                                                    | 98  |
| Table 35. All-causality TEAEs (by ≥2% Subjects) during TP1 in Study B5381002.....                                                                                                                                    | 100 |
| Table 36. All-causality TEAEs (by ≥2% Subjects) during TP2 in Study B5381002.....                                                                                                                                    | 102 |
| Table 37. Incidence of AEs by System Organ Class (SOC) in healthy subjects from two comparative single-dose PK studies .....                                                                                         | 104 |

|                                                                                                                                                                                                                         |     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Table 38. Adverse Events of Special Interest (AESI) during TP1 in Study B5381002 .....                                                                                                                                  | 106 |
| Table 39. Adverse Events of Special Interest (AESI) during TP2 in Study B5381002 .....                                                                                                                                  | 107 |
| Table 40. Injection Site Reactions of PF-06410293 delivered by PFS vs. PFP in Study B5381005 .....                                                                                                                      | 108 |
| Table 41. Injection Site Reactions in TP1 (Study B5381002) .....                                                                                                                                                        | 108 |
| Table 42. Overview of PF-06410293 Clinical Program.....                                                                                                                                                                 | 119 |
| Table 43. Known and Potential Mechanisms of Action of US-Humira .....                                                                                                                                                   | 121 |
| Table 44. Enrollment in the 13 investigators/sites with financial disclosures in Study B5381002 .....                                                                                                                   | 136 |
| Table 45 Summary of the bioanalytical method validation and in-study performance for measurement of EU-Humira, US-Humira, and PF-06410293 .....                                                                         | 137 |
| Table 46. Selected Potential Leachable Compounds from glass vial, PFS, and PFP and Initial Safety Concern Threshold .....                                                                                               | 142 |
| Table 47. Selected Potential Leachable Compounds (b) (4) and Initial Safety Concern Threshold .....                                                                                                                     | 142 |
| Table 48. Leachables detected with highest TDIs or QLs in (b) (4) glass vial, and PFS/PFP drug products .....                                                                                                           | 144 |
| Table 49. Study Design for The 28-day Monkey Toxicology Study .....                                                                                                                                                     | 151 |
| Table 50. Mean Spleen Weight Changes Relative to Vehicle Controls for Monkeys Treated with PF-06410293 and EU-Humira.....                                                                                               | 152 |
| Table 51. Group Incidence and Severity of Test and Control Article-Related Microscopic and Immunohistochemistry Findings.....                                                                                           | 153 |
| Table 52. Mean Toxicokinetic Parameters for PF-06410293 and EU-Humira in Cynomolgus Monkeys after Once Weekly Administration of PF-06410293 or EU-Humira -All Animals.....                                              | 154 |
| Table 53. Analytical Results – PF-06410293 .....                                                                                                                                                                        | 156 |
| Table 54. Probability of ACR20 Response at Other Study Visit Weeks, B5381002.....                                                                                                                                       | 157 |
| Table 55. Change from Baseline for the Individual Components of ACR at Scheduled Visit Weeks Based on all Data Collected Regardless of Study Treatment Discontinuation by Treatment Arm .....                           | 158 |
| Table 56. Change from Baseline for the Individual Components of ACR at Scheduled Visit Weeks Based on all Data Collected Regardless of Study Treatment Discontinuation by Treatment Arm (continued from Table 55) ..... | 159 |
| Table 57. Parameters and Notation for Tipping Point Analysis in Presence of Missing Data .....                                                                                                                          | 162 |
| Table 58. Extent of exposure during TP3 in RA Study.....                                                                                                                                                                | 163 |
| Table 59. Overall AE profile during the open-label extension (TP3) in Safety Population .....                                                                                                                           | 164 |
| Table 60. All-causality non-SAEs (by ≥2% Subjects) during TP3 (open-label extension) .....                                                                                                                              | 165 |
| Table 61. Adverse Events of Special Interest (AESI) during TP3 .....                                                                                                                                                    | 166 |

### Table of Figures

|                                                                                                                                                                                                                                                                                       |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Figure 1. PK profiles following a single SC dose of PF-06410293, EU-Humira, or US-Humira using PFS in healthy subjects (n=120/treatment group) .....                                                                                                                                  | 41  |
| Figure 2. Mean Trough Concentration Following Multiple SC Dosing (40 mg Q2W) of PF-06410293 or EU-Humira in RA Patients (Study B5381002) .....                                                                                                                                        | 43  |
| Figure 3. PF-06410293 PK profiles following a single SC dose of PF-06410293 using PFS or PFP in healthy subjects (n=81-83/treatment group) (Study B5381005) .....                                                                                                                     | 45  |
| Figure 4. PF-06410293 PK comparison using PFS and PFP in different weight groups (Study B5381005): Low weight (>50 kg but ≤60 kg, n=10 for PFS, n=10 for PFP), Average weight (>60 kg but ≤80 kg, n=38 for PFS, n=40 for PFP), High weight (>80 kg, n=33 for PFS, n=33 for PFP) ..... | 46  |
| Figure 5. PF-06410293 PK comparison using PFS and PFP in different weight groups (Study B5381005): Low weight (>50 kg but ≤60 kg, n=10 for PFS, n=10 for PFP), Average weight (>60 kg but ≤80 kg, n=38 for PFS, n=40 for PFP), High weight (>80 kg, n=33 for PFS, n=33 for PFP) ..... | 47  |
| Figure 6. Serum Cmax by Treatment and NAb Status (StudyB5381001).....                                                                                                                                                                                                                 | 54  |
| Figure 7. AUCinf by Treatment and NAb Status (StudyB5381001).....                                                                                                                                                                                                                     | 55  |
| Figure 8. Serum Trough Concentrations by ADA Status at week 26 (StudyB5381002).....                                                                                                                                                                                                   | 56  |
| Figure 9. Serum Trough Concentrations by NAb Status at week 26 (Study B5381002) .....                                                                                                                                                                                                 | 57  |
| Figure 10. Study Design, B5381002 .....                                                                                                                                                                                                                                               | 62  |
| Figure 11 ACR Responder Curve, Regardless of Adherence to Study Treatment for Various Thresholds at Week 12 .....                                                                                                                                                                     | 76  |
| Figure 12 Differences in ACR Response Comparing PF-06410293 vs EU-Humira Using all Possible ACR Thresholds Across Different Study Visits up to Week 26, Regardless of Adherence to Study Treatment .                                                                                  | 77  |
| Figure 13. Cumulative Distribution Curves for Patients with Observed DAS28(CRP) at Week 12 .....                                                                                                                                                                                      | 79  |
| Figure 14. Subgroup Analysis in the Probability of ACR20 Response at Week 12 and on Randomized Treatment .....                                                                                                                                                                        | 83  |
| Figure 15. Substudy B5381002 Schema .....                                                                                                                                                                                                                                             | 84  |
| Figure 16. Mean +/- SD Concentration versus Time for PF-06410293 and EU-Humira on Days 1 and 22155                                                                                                                                                                                    |     |
| Figure 17. Tipping Point Analyses Results for 90% Lower CL (Heatmap) and Point Estimates (Contour Lines): Inference on the Difference Between PF06410293 and EU-Humira in the Probability of Week 12 ACR20 Responses under Varying Assumptions .....                                  | 160 |
| Figure 18. Tipping Point Analyses Results for 90% Upper CL (Heatmap) and Point Estimates (Contour Lines): Inference on the Difference Between PF06410293 and EU-Humira in the Probability of Week 14 ACR20 Responses under Varying Assumptions .....                                  | 161 |
| Figure 19. Observer Assessment Tool (OAT) for Actual PFP Use Evaluation .....                                                                                                                                                                                                         | 167 |
| Figure 20. Patient Assessment Tool for PFP Actual Use Evaluation .....                                                                                                                                                                                                                | 169 |

## Reviewers of Biosimilar Multi-Disciplinary Evaluation and Review

|                                                       |                                                                                        |
|-------------------------------------------------------|----------------------------------------------------------------------------------------|
| <b>Regulatory Project Manager</b>                     | Colette Jackson                                                                        |
| <b>Nonclinical Pharmacology/Toxicology Reviewer</b>   | Xiaochun Chen, Ph.D.                                                                   |
| <b>Nonclinical Pharmacology/Toxicology Supervisor</b> | Andrew Goodwin, Ph.D.                                                                  |
| <b>Clinical Pharmacology Reviewer(s)</b>              | Jianmeng Chen, Ph.D.                                                                   |
| <b>Clinical Pharmacology Team Leader(s)</b>           | Ping Ji, Ph.D.                                                                         |
| <b>Clinical Reviewer(s)</b>                           | Jin Chen, M.D., Ph.D. (DPARP), Wen Yi Gao, M.D., (DGEIP), and Gary Chiang, M.D. (DDDP) |
| <b>Clinical Team Leader(s)</b>                        | Rachel Glaser, M.D. (DPARP), Anil Rajpal, M.D. (DGEIP), David Kettl, M.D. (DDDP)       |
| <b>Clinical Statistics Reviewer(s)</b>                | William Koh, Ph.D.                                                                     |
| <b>Clinical Statistics Team Leader(s)</b>             | Rebecca Rothwell, Ph.D.                                                                |
| <b>Cross-Discipline Team Leader(s)</b>                | Rachel Glaser, M.D.                                                                    |
| <b>Division Signatory (designated)</b>                | Nikolay Nikolov, M.D.                                                                  |

## Additional Reviewers of Application

|                                                                                        |                                                                                                                                    |
|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| <b>Comparative Analytical Assessment and Analytical Component of Scientific Bridge</b> | Xuhong Li, Ph.D., Haoheng Yan, M.D., Ph.D. (Team Leader), Joel Welch, Ph.D. (Chief)                                                |
| <b>CMC - Statistics</b>                                                                | Tianjiao Dai, Chao Wang, Meiyu Shen, Ph.D. (Team Leader)                                                                           |
| <b>CMC - Drug Substance</b>                                                            | Nailing Zhang, Ph.D., Haoheng Yan, M.D., Ph.D. (Team Leader), Joel Welch, Ph.D. (Chief)                                            |
| <b>CMC - Drug Product</b>                                                              | Nailing Zhang, Ph.D., Haoheng Yan, M.D., Ph.D. (Team Leader), Joel Welch, Ph.D. (Chief)                                            |
| <b>CMC - Facility</b>                                                                  | Amy Devlin, Thuy Thanh Nguyen (Team Leader)                                                                                        |
| <b>OBP Immunogenicity</b>                                                              | Nailing Zhang, Ph.D., Haoheng Yan, M.D., Ph.D. (Team Leader), Joel Welch, Ph.D. (Chief)                                            |
| <b>Product Quality Microbiology</b>                                                    | Aimee Cunningham, Ph.D. (Drug Substance), Lakshmi Rani Narasimhan, Ph.D. (Drug Product), Reyes Candau-Chacon, Ph.D., (Team Leader) |
| <b>OPDP</b>                                                                            | Wale Adeleye, Pharm.D.                                                                                                             |

Biosimilar Multi-disciplinary Evaluation and Review (BMER)

BLA 761118

PF-06410293 a proposed biosimilar to Humira

|                  |                                                                                                                                                                                                                                                                |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>DMPP</b>      | Aman Sarai, Pharm.D. (Evaluator), Marcia Williams, Pharm.D. (Team Leader)                                                                                                                                                                                      |
| <b>OSIS</b>      | Gajendiran Mahadevan<br>Angel Johnson                                                                                                                                                                                                                          |
| <b>OSI</b>       | Min Lu                                                                                                                                                                                                                                                         |
| <b>OSE/DMEPA</b> | Sarah Vee, Pharm.D. (TL), Matthew Barlow, Pharm. D. (SE – HF review), Carlos Mena-Grillasca, Pharm.D. (SE – Suffix review), Idalia Rychlik, Pharm.D. (SE – labeling review)                                                                                    |
| <b>OSE/DRISK</b> |                                                                                                                                                                                                                                                                |
| <b>OSE/DPV</b>   | Ann Biehl, Pharm.D. (SE), Lisa Harinstein, Pharm.D. (TL)                                                                                                                                                                                                       |
| <b>Other</b>     | Anh-Thy Ly, Pharm.D. (OBP RPM), Vicky Borders-Hemphill, Pharm.D. (OBP labeling), Keith Marin, Ph.D. (CDRH Reviewer), Sarah Mollo, Ph.D., (CDRH Team Leader), Alan Stevens, Ph.D., (CDRH Division Director), Rumi Young, Ph.D., (CDRH Device/Facility Reviewer) |

CMC=Chemistry, Manufacturing, and Controls

OBP=Office of Biotechnology Products

OPDP=Office of Prescription Drug Promotion

DMPP= Division of Medical Policy Programs

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error and Prevention Analysis

DRISK=Division of Risk Management

DPV=Division of Pharmacovigilance

DPMH=Division of Pediatric and Maternal Health

CDRH=Center for Devices and Radiologic Health

## Glossary

---

|               |                                                                                                                                    |
|---------------|------------------------------------------------------------------------------------------------------------------------------------|
| AC            | Advisory Committee                                                                                                                 |
| ACR           | American College of Rheumatology                                                                                                   |
| ACR20         | ≥20% from baseline in tender and swollen joint counts and ≥20% improvement from baseline in 3 of the 5 other ACR-core set measures |
| ACR50         | ≥50% from baseline in tender and swollen joint counts and ≥50% improvement from baseline in 3 of the 5 other ACR-core set measures |
| ACR70         | ≥70% from baseline in tender and swollen joint counts and ≥70% improvement from baseline in 3 of the 5 other ACR-core set measures |
| ADA           | Anti-drug Antibodies                                                                                                               |
| ADME          | Absorption, Distribution, Metabolism, and Excretion                                                                                |
| AE            | Adverse Event                                                                                                                      |
| BLA           | Biologics License Application                                                                                                      |
| BMER          | Biosimilar Multi-Disciplinary Evaluation and Review                                                                                |
| BMI           | Body Mass Index                                                                                                                    |
| BPD           | Biosimilar Biological Product Development                                                                                          |
| BRG           | Biosimilar Review Guide                                                                                                            |
| BsUFA         | Biosimilar User Fee Agreements                                                                                                     |
| CDER          | Center for Drug Evaluation and Research                                                                                            |
| CDRH          | Center for Devices and Radiological Health                                                                                         |
| CDTL          | Cross-Discipline Team Leader                                                                                                       |
| CFR           | Code of Federal Regulations                                                                                                        |
| CI            | Confidence Interval                                                                                                                |
| CMC           | Chemistry, Manufacturing, and Controls                                                                                             |
| CRF           | Case Report Form                                                                                                                   |
| CRO           | Contract Research Organization                                                                                                     |
| CRP           | C-reactive Protein                                                                                                                 |
| CSC           | Computational Science Center                                                                                                       |
| CTD           | Common Technical Document                                                                                                          |
| CV            | Coefficient of Variation                                                                                                           |
| DAS           | Disease Activity Score                                                                                                             |
| DAS28-4 (CRP) | DAS Score-28 based on 4 components: Swollen Joints, Tender Joints, hs-CRP and Patient's Global Assessment of Arthritis             |
| DEPI          | Division of Epidemiology                                                                                                           |
| DIP           | Distal InterPhalangeals                                                                                                            |
| DMARD         | Disease Modifying Anti-Rheumatic Drug                                                                                              |
| DMC           | Data Monitoring Committee                                                                                                          |
| DMEPA         | Division of Medication Error Prevention and Analysis                                                                               |
| DPMH          | Division of Pediatric and Maternal Health                                                                                          |
| DRISK         | Division of Risk Management                                                                                                        |

|           |                                                                            |
|-----------|----------------------------------------------------------------------------|
| eCTD      | Electronic Common Technical Document                                       |
| EU        | European Union                                                             |
| EU-Humira | E.U.-approved Humira                                                       |
| EULAR     | European League Against Rheumatism                                         |
| FDA       | Food and Drug Administration                                               |
| FISH      | Fluorescence In Situ Hybridization                                         |
| GCP       | Good Clinical Practice                                                     |
| GMR       | Geometric Mean Ratio                                                       |
| GRP       | Good Review Practice                                                       |
| HAQ-DI    | Health Assessment Questionnaire-Disability Index                           |
| HDL       | High-density Lipoprotein                                                   |
| Hs-CRP    | high-sensitivity C-reactive protein                                        |
| ICH       | International Conference on Harmonization                                  |
| IND       | Investigational New Drug                                                   |
| ITT       | Intention to Treat                                                         |
| LDL       | Low-density Lipoprotein                                                    |
| LLOQ      | Lower Limit of Quantitation                                                |
| MAPP      | Manual of Policy and Procedure                                             |
| MCP       | MetaCarpophalangeals                                                       |
| MedDRA    | Medical Dictionary for Regulatory Activities                               |
| MTP       | MetaTarsophalangeals                                                       |
| mITT      | Modified Intention to Treat                                                |
| MOA       | Mechanism of Action                                                        |
| NAb       | Neutralizing Antibody                                                      |
| NCI-CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| NCT       | National Clinical Trial                                                    |
| OBP       | Office of Biotechnology Products                                           |
| OCP       | Office of Clinical Pharmacology                                            |
| OPDP      | Office of Prescription Drug Promotion                                      |
| OSE       | Office of Surveillance and Epidemiology                                    |
| OSI       | Office of Scientific Investigations                                        |
| OSIS      | Office of Study Integrity and Surveillance                                 |
| PAAP      | Patient's Assessment of Arthritis Pain                                     |
| PD        | Pharmacodynamics                                                           |
| PeRC      | Pediatric Review Committee                                                 |
| PGA       | Patient's Global Assessment of Arthritis                                   |
| PGAA      | Physician's Global Assessment of Arthritis                                 |
| PIP       | Proximal InterPhalangeals                                                  |
| PK        | Pharmacokinetics                                                           |
| PMC       | Postmarketing Commitments                                                  |
| PMR       | Postmarketing Requirements                                                 |

Biosimilar Multi-disciplinary Evaluation and Review (BMER)

BLA 761118

PF-06410293 a proposed biosimilar to Humira

|           |                                           |
|-----------|-------------------------------------------|
| PREA      | Pediatric Research Equity Act             |
| REMS      | Risk Evaluation and Mitigation Strategies |
| ROA       | Route of Administration                   |
| SAE       | Serious Adverse Event                     |
| SAP       | Statistical Analysis Plan                 |
| SGE       | Special Government Employee               |
| SOC       | System Organ Class                        |
| SOP       | Standard Operating Procedures             |
| SP        | SharePoint                                |
| TEAE      | Treatment-Emergent Adverse Events         |
| ULOQ      | Upper Limit of Quantitation               |
| US-Humira | U.S.-licensed Humira                      |

| Discipline and Title or Role         | Reviewer Name                                                                                                                                                                                                                                 | Office/Division | Sections Authored/Approved                        |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|---------------------------------------------------|
| Nonclinical Reviewer<br>DPARP        | Xiaochun Chen                                                                                                                                                                                                                                 | ODEII/DPARP     | 5, 13.4                                           |
|                                      | Signature: Xiaochun Chen -S<br>Digitally signed by Xiaochun Chen -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaochun Chen -S,<br>0.9.2342.19200300.100.1.1 2002051210<br>Date: 2019.11.15 09 22 04 -05'00'              |                 |                                                   |
| Nonclinical Team Leader<br>DPARP     | Andrew Goodwin                                                                                                                                                                                                                                | ODEII/DPARP     | 5, 13.4                                           |
|                                      | Signature: Andrew C. Goodwin -S<br>Digitally signed by Andrew C. Goodwin -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew C. Goodwin -S,<br>0.9.2342.19200300.100.1.1 2001026825,<br>Date: 2019.11.15 09 06 32 -05'00' |                 |                                                   |
| Clinical Pharmacology<br>Reviewer    | Jianmeng Chen                                                                                                                                                                                                                                 | OCP/DIIP        | 6, 13.3                                           |
|                                      | Signature: Jianmeng Chen -S<br>Digitally signed by Jianmeng Chen -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianmeng Chen -S,<br>0.9.2342.19200300.100.1.1=2000743816<br>Date: 2019.11.15 09:11:13 -05'00'              |                 |                                                   |
| Clinical Pharmacology<br>Team Leader | Ping Ji                                                                                                                                                                                                                                       | OCP/DIIP        | 6, 13.3                                           |
|                                      | Signature: Ping Ji -S<br>Digitally signed by Ping Ji -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ping Ji -S,<br>0.9.2342.19200300.100.1.1 2000364393<br>Date: 2019.11.15 09 18 46 -05'00'                                |                 |                                                   |
| Clinical Reviewer DPARP              | Jin Chen                                                                                                                                                                                                                                      | ODEII/DPARP     | 2, 3, 4, 7, 8, 9, 10, 11,<br>13.2, 13.5.3, 13.5.4 |
|                                      | Signature: Jin Chen -S<br>Digitally signed by Jin Chen -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jin Chen -S,<br>0.9.2342.19200300.100.1.1 1300143223<br>Date: 2019.11.15 09 02 10 -05'00'                             |                 |                                                   |
| Clinical Team Leader<br>DPARP        | Rachel Glaser                                                                                                                                                                                                                                 | ODEII/DPARP     | 2, 3, 4, 7, 8, 9, 10, 11,<br>13.2, 13.5.3, 13.5.4 |
|                                      | Signature: Rachel Glaser -S<br>Digitally signed by Rachel Glaser -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rachel Glaser -S,<br>0.9.2342.19200300.100.1.1=0013432915<br>Date: 2019.11.15 11:39:03 -05'00'              |                 |                                                   |
| Clinical Reviewer<br>DGIEP           | Wen-Yi Gao                                                                                                                                                                                                                                    | ODEIII/DGIEP    | 7.6.1                                             |
|                                      | Signature: Wen-yi Gao -S<br>Digitally signed by Wen-yi Gao -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wen-yi Gao -S,<br>0.9.2342.19200300.100.1.1=1300218453<br>Date: 2019.11.15 12:04:51 -05'00'                       |                 |                                                   |
| Clinical Reviewer<br>DGIEP           | Anil Rajpal                                                                                                                                                                                                                                   | ODEIII/DGIEP    | 7.6.1                                             |
|                                      | Signature: Anil K. Rajpal -S<br>Digitally signed by Anil K. Rajpal -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Anil K. Rajpal -S,<br>0.9.2342.19200300.100.1.1 1300170204<br>Date: 2019.11.15 09 46 00 -05'00'           |                 |                                                   |

|                                    |                                                                                                                                                                                                                                                                              |              |       |
|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-------|
| Clinical Team Leader<br>DGIEP      | Jessica Lee                                                                                                                                                                                                                                                                  | ODEIII/DGIEP | 7.6.1 |
|                                    | Signature: Jessica J. Lee -S<br><small>Digitally signed by Jessica J. Lee -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica J. Lee -S,<br/> 0.9.2342.19200300.100.1.1.2000596373<br/> Date: 2019.11.15 12 16 23 -05'00'</small>                     |              |       |
| Clinical Reviewer<br>DDDP          | Gary Chiang                                                                                                                                                                                                                                                                  | ODEIII/DDDP  | 7.6.2 |
|                                    | Signature: Gary Chiang -S<br><small>Digitally signed by Gary Chiang -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Gary Chiang -S,<br/> 0.9.2342.19200300.100.1.1.2000332370<br/> Date: 2019.11.15 09 44 42 -05'00'</small>                              |              |       |
| Clinical Team Leader<br>DDDP       | David Kettl                                                                                                                                                                                                                                                                  | ODEIII/DDDP  | 7.6.2 |
|                                    | Signature: David L. Kettl -S<br><small>Digitally signed by David L. Kettl -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David L. Kettl -S,<br/> 0.9.2342.19200300.100.1.1.1300383857<br/> Date: 2019.11.15 09 55 02 -05'00'</small>                     |              |       |
| Clinical Statistics<br>Reviewer    | William Koh                                                                                                                                                                                                                                                                  | OB/DBIII     | 7     |
|                                    | Signature: William Jen Hoe Koh -S<br><small>Digitally signed by William Jen Hoe Koh -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/> 0.9.23 2.19200300.100.1.1=2002137835,<br/> cn=William Jen Hoe Koh -S<br/> Date: 2019.11.15 09:58:55 -05'00'</small> |              |       |
| Clinical Statistics<br>Team Leader | Rebecca Rothwell                                                                                                                                                                                                                                                             | OB/DBIII     | 7     |
|                                    | Signature: Rebecca Rothwell -S<br><small>Digitally signed by Rebecca Rothwell -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/> 0.9.2342.19200300.100.1.1.2000455521,<br/> cn=Rebecca Rothwell -S<br/> Date: 2019.11.15 09 13 52 -05'00'</small>          |              |       |
| Cross-Discipline Team<br>Leader    | Rachel Glaser                                                                                                                                                                                                                                                                | ODEII/DPARP  | All   |
|                                    | Signature: Rachel Glaser -S<br><small>Digitally signed by Rachel Glaser -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rachel Glaser -S,<br/> 0.9.2342.19200300.100.1.1=0013432915<br/> Date: 2019.11.15 13:21:34 -05'00'</small>                        |              |       |
| Designated Signatory               | Nikolay Nikolov                                                                                                                                                                                                                                                              | ODEII/DPARP  | All   |
|                                    | Signature: Nikolay P. Nikolov -S<br><small>Digitally signed by Nikolay P. Nikolov -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/> 0.9.2342.19200300.100.1.1.0011314790,<br/> cn=Nikolay P. Nikolov -S<br/> Date: 2019.11.15 13 31 58 -05'00'</small>    |              |       |

## 1. Executive Summary

---

### 1.1. Product Introduction

Pfizer (also referred to as “Applicant” in this review) has submitted a biologic license application (BLA) under section 351 (k) of the Public Health Service Act (PHS Act) for PF-06410293 as a proposed biosimilar to US-Humira (adalimumab).

PF-06410293 is a fully human anti-TNF $\alpha$  IgG1 monoclonal antibody produced in Chinese Hamster Ovary cells using recombinant DNA technology. It is proposed as a biosimilar to US-licensed Humira. PF-06410293 binds to TNF- $\alpha$ , blocks its interaction with the p55 and p75 cell surface TNF receptors and neutralizes its biological function.

Pfizer is seeking licensure of PF-06410293 for the following indications for which US-licensed Humira is licensed:<sup>2</sup>

- 1) Rheumatoid Arthritis (RA):
  - Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- 2) Juvenile Idiopathic Arthritis (JIA):
  - Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
- 3) Psoriatic Arthritis (PsA):
  - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- 4) Ankylosing Spondylitis (AS):
  - Reducing signs and symptoms in adult patients with active AS.
- 5) Adult Crohn’s Disease (adult CD):
  - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab products.
- 6) Ulcerative Colitis (UC):
  - Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine

---

<sup>2</sup> FDA-approved Humira labeling

(6-MP). The effectiveness of (b) (4) has not been established in patients who have lost response to or were intolerant to TNF blockers.

7) Plaque Psoriasis (PsO):

- The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

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

### 1.2. Determination Under Section 351(k)(2)(A)(ii) of the PHS Act

Not applicable.

### 1.3. Mechanism of Action, Route of Administration, Dosage Form and Strength Assessment

PF-06410293 binds specifically to TNF-alpha and block its interaction with the p55 and p75 cell surface TNF receptors. PF-06410293 also lyses surface TNF expressing cells *in vitro* in the presence of complement. PF-06410293 does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques.

PF-06410293 product is a sterile liquid solution for subcutaneous injection available as below:

- Prefilled pen (ABRILADA pen)  
Injection: 40 mg/0.8 mL in a single-dose prefilled pen
- Prefilled syringe  
Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe  
Injection: 20 mg/0.4 mL in a single-dose prefilled glass syringe  
Injection: 10 mg/0.2 mL in a single-dose prefilled glass syringe
- Vial  
Injection: 40 mg/0.8 mL in a single-dose glass vial for institutional use only

Each strength of PF-06410293 in prefilled syringes, prefilled pen, and vial is the same as that of US-Humira. PF-06410293 also has the same dosage form and route of administration as that of US-Humira.

#### **1.4. Inspection of Facilities**

FDA's Office of Process and Facilities (OPF) conducted an assessment of the manufacturing facilities for this BLA.

Wyeth BioPharma, Division of Wyeth Pharmaceuticals LLC (FEI 1222181) is responsible for drug substance (DS) manufacturing. A pre-license inspection (PLI) was conducted 4/29-5/3/2019. A 3-item FDA Form 483 issued at the conclusion of the inspection. Refer to the FDA Form 483 for a list of the 483 observations. Deficiencies were adequately addressed in the firm's written response. The inspection was classified as voluntary action indicated (VAI). The PLIs on the DP manufacturing site ( (b) (4) FEI: (b) (4) ) and the prefilled pen assembly site ( (b) (4) FEI: (b) (4) ) were waived based on their inspection history and information provided by the Applicant regarding its GMP operating system. The OPF team has determined that all proposed manufacturing and testing facilities are acceptable based on their currently acceptable cGMP compliance status and recent relevant inspectional coverage.

The OPF team recommended that BLA 761118 be approved from the standpoint of facilities assessment. CDRH has also recommended approval of this application. I concur with these recommendations.

#### **1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product**

Pfizer provided adequate data to establish the scientific bridge to justify the relevance of data generated from the comparative clinical study B5381002, which used EU-Humira as the comparator, to the assessment of biosimilarity:

- The Office of Pharmaceutical Products, OPQ, CDER has determined, and I agree, that based on the data provided by the Applicant, the analytical component of the scientific bridge between PF-06410293, US-Humira, and EU-Humira was established.
- The Office of Clinical Pharmacology (OCP) has determined, and I agree, that based on the data provided by the Applicant, the PK data establish the PK component of the scientific bridge.

## 1.6. Biosimilarity Assessment

**Table 1: Summary and Assessment of Biosimilarity**

| <b>Comparative Analytical Studies: The Office of Pharmaceutical Products, OPQ, CDER has concluded, and I agree, that:</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Summary of evidence                                                                                                       | <ul style="list-style-type: none"> <li>• PF-06410293 is highly similar to US-Humira notwithstanding minor differences in clinically inactive components</li> <li>• Each strength of PF-06410293 in prefilled syringes, prefilled pen, and vial is the same as that of US-Humira</li> <li>• The dosage form and route of administration is also the same as that of US-Humira</li> <li>• The analytical component of the scientific bridge between PF-06410293, US-Humira, and EU-Humira was established to support the relevance of the data generated from studies using EU-Humira as the comparator to the assessment of biosimilarity</li> </ul> |
| Residual uncertainties and outcome                                                                                        | <ul style="list-style-type: none"> <li>• There are no residual uncertainties from the product quality assessment</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Animal Studies: The Pharmacology and Toxicology team concluded, and I agree, that:</b>                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Summary of evidence                                                                                                       | <ul style="list-style-type: none"> <li>• The PF-06410293 nonclinical development program was considered adequate to support clinical development</li> <li>• Since an adequate scientific bridge was established to support the relevance of data generated with EU-Humira to the assessment of biosimilarity, the information in the pharmacology/toxicology assessment support the determination of biosimilarity</li> </ul>                                                                                                                                                                                                                       |
| Residual uncertainties and outcome                                                                                        | <ul style="list-style-type: none"> <li>• There are no residual uncertainties from the pharmacology/toxicology assessment</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Clinical Pharmacology: The Clinical Pharmacology team concluded, and I agree, that:</b>                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

|                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Summary of evidence                                                                       | <ul style="list-style-type: none"><li>• PK similarity has been demonstrated between PF-06410293 and US- Humira, and supports a demonstration of no clinically meaningful differences between PF-06410293 and US- Humira.</li><li>• PK similarity between PF-06410293, EU-Humira, and US-Humira provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Humira to the assessment of biosimilarity.</li><li>• Comparable incidence of ADA formation between PF-06410293 and US-Humira in healthy subjects supports a demonstration of no clinically meaningful differences</li><li>• Given the scientific bridge was established (based on the analytical and PK comparisons) between PF-06410293, US-Humira, and EU-Humira to justify the relevance of data generated with EU-Humira as the comparator, comparable incidence of ADA formation between PF-06410293 and EU-Humira in patients with RA supports a demonstration of no clinically meaningful differences between PF-06410293 and US-licensed Humira.</li></ul> |
| Residual uncertainties and outcome                                                        | <ul style="list-style-type: none"><li>• There are no clinical pharmacology residual uncertainties regarding the PK assessments</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Clinical Studies: The Clinical and Statistical teams concluded, and I agree, that:</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

|                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Summary of evidence</p>                                               | <ul style="list-style-type: none"> <li>• In Study B5381002, there were no meaningful differences in terms of efficacy between PF-06410293 and EU-Humira, and the frequency of treatment emergent adverse events, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms</li> <li>• Given the scientific bridge was established (based on the analytical and PK comparisons) between PF-06410293, US-Humira, and EU-Humira to justify the relevance of the data generated with EU-Humira as the comparator, the collective evidence from submitted clinical studies, including the comparative clinical study B5381002, supports a demonstration of no clinically meaningful differences between PF-06410293 and US-Humira in the studied indication (RA)</li> </ul>                                                                                                                         |
| <p>Residual uncertainties and outcome</p>                                | <ul style="list-style-type: none"> <li>• There are no residual uncertainties from the clinical or statistical perspective regarding the demonstration of no clinically meaningful differences between PF06410293 and US-Humira</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p><b>Extrapolation of Data to Support Licensure as a Biosimilar</b></p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p>Summary of evidence</p>                                               | <ul style="list-style-type: none"> <li>• DGIEP, DDDP and DPARP teams have determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (RA), to support licensure of PF-06410293 as a biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Humira has been previously approved:             <ul style="list-style-type: none"> <li>○ Treatment of inflammatory bowel disease indications (ulcerative colitis and adult Crohn’s disease)</li> <li>○ Treatment of moderate to severe plaque psoriasis</li> <li>○ Treatment of juvenile idiopathic arthritis in patients 4 years of age and older</li> <li>○ Treatment of psoriatic arthritis</li> <li>○ Treatment of ankylosing spondylitis</li> </ul> </li> </ul> |

|                                    |                                                                                                                                                                                                                                       |
|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Residual uncertainties and outcome | <ul style="list-style-type: none"><li>• There were no residual uncertainties regarding the extrapolation of data and information to support licensure of PF-06410293 as a biosimilar to US-Humira for the above indications</li></ul> |
|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 1.7. Conclusions on Licensure

In considering the totality of the evidence, the data submitted by the Applicant show that PF-06410293 is highly similar to U.S.-licensed Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between PF-06410293 and U.S.-licensed Humira in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of PF-06410293 for JIA in patients 4 years and older, PsA, AS, PsO, Adult CD, and UC. The information submitted by the Applicant demonstrates that PF-06410293 is biosimilar to U.S.-licensed Humira for each of the following indications for which U.S.-licensed Humira has been previously approved and the Applicant is seeking licensure for PF-06410293: RA, JIA in patients 4 years and older, PsA, AS, PsO, Adult CD, and UC and should be licensed.<sup>3</sup>

### Author:

Rachel Glaser, M.D.

Cross-Discipline Team Leader (CDTL)

---

<sup>3</sup> The proposed PF-06410293 labeling states: "Biosimilarity of ABRILADA has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information."

## 2. Introduction and Regulatory Background

---

### 2.1. Important Safety Issues with Consideration to US-Humira

The US-licensed Humira label (USPI) includes a boxed warning (see below) and several warnings and precautions, in particular serious infections, including tuberculosis and other opportunistic infections, and malignancies including non-melanoma skin cancer and lymphoproliferative disorders, which also apply to other TNF blockers.

US-Humira labeling's boxed warning provides:

#### “SERIOUS INFECTIONS

Patients treated with Humira are at increased risk for developing serious infections that may lead to hospitalization or death [...]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before Humira use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric antifungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy [...].

#### MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and

adolescent patients treated with TNF blockers including HUMIRA [...]. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants [...].”

The warning and precautions section (section 5 of the USPI) lists other known safety issues with Humira and other TNF blockers, including:

- Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystosis have been reported in patients receiving HUMIRA. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicemia. Hospitalization or fatal outcomes associated with infections have been reported. Tuberculosis (including pulmonary and extra-pulmonary tuberculosis) reactivation and new onset cases have been reported in patients receiving HUMIRA. If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, invasive fungal infection is to be considered in the differential diagnosis.
- Malignancies including breast, colon, prostate, lung, and melanoma, nonmelanoma skin cancer, lymphoma and leukemia. Additionally, lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA. Rare cases of hepatosplenic T cell lymphoma have occurred in adolescents and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.
- Hypersensitivity reactions including anaphylaxis
- Hepatitis B reactivation, some cases with fatal outcome, has occurred in patients who are chronic carriers of this virus
- Neurologic reactions (rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome)
- Hematological reactions (rare cases of pancytopenia including aplastic anemia, and adverse reactions of the hematologic system, including medically significant cytopenia, e.g. thrombocytopenia, leukopenia)
- Concurrent use of anakinra or abatacept (associated with a greater proportion of serious infections and, in case of anakinra, neutropenia). Both anakinra and abatacept were prohibited treatments during study, and patients were only randomized after a 6-month washout period after anakinra or abatacept treatment.

- Heart failure, i.e. onset or worsening of congestive heart failure
- Autoimmunity, i.e. formation of autoantibodies and, rarely, development of a lupus-like syndrome
- Immunizations; patients on Humira may receive concurrent vaccinations, except for live vaccines

US-Humira use has been previously described as leading to the development of anti-drug antibody (ADA) formation in clinical studies, and according to the FDA-approved labeling for US-Humira, there was a trend toward higher adalimumab apparent clearance in the presence of anti-adalimumab antibodies, but no apparent correlation between the development of anti-adalimumab antibodies and the occurrence of adverse events (AEs). In the published literature, however, anti-adalimumab antibodies are described to be associated with increased frequency of clinical adverse effects, such as thromboembolic events or hypersensitivity reactions (Korswagen et al 2011, van Schouwenburg et al 2013) but other authors do not describe such an association (Vincent et al 2013).

## **2.2. Summary of Presubmission Regulatory Activity Related to Submission**

The Division had multiple interactions with the Applicant during the development of PF-06410293. Key discussions are detailed below:

Initial interactions included pre-IND written responses on November 13, 2012 and a Biosimilar Biological Product Development (BPD) Type 2 meeting on February 20, 2014, that focused on the analytical data needed to support the development of PF-06410293 as a proposed biosimilar to Humira and the use of EU-Humira in the comparative clinical study.

A BPD Type 2 meeting took place on May 6, 2014 to discuss further development of PF-06410293, including available results of the comparative analytical assessment and Study B5381001, which did not meet the study objectives for two PK comparisons. A subsequent BPD Type 2 meeting took place on March 27, 2017, which included further discussion on certain quality attributes as well as PK results from Study B5381001. At a BPD Type 3 meeting on March 8, 2018, FDA provided additional feedback on the comparative analytical data, and agreed that the PK results from Study B5381007 were within the prespecified range.

There was general agreement on the proposed design of the comparative clinical study, the real-life patient handling assessment, as well as discussion of the need for human factors studies (BPD Type 2 meeting, May 6, 2014). The Agency agreed to the justification for an asymmetric margin of (-12%, +15%) with a 90% CI for the similarity assessment of the comparative clinical trial (Advice Letter dated September 16, 2015). There was general agreement on the proposed design of Study B53381005 for the purpose of supporting the proposed prefilled pen (BPD Type 2 meeting, December 2, 2014).

A pre-BLA BPD Type 4 meeting was held on June 12, 2018 which focused on the content and format of the BLA submission. The Agency agreed with the Applicant's plan to submit data to support licensure of the 10 mg/0.2mL PFS in the original BLA. The Applicant submitted an initial pediatric study plan (iPSP) on April 6, 2018. The FDA agreed to the iPSP on August 14, 2018.

### 2.3. Studies and Publicly Available Information Submitted by the Applicant

The studies submitted to support the biosimilarity of PF-06410293 to US-Humira include one animal study (Table 2), two 3-way single-dose bridging PK studies (between PF-06410293, US-Humira and EU-Humira), one comparative PK study for pre-filled syringe (PFS) and pre-filled pen (PFP), and one comparative clinical study in patients with RA. See Table 3.

**Table 2. PF-06410293 Nonclinical Studies Submitted**

| Study Title                | Study Number | Duration/Dose | Regimen/Route     | Number of Subjects | Population        |
|----------------------------|--------------|---------------|-------------------|--------------------|-------------------|
| <b>Nonclinical Studies</b> |              |               |                   |                    |                   |
| 12GR307                    | 114729       | 1 month       | subcutaneous (SC) | 3/sex/group        | Cynomolgus Monkey |

**Table 3. PF-06410293 Clinical Studies Submitted**

| Study Identity                         | NCT no.                  | Study Objective                                         | Study Design                                 | Study Population                        | Treatment Groups                                  |
|----------------------------------------|--------------------------|---------------------------------------------------------|----------------------------------------------|-----------------------------------------|---------------------------------------------------|
| <b>PK Similarity Study</b>             |                          |                                                         |                                              |                                         |                                                   |
| B5381001                               | <a href="#">01870986</a> | Comparative PK, safety immunogenicity                   | Randomized, double-blind, single-dose, 3-arm | Healthy adults<br>N=210 (1:1:1)         | 40 mg SC<br>PF-06410293<br>US-Humira<br>EU-Humira |
| B5381007                               | <a href="#">02237729</a> | Comparative PK, safety immunogenicity                   | Randomized, double-blind, single-dose, 3-arm | Healthy adults<br>N=362 (1:1:1)         | 40 mg SC<br>PF-06410293<br>US-Humira<br>EU-Humira |
| <b>Comparative Clinical Study(ies)</b> |                          |                                                         |                                              |                                         |                                                   |
| B5381002                               | <a href="#">02480153</a> | Comparative efficacy, safety, immunogenicity and pop-PK | Randomized, double-blinded, 2-arm            | Moderately to severely active RA, N=597 | 40 mg SC q2-week<br>PF-06410293<br>EU-Humira      |
| B5381002 Substudy                      | <a href="#">02480153</a> | Self-use PFP                                            | Open-label, single-arm                       | Moderately to severely active RA, n=50  | 40 mg SC q2-week<br>PF-06410293 PFP               |
| <b>Other Studies</b>                   |                          |                                                         |                                              |                                         |                                                   |
| B5381005                               | <a href="#">02572245</a> | Comparative PK and safety of PFS and PFP                | Randomized, open-label, single-dose 2-arm    | Healthy adults<br>N=164                 | 40 mg SC<br>PF-06410293 in PFS and PFP            |

PFS = pre-filled syringe; PFP = pre-filled pen; pop-PK = population pharmacokinetics; RA = rheumatoid arthritis; SC = subcutaneously; US = United States.

**Authors:**

Jin Chen, MD, PhD  
Clinical Reviewer

Rachel Glaser, MD  
Clinical Team Leader

### **3. Clinical Studies: Ethics and Good Clinical Practice**

---

#### **3.1. Submission Quality and Integrity**

The BLA submission is consistent with the Agency's guidance that was provided to the sponsor during pre-BLA submission meeting (BPD Type 4 meeting). The data quality and integrity of the studies were acceptable and the amount of missing data was minimal and did not impact overall conclusions regarding biosimilarity. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

#### **3.2. Statistical Analysis of Clinical Data**

The submitted datasets for all clinical studies were consistent with Clinical Data Interchange Standards Consortium (CDISC) standards. Documentation for the datasets was sufficiently detailed. In general, the quality of data submitted for analyses was adequate.

All versions of the statistical analysis plan (SAP) were included in this submission. The statistical reviewer was able to reproduce the relevant key analyses based on the SAP.

The comparative clinical study had an external data monitoring committee (DMC) consisting of three members who reviewed blinded and unblinded the comparative safety and efficacy data. A Pfizer statistician, independent from the Pfizer study team, prepared the unblinded data reports to the DMC for closed sessions. There were sufficient firewalls between the Pfizer statistician and study team and documentation to operationally avoid unintentional unblinding. During the study, the DMC met six times and the open and closed sessions were submitted for review. In summary, the overall conduct of the study was acceptable.

#### **3.3. Compliance with Good Clinical Practices**

All studies were conducted according to Good Clinical Practice (GCP) as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters for the studies received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Subjects signed informed consent documents. Written informed consent was obtained prior to subjects entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the

pertinent regulatory authority.

### **3.4. Financial Disclosures**

The Applicant has adequately disclosed financial interests with clinical investigators who participated in the four covered clinical studies listed in Table 3 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 21CFR part 54. There were no potentially conflicting financial interests identified for 919 of 934 clinical investigators.

A total of 13 investigators from 13 study sites in Study B5381002 had financial disclosures >\$25,000 (see Appendix 16.2 for details). Total enrollment from the 13 sites was 32 subjects (2.2% of total enrolled 597), well balanced between two treatment arms (n=16/arm). One of 13 sites, Site #2331, had a high enrollment (n=9) with unbalanced assignment between the two treatment arms (n=7 on PF-06410293 , n=2 on EU-Humira), however, this site was selected for the OSI inspection (see Section 4.5) and no outstanding issues were identified.

The number of patients enrolled at the individual investigator sites were small compared to the total number of patients enrolled in the overall study. Furthermore, the multi-center and blinded nature of Study B5381002 make it unlikely that the financial interest could have influenced or biased the results of the study. Accordingly, any outstanding concerns regarding the impact of the disclosed financial interests with the involved study investigators/study studies has been adequately addressed.

#### **Authors:**

Jin Chen, MD, PhD  
Clinical Reviewer

Rachel Glaser, MD  
Clinical Team Leader

## 4. Summary of Conclusions of Other Review Disciplines

---

### 4.1. Chemistry, Manufacturing and Controls

The Office of Pharmaceutical Products, OPQ, CDER, recommends approval of BLA 761118 for PF-06410293 manufactured by Pfizer. The OPQ team determined that the data submitted in this application are adequate to support the following conclusions:

- The manufacture of PF-06410293 is well-controlled and leads to a product that is pure, potent, and safe
- PF-06410293 is highly similar to US-Humira notwithstanding minor differences in clinically inactive components
- Each strength of PF-06410293 in prefilled syringe, prefilled pen, and vial is the same as that of US-Humira. PF-06410293 also has the same dosage form and route of administration as that of US-Humira.
- The analytical component of the scientific bridge between PF-06410293, US-Humira, and EU-Humira was established to support the relevance of the data generated from clinical studies using EU-Humira as the comparator to the assessment of biosimilarity.

### 4.2. Clinical Microbiology

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for approval from a microbial control, sterility assurance and product quality perspective.

### 4.3. Devices

PF-06410293 drug product is a sterile liquid solution with the following proposed strengths and presentations:

- Prefilled syringe
  - Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe
  - Injection: 20 mg/0.4 mL in a single-dose prefilled glass syringe
  - Injection: 10 mg/0.2 mL in a single-dose prefilled glass syringe
- Prefilled pen (ABRILADA pen)
  - Injection: 40 mg/0.8 mL in a single-dose prefilled pen
- Vial
  - Injection: 40 mg/0.8 mL in a single-dose glass vial for institutional use only

#### Container closure:

- ABRILADA PFS: DP is supplied in a 1 mL long (b) (4) glass prefilled syringe with a 29 gauge thin walled ½ inch staked needle. Each PFS contains 40 mg/0.8 mL, 20 mg/0.4 mL, or 10 mg/0.2 mL of PF-06410293 solution for injection. All PFS presentations comprise the same primary container closure system and device components (a backstop and a plunger rod). Color-coded labels are used to help the user differentiate between the dose strengths.
- ABRILADA PFP: the autoinjector encloses a 40 mg/0.8 mL PF-06410293 PFS. The PFS is the primary CCS. The autoinjector assembly is 150 mm in length and 17 mm in diameter, with a white cap and activation button with a purple bezel.
- ABRILADA vial: DP is supplied in a 2 mL (b) (4) clear glass vials with (b) (4) stoppers and crimp seals with flip-off caps. Each vial contains 40 mg/0.8 mL PF-06410293 solution for injection.

#### 4.3.1. Center for Devices and Radiological Health (CDRH)

CDRH recommends approval based on assessment of device constituents parts of the combination product. See review by Dr. Rumi Young dated July 2, 2019 for additional details.

#### 4.3.2. Division of Medication Error Prevention and Analysis (DMEPA)

PF-06410293 is a proposed combination product, with three proposed presentations, a prefilled syringe, prefilled pen, and vial (for institutional use only). To support the proposed presentations, the Applicant has submitted product quality, clinical pharmacology, and device data, reviewed elsewhere in this document. In addition, the Applicant provided a Use-Related Risk Analysis (URRA) to support the use of these devices in the intended patient populations, which were reviewed by DMEPA. The Applicant submitted human factors (HF) data for use of the PFP and submitted a justification for not submitting HF study results to support use of the PFS.

To support the use of the PFS, the DMEPA team determined, and I agree, that additional HF data would not be needed to support the PFS user interface for all intended users, in the intended use environments, for its intended uses.

With regards to the PF-06410293 PFP presentation, DMEPA finds that no additional HF data was necessary for the adult populations. With respect to the pediatric/adolescent JIA patients, although the HF validation study included only 9 JIA patients, less than the recommended 15 study participants per distinct user group, DMEPA evaluated the data for all adolescent patients (including JIA surrogates). DMEPA deferred to DPARP on addressing this data gap and determining the appropriate labeling for this user group.

DPARP acknowledges the DMEPA assessment and recommendations. However, in reviewing the DMEPA recommendations, DPARP also considered that irrespective of whether the patient

is an adult with RA or a JIA patient, it is expected that the patient will only self-administer PF-06410293 when willing to do so, having received appropriate training, and having demonstrated the ability to self-inject. This is explicitly stated in the product labeling, Section 2. Dosage and Administration:

*ABRILADA is intended for use under the guidance and supervision of a physician. A patient may self-inject ABRILADA or a caregiver may inject ABRILADA using either the ABRILADA pen or prefilled syringe if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.*

Additional instructions are included in Section 17. Patient Counseling Information.

Considering the above contextual information, DPARP concludes that no additional HF studies are needed in JIA for this application and the current labeling is appropriate and sufficient to ensure the safe and effective use of both the PF-06410293 PFS and PF-06410293 PFP when used as labeled.

DMEPA also provided recommendations for labeling changes based on the available data within the submitted HF study results reports, as well as heuristic and expert review of the user interface. For this particular review, DMEPA determined the changes can be implemented without additional validation testing, and I agree that these do not require additional human factors (HF) validation data. These changes were incorporated in the product labeling.

#### **4.4. Office of Study Integrity and Surveillance (OSIS)**

An inspection was requested for both clinical site and bioanalytical site of Study B5381007. A clinical site inspection of Altasciences Clinical Kansas, Inc in Overland Park, KS was conducted. No objectional conditions were observed and the final inspection classification is No Action Indicated. OSIS recommends that the clinical data from Study B5381007 are reliable to support a regulatory decision. Refer to the review memo by Dr. Gajendiran Mahadevan dated August 7, 2019.

OSIS determined that an analytical site inspection was not warranted for [REDACTED] (b) (4) based on the results of a previous inspection [REDACTED] (b) (4) which was classified as No Action Indicated. Refer to the review memo by Dr. Angel Johnson dated March 13, 2019.

#### **4.5. Office of Scientific Investigations (OSI)**

The following three clinical study sites were selected from the comparative clinical study B5381002 for inspection by CDER Office of Scientific Investigations (OSI).

- Site #2331 (Dr. Wassim Saikali, Beckly, West Virginia, USA): enrolled N=9
- Site #2231 (Dr. Raul Maria Veiga, Cabello, Madrid, Spain): enrolled N=11
- Site #2154 (Dr. Margarita Pileckyte, Kauno Apskritis, Lithuania): enrolled N=19

These sites were selected for inspection based on high overall enrollment, response rates, serious adverse event reporting, and discontinuation rates by using the Clinical Site Selection Tool. Upon completion of the study site investigations, OSI concluded that the study data derived from these clinical sites, based on the inspections, are considered reliable and the studies in support of this application appear to have been conducted adequately. At the time of this review, the final classification for the three study sites is No Action Indicated (NAI). Refer to the review by Dr. Min Lu dated May 22, 2019 for detailed information regarding the clinical site inspections.

**Authors:**

Jin Chen, MD, PhD  
Clinical Reviewer

Rachel Glaser, MD  
Clinical Team Leader

## 5. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

### 5.1. Nonclinical Executive Summary and Recommendation

Early in the development of PF-06410293, the sponsor requested advice on the nonclinical program. At that time, limited comparative analytical assessment between PF-06410293 and US-Humira was available. Therefore, a 4-week general toxicity study in male and female cynomolgus monkeys was recommended. FDA noted that the extent and results of the analytical data package could alter the recommended nonclinical program. In the IND application submitted on April 24, 2013, the sponsor provided comparative analytical data among PF-06410293, US-Humira and EU-Humira encompassing physicochemical, potency, and biological activity attributes. In addition, results from a one-month subcutaneous (SC) toxicology study in cynomolgus monkeys were provided. The sponsor submitted the BLA 761118 on November 16, 2018. In response to comment from our filing review dated January 22, 2019, the sponsor also submitted a safety assessment of extractables and leachables from several container closure systems for drug substance and drug products on February 22, 2019.

In the 1-month repeat-dose general toxicity study, cynomolgus monkeys (3/sex/group) received 5 SC doses (157 mg/kg QW) of PF-06410293 or EU-Humira. The study included histopathological examinations of a complete panel of organs and tissues. Observed drug-related spleen findings (i.e., decreased organ weights and lymphoid cellularity) in the two test article groups were considered to be pharmacodynamic (PD) effects. The toxicity profiles of PF-06410293 and EU-Humira were considered to be similar at the 157 mg/kg/week dose.

For the toxicokinetic (TK) assessment, there were no apparent sex-related differences in exposures for PF-06410293 or EU-Humira. On Days 1 and 22, the TK parameters for the PF-06410293 or EU-Humira-treated groups were generally similar based on exposure and drug accumulation ratios. The serum concentration-time profiles of PF-06410293 and EU-Humira in monkeys on both Days 1 and 22 were similar. No incidence of anti-drug antibody (ADA) induction to PF-06410293 was noted. The induction of ADA in one EU-Humira-treated animal was noted but did not impact the overall TK interpretation in this study.

The PF-06410293 drug substance is filled (b) (4). The PF-06410293 drug product is packaged either in glass vial (40 mg) or in Prefilled Syringe (PFS, 10/20/40 mg) that can be further enclosed in Prefilled Pen (PFP) for 40 mg/0.8 ml strength. The primary container closure system for glass vial includes 2 mL (b) (4) clear glass vial with (b) (4) stopper and crimp seal with flip-off cap. The primary container closure systems for PFS and PFP are the same and include a 1 mL (b) (4) glass syringe (b) (4) with a (staked) needle, a (b) (4) elastomer needle shield with a (b) (4) rigid cover, and a (b) (4) elastomeric plunger stopper. Critical components having direct/potential contact with formulation during storage or dosing or contact with patient during dosing were identified from (b) (4) the glass vial (stopper) and PFS/PFP (plunger stopper,

tip cap, syringe barrel, syringe needle, and syringe needle (b) (4) ) and were subjected to controlled extraction and leachable studies. These critical components have been included in many FDA approved drug products for injection. Safety evaluations of potential extractables and leachables were performed. There were no nonclinical safety concerns for observed extractables and leachables.

The toxicity and TK profiles of PF-06410293 and EU-Humira were considered to be similar. Assuming a scientific bridge between PF-06410293, US-Humira and EU-Humira was established to justify the relevance of data generated using EU-Humira in the 1-month repeat-dose general toxicity study in cynomolgus monkeys, the nonclinical repeat-dose toxicology and TK study in monkeys supports a demonstration of biosimilarity between PF-06410293 and US-Humira. See Sections 5.2 and 16.4.4 for additional information from the nonclinical assessment.

### 5.1.1. Nonclinical Residual Uncertainties Assessment

There were no residual uncertainties identified based on review of the animal study regarding safety or TK parameters.

## 5.2. Product Information

### Product Formulation

PF-06410293 will be supplied as a sterile solution designed for subcutaneous injection with clarity (b) (4) nephelometric turbidity units (NTU) and coloration (b) (4) of the brown color standard. The PF-06410293 drug products contain a formulation of 50 mg/mL PF-06410293 drug substance, 0.786 mg/mL L-histidine, 3.132 mg/mL L-histidine HCl monohydrate, 0.05 mg/mL edetate disodium dihydrate, 85 mg/mL sucrose, 0.2 mg/mL L-methionine, 0.2 mg/mL polysorbate 80 and water for injection (Table 4).

**Table 4. Composition of PF-06410293 Drug Products, for injection**

| Ingredients                 | Reference to Standards    | Function       | Unit Formula  |               |                              |               |
|-----------------------------|---------------------------|----------------|---------------|---------------|------------------------------|---------------|
|                             |                           |                | 10mg PFS (mg) | 20mg PFS (mg) | 40mg vial or PFS or PFP (mg) | (mg/mL)       |
| PF-06410293                 | Pfizer                    | Drug Substance | 10            | 20            | 40                           | 50            |
| L-Histidine                 | USP, Ph. Eur.             | (b) (4)        | 0.157         | 0.314         | 0.629                        | 0.786         |
| L-Histidine HCl monohydrate | Ph. Eur., JP              |                | 0.626         | 1.253         | 2.506                        | 3.132         |
| Edetate Disodium Dihydrate  | USP, Ph. Eur., BP, NF, JP |                | 0.01          | 0.02          | 0.04                         | 0.05          |
| Sucrose                     | USP, Ph. Eur., JP         |                | 17            | 34            | 68                           | 85            |
| L-Methionine                | USP, Ph. Eur.             |                | 0.04          | 0.08          | 0.16                         | 0.2           |
| Polysorbate 80              | NF, Ph. Eur., JP          |                | 0.04          | 0.08          | 0.16                         | 0.2           |
| Water for injection         | USP, Ph. Eur., JP         |                | q.s to 0.2 mL | q.s to 0.4 mL | q.s to 0.8 mL                | q.s to 1.0 mL |

pH 5.5, 20 mM Histidine concentration

q.s: quantity sufficient

**Comments on Novel Excipients**

The excipients used in the formulation of the PF-06410293 drug products differ from that of US-Humira (concentration of 50 mg/ml). The only excipient found in both the PF-06410293 formulation and US-Humira 50 mg/ml formulation was polysorbate 80. The maximal quantity of the polysorbate 80 in PF-06410293 drug products for the proposed maximal dose of 160 mg/day for PF-06410293 was lower than that used in US-Humira. All excipients for PF-06410293 were compendial and their quality standards met the current version of the USP or NF, Ph. Eur., JP or BP. None of the excipients used in PF-06410293 were of human or animal origin. The total quantity of histidine from L-histidine and L-histidine hydrochloride monohydrate was combined to accurately assess the total amount of histidine. Excipients are within the ranges that are found in the inactive ingredient database..

**Authors:**

Xiaochun Chen, PhD  
Nonclinical Reviewer

Andrew Goodwin, PhD  
Nonclinical Supervisor

## 6. Clinical Pharmacology Evaluation and Recommendations

### 6.1. Clinical Pharmacology Executive Summary and Recommendation

**Table 5. Clinical Pharmacology Major Review Issues and Recommendations**

| Review Issue                        | Recommendations and Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PK similarity                       | <ul style="list-style-type: none"> <li>PK similarity has been demonstrated between PF-06410293 and US-Humira, and supports a demonstration of no clinically meaningful differences between PF-06410293 and US-Humira.</li> <li>PK similarity between PF-06410293, EU-Humira, and US-Humira provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Humira to the assessment of biosimilarity .</li> </ul>                                                                                                                                                         |
| PD similarity, if applicable        | <ul style="list-style-type: none"> <li>Not applicable</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Immunogenicity assessment           | <ul style="list-style-type: none"> <li>Comparable incidence of ADA formation between PF-06410293 and US-Humira in healthy subjects supports a demonstration of no clinically meaningful differences.</li> <li>There was comparable incidence of ADA formation between PF-06410293, EU-Humira, and US-Humira in healthy subjects and between PF-06410293 and EU-Humira in patients with RA. Because the scientific bridge was established to justify the relevance of data generated with EU-Humira, these data support a demonstration of no clinically meaningful differences between PF-06410293 and US-Humira.</li> </ul> |
| Other (PK comparability assessment) | <ul style="list-style-type: none"> <li>PK of PF-06410293 administered using PFS and PFP (prefilled pen) was comparable.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

In the 3-way PK similarity study (Study B5381007), the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of PF-06410293 to EU-Humira, PF-06410293 to US-Humira, and EU-Humira to US-Humira for the tested PK parameters (i.e., C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-inf</sub>) were all within the pre-specified PK similarity acceptance criteria of 80-125% (Table 6). Thus, the PK portion of the scientific bridge was established to justify the relevance of the data generated using EU-Humira as the comparator in addition to demonstrating PK similarity between PF-

06410293 and US-Humira.

**Table 6. Summary of statistical analyses for assessment of PK similarity (Study B5381007)**

| Parameter                      | Statistic      | PF-06410293 (n=106) | US-HUMIRA (n=101) | EU-HUMIRA (n=104) | Geometric Mean Ratio* (90% CI) |                          |                        |
|--------------------------------|----------------|---------------------|-------------------|-------------------|--------------------------------|--------------------------|------------------------|
|                                |                |                     |                   |                   | PF-06410293 vs US-HUMIRA       | PF-06410293 vs EU-HUMIRA | EU-HUMIRA vs US-HUMIRA |
| <b>Primary</b>                 |                |                     |                   |                   |                                |                          |                        |
| AUC <sub>0-inf</sub> (µg•h/mL) | Geometric Mean | 2910                | 2534              | 2757              | 112.00 (102.39, 122.50)        | 104.86 (95.93, 114.62)   | 106.81 (97.62, 116.85) |
| AUC <sub>last</sub> (µg•h/mL)  | Geometric Mean | 2569                | 2275              | 2414              | 112.90 (103.60, 123.03)        | 106.42 (97.72, 115.90)   | 106.09 (97.31, 115.65) |
| C <sub>max</sub> (µg/mL)       | Geometric Mean | 4.344               | 3.891             | 3.901             | 111.64 (104.18, 119.64)        | 111.36 (103.97, 119.27)  | 100.25 (93.52, 107.46) |

\*Presented as percent. Source: FDA analysis

Overall, from a clinical pharmacology perspective, the submitted clinical pharmacology studies (1) support a demonstration that there are no clinically meaningful differences between PF-06410293 and US-Humira and (2) establish the PK component of the scientific bridge that justifies the relevance of comparative data generated using EU-Humira to the assessment of biosimilarity.

### 6.1.1. Clinical Pharmacology Residual Uncertainties Assessment

PK similarity was demonstrated across PF-06410293, US-Humira, and EU-Humira in the 3-way PK similarity study (B5381007). There were no clinical pharmacology residual uncertainties regarding the PK or immunogenicity assessments for PF-06410293, US-Humira and EU-Humira.

## 6.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

In Study B5381007, a PK similarity study in healthy subjects (N=120/arm), following a single SC 40 mg dose of PF-06410293, EU-Humira, or US-Humira, the 90% CIs for the GMRs of PF-06410293 to EU-Humira, PF-06410293 to US-Humira, and EU-Humira to US-Humira for the tested PK parameters (i.e., C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-inf</sub>) were all within the PK similarity acceptance interval of 80-125%. These pairwise comparisons met the pre-specified criteria for PK similarity; thus, the PK portion of the scientific bridge was established to support the

relevance of the data generated using EU-Humira as the comparator in the comparative clinical study (Study B5381002).

### 6.3. Human Pharmacokinetics and Pharmacodynamics

#### Clinical Pharmacology Study Design Features

Four clinical studies collected PK data (**Table 3**).

- Study B5381001 was designed as a 3-way PK similarity study in healthy subjects. However, the upper limits of the 90% confidence intervals (CIs) exceeded 125.00% for the AUC<sub>t</sub> comparison of PF-06410293 to US-Humira, and for the AUC<sub>inf</sub> comparisons of PF-06410293 to EU-Humira and to US-Humira. The PK information from Study B5381001 was subsequently used to support the study design and sample size calculation in PK similarity study B5381007.
- Study B5381007 is a 3-way PK similarity study to compare the PK, immunogenicity, and safety of PF-06410293, US-Humira, and EU-Humira in healthy adult subjects.
- In addition, trough concentrations were collected in RA patients receiving PF-06410293 or EU-Humira in study B5381002.
- Also, to compare the PK profiles of PF-06410293 using PFS and PFP, a comparability study was conducted in healthy subjects (B5381005).

Refer to **Table 3** for a summary of the studies listed above. This clinical pharmacology review primarily focused on the PK similarity Study B5381007. We also evaluated the PK and immunogenicity in Studies B5381001, B5381002 and B5381005.

#### Clinical Pharmacology Study Endpoints

PK (AUC<sub>0-inf</sub>, AUC<sub>0-t</sub>, and C<sub>max</sub>) was assessed as primary endpoint in the Studies B5381001 and B5381007. Safety, tolerability and immunogenicity were the secondary endpoints. The endpoints are acceptable. The study design elements and the PK similarity assessments were aligned with the FDA guidance for industry *Clinical Pharmacology Data To Support A Demonstration Of Biosimilarity To A Reference Product*, (May 2016).

Study B5381002 was the comparative clinical study in patients with RA. C<sub>trough</sub> was assessed in this study, and allowed for the assessment of impact of immunogenicity on PK.

Primary PK endpoints for Study B5381005 is C<sub>max</sub> and area under the serum concentration-time profile from time 0 to 2 weeks after dosing (AUC<sub>0-2wk</sub>) for PF-06410293.

#### Bioanalytical PK Method and Performance

The serum concentrations of PF-06410293, EU-Humira and US-Humira were appropriately quantified using validated enzyme-linked immunosorbent assay (ELISA) in Study B5381007 (validation report B5389001) and Study B5381005 (validation report B5389001). During the method validation, EU-Humira was used to establish the standard curves. The accuracy and precision were evaluated using PF-06410293, EU-Humira and US-Humira as QC samples. See detailed information about the assay validation in **Appendix 13.3.1**.

### **PK Similarity Assessment**

PK similarity assessment was conducted in healthy subjects in Study B5381001 and Study B5381007.

Study B5381001 was designed as a 3-way PK similarity study in healthy subjects. Sample size calculation assumed a CV% of 30% for AUC and an AUC ratio equal to 1.05 or less for each AUC comparison. A sample size of 65 subjects per arm was estimated to provide 90% power to achieve PK similarity with 90% confidence interval within 80% to 125%. The PK similarity analysis showed that while the 90% confidence intervals (CIs) for C<sub>max</sub> was met for each comparison, the upper limits of the 90% CIs exceeded 125.00% for the AUC<sub>t</sub> comparison of PF-06410293 to US-Humira, and for the AUC<sub>inf</sub> comparisons of PF-06410293 to EU-Humira and to US-Humira (**Table 7**).

The PK data from Study B5381001 showed that the inter-subject variability was similar across the 3 study drugs, with percent coefficient of variation (%CV) values of 30% to 31% for C<sub>max</sub>, 30% to 33% for AUC<sub>t</sub>, and 39% to 43% for AUC<sub>inf</sub>. Also, the point estimate of AUC ratio for PF-06410293 vs EU-Humira and PF-06410293 vs US-Humira exceeded 1.05 (**Table 7**).

**Table 7. Summary of Statistical Comparisons of PK Exposure Parameters (C<sub>max</sub>, AUC<sub>0-2wk</sub>, AUC<sub>t</sub>, and AUC<sub>inf</sub>) Between Study Products (Day 1-43, PP Analysis Set)**

| Parameter (units)                                             | Adjusted Geometric Means |           | Ratio <sup>a</sup> (Test/Reference)<br>of Adjusted Means | 90% CI for<br>Ratio <sup>a</sup> |
|---------------------------------------------------------------|--------------------------|-----------|----------------------------------------------------------|----------------------------------|
|                                                               | Test                     | Reference |                                                          |                                  |
| <b>Adalimumab-Pfizer (Test) vs. Adalimumab-EU (Reference)</b> |                          |           |                                                          |                                  |
| C <sub>max</sub> (µg/mL)                                      | 3.44                     | 3.20      | 107.58                                                   | 97.73, 118.42                    |
| AUC <sub>0-2wk</sub> (µg•hr/mL)                               | 932.7                    | 851.9     | 109.48                                                   | 98.77, 121.35                    |
| AUC <sub>t</sub> (µg•hr/mL)                                   | 2075                     | 1866      | 111.21                                                   | 100.77, 122.72                   |
| AUC <sub>inf</sub> (µg•hr/mL)                                 | 2700                     | 2388      | 113.10                                                   | 100.08, 127.82                   |
| <b>Adalimumab-Pfizer (Test) vs. Adalimumab-US (Reference)</b> |                          |           |                                                          |                                  |
| C <sub>max</sub> (µg/mL)                                      | 3.44                     | 3.25      | 106.07                                                   | 96.39, 116.72                    |
| AUC <sub>0-2wk</sub> (µg•hr/mL)                               | 932.7                    | 880.0     | 105.99                                                   | 95.65, 117.44                    |
| AUC <sub>t</sub> (µg•hr/mL)                                   | 2075                     | 1768      | 117.39                                                   | 106.41, 129.50                   |
| AUC <sub>inf</sub> (µg•hr/mL)                                 | 2700                     | 2177      | 124.04                                                   | 109.81, 140.11                   |
| <b>Adalimumab-EU (Test) vs. Adalimumab-US (Reference)</b>     |                          |           |                                                          |                                  |
| C <sub>max</sub> (µg/mL)                                      | 3.20                     | 3.25      | 98.59                                                    | 89.60, 108.49                    |
| AUC <sub>0-2wk</sub> (µg•hr/mL)                               | 851.9                    | 880.0     | 96.81                                                    | 87.37, 107.27                    |
| AUC <sub>t</sub> (µg•hr/mL)                                   | 1866                     | 1768      | 105.56                                                   | 95.69, 116.45                    |
| AUC <sub>inf</sub> (µg•hr/mL)                                 | 2388                     | 2177      | 109.67                                                   | 97.09, 123.88                    |

Source: **Table 14**, CSR B5381001

Based, in part, on the higher than expected observed inter-subject variability in PK for Study B5381001, the study was not considered to be adequately powered to sensitively assess certain differences. The results from Study B5381001 were used to support and inform the study design of the subsequent PK similarity Study B5381007. For example, an assumed variability of 45% CV was used for the sample size calculation for Study B5381007. Therefore, Study B5381007 was considered to be more appropriately powered due to these differences observed in Study B5381001. Other aspects of Study B5381001 were also changed for the Study B5381007 design (**Table 8**).

**Table 8. Comparison of Study Design Differences Between Studies B5381001 and B5381007**

| Study Design Element                        | B5381001                                                                                                                                                                | B5381007                                                                                                                                                                                |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Planned sample size                         | 210<br>(70 per treatment arm)                                                                                                                                           | 360<br>(120 per treatment arm)                                                                                                                                                          |
| PK sampling duration                        | 42 days                                                                                                                                                                 | 49 days                                                                                                                                                                                 |
| Body weight stratification at randomization | No                                                                                                                                                                      | Yes (randomization stratified by 3 weight groups based on Day 0 weight: <75 kg, 75 to <90 kg, and ≥90 kg)                                                                               |
| Subject eligibility                         | Healthy males and non-childbearing potential females between the ages of 18 and 55 years, inclusive BMI of 17.5-30.5 kg/m <sup>2</sup> ; and a total body weight >50 kg | Healthy males and childbearing /non-childbearing potential females between the ages of 18 and 45 years, inclusive BMI of 19.0 - 30.5 kg/m <sup>2</sup> ; and a total body weight >60 kg |

BMI = body mass index; PK = pharmacokinetic.

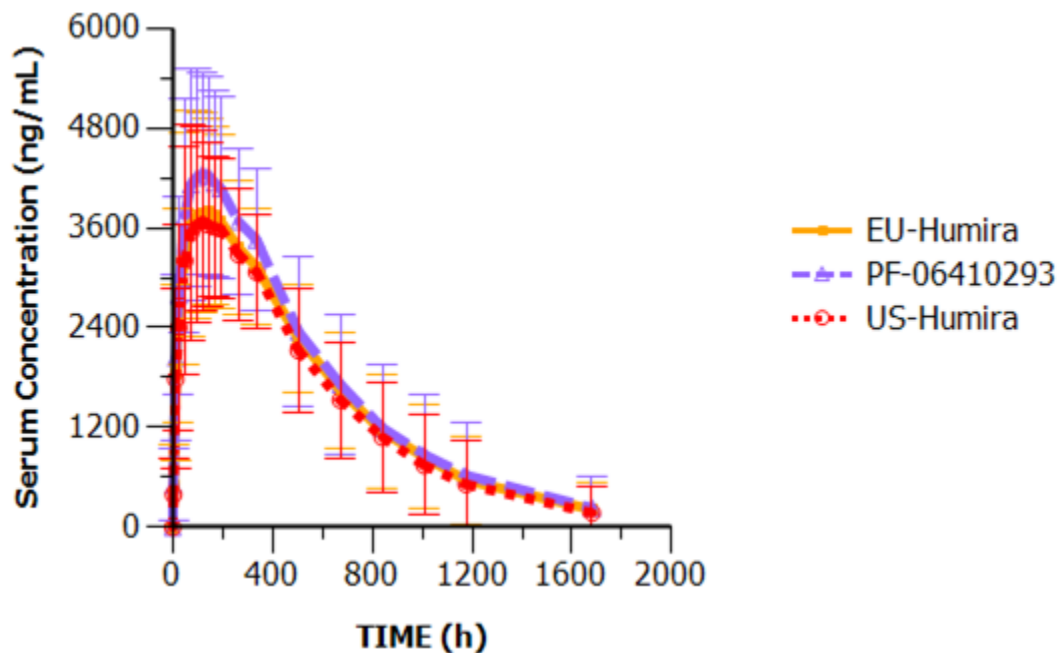
Source: **Table 20**, meeting briefing package for BPD Type 2 meeting, May 2017.

In Study B5381007, blood Samples for PK assessment were collected at pre-dose, and on day 1 (3 and 12 hour), 2, 3, 4, 5, 6, 7, 8, 9, 12, 15, 22, 29, 36, 43, and day 49 (1176 hour) post-dose. For the majority of subjects in each treatment arm (280/311), AUC<sub>last</sub> accounted for at least 80% of the total AUC, confirming the adequacy of the duration of PK sampling across the 3 treatments. The PK parameters are summarized in

**Table 9.** The mean serum concentration-time profiles were similar between the PF-06410293, EU-Humira and US-Humira treatment groups (**Figure 1**).

In the 3-way PK similarity comparisons (PF-06410293 vs. US-Humira, PF-06410293 vs. EU-Humira, and EU-Humira vs. US-Humira), the 90% CIs for the geometric mean ratios of C<sub>max</sub>, AUC<sub>t</sub> and AUC<sub>inf</sub> were all within the pre-defined criteria of 80% –125% (**Table 6**). These data establish the PK similarity between PF-06410293 and US-Humira. These data also establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-Humira to support a demonstration of the biosimilarity of PF-06410293 to US-Humira.

**Figure 1. PK profiles following a single SC dose of PF-06410293, EU-Humira, or US-Humira using PFS in healthy subjects (n=120/treatment group)**



Source: FDA analysis, Study B5381007

**Table 9. Summary of PK parameters (Study B5381007)**

| PK parameters                      | Geometric Mean (% CV) |                   |                   |
|------------------------------------|-----------------------|-------------------|-------------------|
|                                    | PF-06410293 (n=106)   | US-HUMIRA (n=101) | EU-HUMIRA (n=104) |
| C <sub>max</sub> (ng/mL)           | 4343.9 (30.7%)        | 3890.9 (27.9%)    | 3900.8 (33.7%)    |
| AUC <sub>0-t</sub> (µg/mL*hr)      | 2568.5 (42.6%)        | 2275.0 (36.1%)    | 2413.5 (37.4%)    |
| AUC <sub>0-inf</sub> (ng/mL*hr)    | 2909.8 (44.0%)        | 2534.5 (40.0%)    | 2757.0 (38.6%)    |
| T <sub>max</sub> (hr) <sup>a</sup> | 120 (48, 362)         | 144 (48, 363)     | 132 (24, 336)     |
| T <sub>1/2</sub> (hr) <sup>b</sup> | 354±225               | 337±209           | 372±252           |

% CV: coefficient of variation, T<sub>1/2</sub>: terminal half-time

<sup>a</sup>presented as median (minimum, maximum)

<sup>b</sup>presented as arithmetic mean ± standard deviation

Source: FDA analysis

**PK of PF-06410293 and EU-Humira in RA patients (Study B5381002)**

In Study B5381002, blood Samples for PK assessment were collected pre-dose on day 1 and at weeks 1, 2, 6, 12, 26 and weeks 30, 36, 52, 56, 66, 78, and 82.

### PK Results in Treatment Period 1

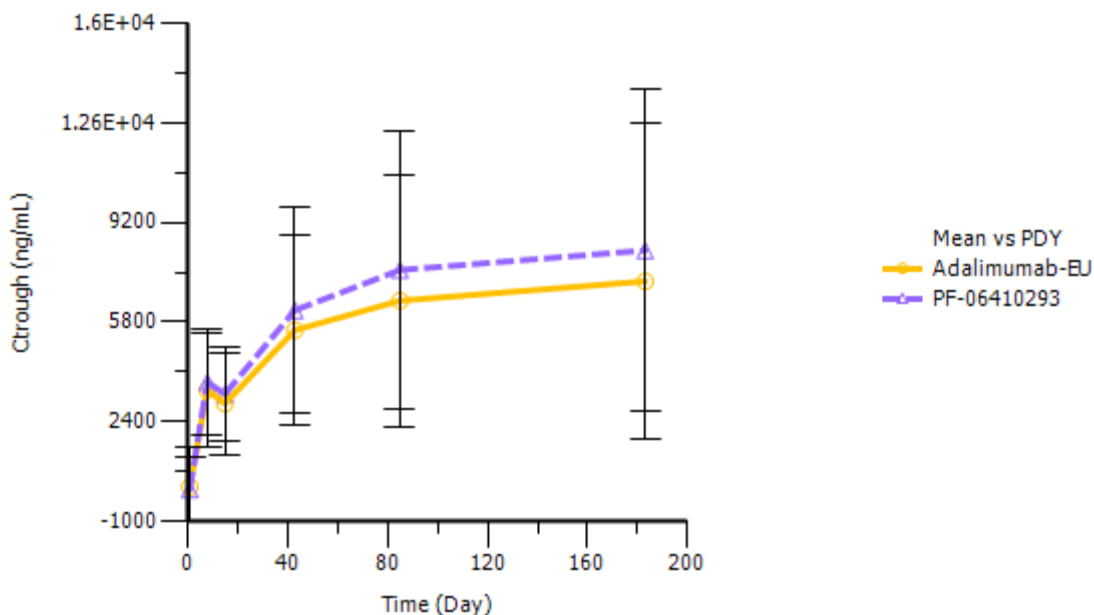
In RA patients, the mean and median serum drug concentrations were numerically slightly higher for the PF-06410293 arm compared to the EU-Humira arm (**Table 10, Figure 2**). However, this was a descriptive assessment with no prespecified endpoint evaluation. Additionally, despite the slightly higher concentrations observed for the PF-06410293 arm compared to the EU-Humira arm, there is no clinically significant difference in efficacy or safety between the two arms (See **Section 7**). Accordingly, these minor differences in drug concentrations observed in treatment period 1 in patients with RA in Study B5381002 do not preclude a finding of PK similarity.

**Table 10. Serum PF-06410293 and EU-Humira Concentrations Versus Time by ADA Status, PK Population – Study B5381002 TP1**

| Page 1 of 2                                    |              |               |                       |               |                       |               |
|------------------------------------------------|--------------|---------------|-----------------------|---------------|-----------------------|---------------|
| Visit                                          | All Subjects |               | ADA Positive Subjects |               | ADA Negative Subjects |               |
|                                                | PF-06410293  | Adalimumab-EU | PF-06410293           | Adalimumab-EU | PF-06410293           | Adalimumab-EU |
| <b>Concentration (ng/mL)</b>                   |              |               |                       |               |                       |               |
| Week 0<br>(Day 1)                              | N=295        | N=295         | N=130                 | N=150         | N=165                 | N=145         |
| Median                                         | 0            | 0             | 0                     | 0             | 0                     | 0             |
| (5 <sup>th</sup> -95 <sup>th</sup> percentile) | (0-0)        | (0-283.0)     | (0-0)                 | (0-0)         | (0-0)                 | (0-825.0)     |
| Mean                                           | 104.8        | 187.3         | 150.4                 | 104.4         | 68.87                 | 273.1         |
| CV%                                            | 1073         | 733           | 928                   | 755           | 1244                  | 654           |
| Week 1                                         | N=288        | N=294         | N=130                 | N=148         | N=158                 | N=146         |
| Median                                         | 3645         | 3280          | 3335                  | 2945          | 3815                  | 3645          |
| (5 <sup>th</sup> -95 <sup>th</sup> percentile) | (985-6830)   | (752-7010)    | (671-6560)            | (752-6630)    | (1550-6990)           | (1070-7530)   |
| Mean                                           | 3756         | 3488          | 3475                  | 3178          | 3988                  | 3803          |
| CV%                                            | 49           | 56            | 55                    | 55            | 44                    | 55            |
| Week 2                                         | N=293        | N=296         | N=131                 | N=150         | N=162                 | N=146         |
| Median                                         | 3150         | 2770          | 2840                  | 2420          | 3395                  | 3140          |
| (5 <sup>th</sup> -95 <sup>th</sup> percentile) | (1090-6180)  | (911-6020)    | (0-5900)              | (271-5430)    | (1360-6400)           | (1420-6840)   |
| Mean                                           | 3349         | 3025          | 3051                  | 2665          | 3591                  | 3395          |
| CV%                                            | 48           | 57            | 52                    | 59            | 44                    | 53            |
| Week 6                                         | N=293        | N=292         | N=129                 | N=147         | N=164                 | N=145         |
| Median                                         | 6380         | 5665          | 4290                  | 3460          | 7355                  | 7210          |
| (5 <sup>th</sup> -95 <sup>th</sup> percentile) | (0-11800)    | (0-11200)     | (0-9780)              | (0-8820)      | (3200-13500)          | (3160-12100)  |
| Mean                                           | 6205         | 5526          | 4423                  | 3839          | 7607                  | 7235          |
| CV%                                            | 57           | 59            | 73                    | 73            | 41                    | 38            |
| Week 12                                        | N=292        | N=286         | N=130                 | N=147         | N=162                 | N=139         |
| Median                                         | 7870         | 6465          | 4630                  | 3500          | 9065                  | 8920          |
| (5 <sup>th</sup> -95 <sup>th</sup> percentile) | (0-16000)    | (0-14000)     | (0-11600)             | (0-9560)      | (4670-17300)          | (4090-16900)  |
| Mean                                           | 7575         | 6531          | 4629                  | 4038          | 9939                  | 9168          |
| CV%                                            | 62           | 66            | 88                    | 84            | 38                    | 38            |
| Week 26                                        | N=286        | N=271         | N=127                 | N=138         | N=159                 | N=133         |
| Median                                         | 8790         | 6790          | 3730                  | 3035          | 10800                 | 9780          |
| (5 <sup>th</sup> -95 <sup>th</sup> percentile) | (0-17100)    | (0-17700)     | (0-13400)             | (0-12200)     | (4260-19500)          | (4380-18400)  |
| Mean                                           | 8244         | 7190          | 4683                  | 4041          | 11090                 | 10460         |
| CV%                                            | 67           | 75            | 99                    | 102           | 39                    | 44            |

Source: **Table 48**, CSR B5381002

**Figure 2. Mean Trough Concentration Following Multiple SC Dosing (40 mg Q2W) of PF-06410293 or EU- Humira in RA Patients (Study B5381002)**



Source: FDA analysis of data; Adalimumab-EU refers to EU-Humira

### PK Results in Treatment Period 2 (TP2)

Summary descriptive statistics of serum PF-06410293 and EU-Humira concentrations in the TP2 PK population are presented in **Table 11** for all subjects combined, and for the ADA positive and negative subgroups. For all subjects combined, the mean and median serum drug concentrations were numerically slightly higher for the PF-06410293/PF-06410293 and EU-Humira/PF-06410293 groups as compared to the EU-Humira/EU-Humira group. However, this was a descriptive PK assessment and there is no clinically significant difference in efficacy or safety between the two arms for this treatment period.

**Table 11. Serum Drug Concentration (ng/mL) Versus Time Summary by ADA Status, TP2 PK Population – TP2**

| Visit                        | PF-06410293/<br>PF-06410293 |                 |                 | Adalimumab-EU/<br>Adalimumab-EU |                 |                 | Adalimumab-EU/<br>PF-06410293 |                 |                 |
|------------------------------|-----------------------------|-----------------|-----------------|---------------------------------|-----------------|-----------------|-------------------------------|-----------------|-----------------|
|                              | All                         | ADA<br>Negative | ADA<br>Positive | All                             | ADA<br>Negative | ADA<br>Positive | All                           | ADA<br>Negative | ADA<br>Positive |
| <b>Concentration (ng/mL)</b> |                             |                 |                 |                                 |                 |                 |                               |                 |                 |
| Week 26                      |                             |                 |                 |                                 |                 |                 |                               |                 |                 |
| N                            | 281                         | 135             | 146             | 133                             | 54              | 79              | 130                           | 64              | 66              |
| NALQ                         | 253                         | 135             | 118             | 119                             | 54              | 65              | 115                           | 63              | 52              |
| Median                       | 8790                        | 11100           | 4445            | 6810                            | 9630            | 4090            | 7105                          | 10350           | 3375            |
| P5                           | 0                           | 4740            | 0               | 0                               | 4400            | 0               | 0                             | 3600            | 0               |
| P95                          | 17100                       | 19500           | 15400           | 16700                           | 17700           | 12900           | 18300                         | 18400           | 12100           |
| Mean                         | 8346                        | 11370           | 5546            | 7058                            | 10510           | 4700            | 7557                          | 10750           | 4459            |
| CV%                          | 65                          | 37              | 89              | 73                              | 43              | 89              | 73                            | 43              | 100             |
| Week 30                      |                             |                 |                 |                                 |                 |                 |                               |                 |                 |
| N                            | 276                         | 132             | 144             | 131                             | 53              | 78              | 131                           | 65              | 66              |
| NALQ                         | 252                         | 132             | 120             | 119                             | 53              | 66              | 120                           | 65              | 55              |
| Median                       | 8465                        | 10950           | 4765            | 6600                            | 9500            | 3880            | 7450                          | 9950            | 3415            |
| P5                           | 0                           | 4790            | 0               | 0                               | 4890            | 0               | 0                             | 3310            | 0               |
| P95                          | 17500                       | 19500           | 15600           | 16100                           | 17700           | 12700           | 16800                         | 17200           | 12700           |
| Mean                         | 8314                        | 11530           | 5365            | 6831                            | 10300           | 4470            | 7626                          | 10650           | 4653            |
| CV%                          | 69                          | 42              | 90              | 75                              | 44              | 91              | 70                            | 43              | 91              |
| Week 36                      |                             |                 |                 |                                 |                 |                 |                               |                 |                 |
| N                            | 266                         | 127             | 139             | 123                             | 50              | 73              | 128                           | 64              | 64              |
| NALQ                         | 238                         | 127             | 111             | 114                             | 50              | 64              | 116                           | 64              | 52              |
| Median                       | 8030                        | 10500           | 4670            | 6850                            | 9400            | 3590            | 7745                          | 11350           | 3770            |
| P5                           | 0                           | 4900            | 0               | 0                               | 3870            | 0               | 0                             | 4840            | 0               |
| P95                          | 17100                       | 19300           | 13600           | 17800                           | 19100           | 15700           | 17600                         | 18500           | 13900           |
| Mean                         | 8066                        | 11110           | 5289            | 7063                            | 10040           | 5025            | 8198                          | 11600           | 4800            |
| CV%                          | 66                          | 39              | 86              | 74                              | 45              | 94              | 69                            | 39              | 94              |
| Week 52                      |                             |                 |                 |                                 |                 |                 |                               |                 |                 |
| N                            | 259                         | 123             | 136             | 122                             | 50              | 72              | 126                           | 62              | 64              |
| NALQ                         | 229                         | 123             | 106             | 109                             | 49              | 60              | 115                           | 62              | 53              |
| Median                       | 7360                        | 9850            | 4345            | 5415                            | 8060            | 3180            | 8185                          | 10600           | 3655            |
| P5                           | 0                           | 4560            | 0               | 0                               | 3100            | 0               | 0                             | 4020            | 0               |
| P95                          | 16300                       | 18500           | 12000           | 15100                           | 16300           | 12800           | 17900                         | 18600           | 15200           |
| Mean                         | 7491                        | 10400           | 4855            | 6252                            | 9102            | 4273            | 8157                          | 11430           | 4991            |
| CV%                          | 66                          | 40              | 84              | 81                              | 55              | 95              | 69                            | 41              | 93              |

Source: Table 49, CSR B5381002

**PF-06410293 PK comparability when administered using a PFS vs. PFP**

The PK profiles of PF-06410293 using PFS or PFP were compared in Study B5381005. A total of 164 healthy subjects (81-83 subjects/arm) were randomized to receive a single dose of 40 mg PF-06410293 through SC injection using PFS or PFP. Blood Samples for PK assessment were collected pre-dose, and post-dose on day 1 (3, 8, and 12 hour), 2, 3, 4, 5, 6, 7, 8, 9, 12, 15, 22, 29, 36 and day 43 (1008 hour).

The mean serum concentration-time profiles were similar between the PF-06410293 PFS and PF-06410293 PFP (**Figure 3** and **Table 12**). Among the 163 subjects included in the primary PK data analysis, 48 and 58 subjects in the PFS and PFP arm, respectively, had a well-defined disposition terminal phase and, therefore, estimation of AUC<sub>inf</sub> was performed for those

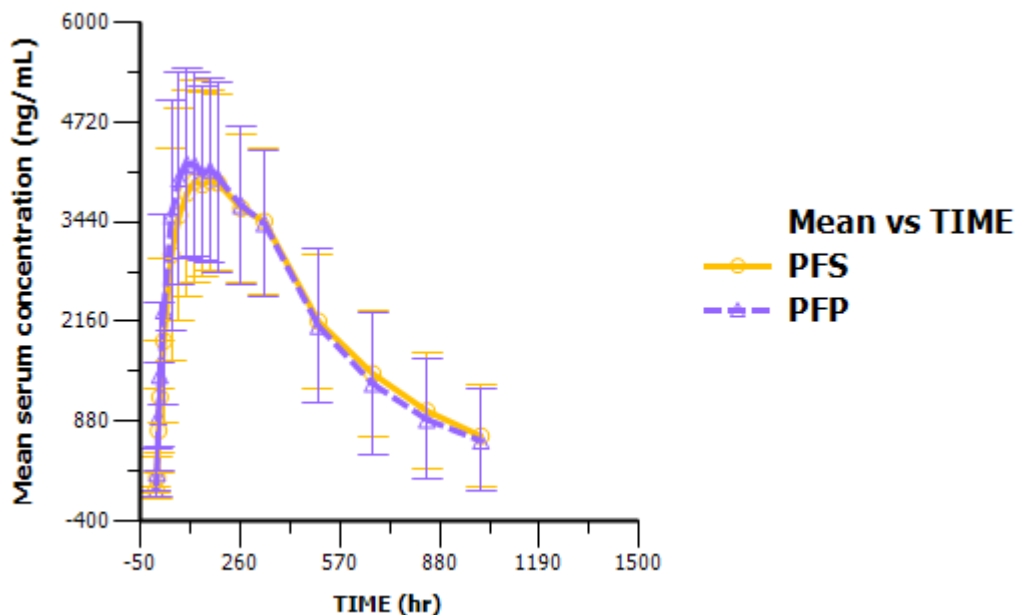
subjects. In the statistical analysis, the 90% CIs for the geometric mean ratios of C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> were all within the range of 80%–125% (**Table 12**). The variability of C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> evaluated as coefficient of variation (CV) are also generally comparable between PF-06410293 PFS and PF-06410293 PFP (**Table 12**).

The impact of body weight on PK comparison has been explored by the reviewer. As shown in **Figure 4**, PF-06410293 PK remains comparable using PFS and PFP in different weight groups: Low weight (>50 kg but ≤60 kg, n=10 for PFS, n=10 for PFP), Average weight (>60 kg but ≤80 kg, n=38 for PFS, n=40 for PFP), High weight (>80 kg, n=33 for PFS, n=33 for PFP).

Same as US-Humira, PF-06410293 is proposed to be injected subcutaneously using PFS or PFP in rotating injection sites, thigh or abdomen. In Study B5381005, PF-06410293 was injected in the lower abdomen and upper anterior thigh. As shown in **Figure 5**, PF-06410293 PK remains comparable using PFS and PFP in different injection sites.

Overall, PF-06410293 PK is comparable using PFS and PFP.

**Figure 3. PF-06410293 PK profiles following a single SC dose of PF-06410293 using PFS or PFP in healthy subjects (n=81-83/treatment group) (Study B5381005)**



Source: FDA analysis

**Table 12. PK comparability assessment - statistical analysis for PF-06410293 PK parameters using PFS and PFP (B5381005)**

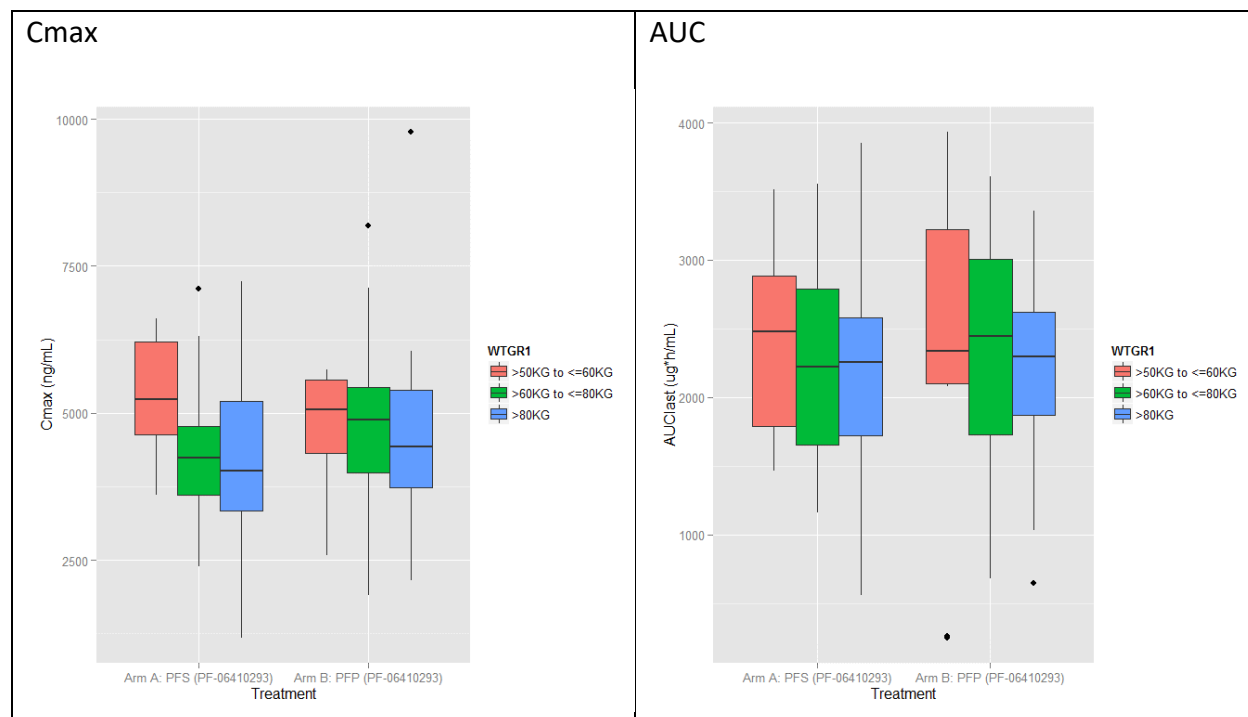
|                  | Geo LSM (CV%) (PFP, Test) | N  | Geo LSM (CV%) (PFS, Reference) | N  | GMR (%) | 90% CI (%)      |
|------------------|---------------------------|----|--------------------------------|----|---------|-----------------|
| <b>Cmax</b>      | 4454.5 (31.5%)            | 83 | 4131.1 (34.0%)                 | 81 | 107.83  | (99.29, 117.09) |
| <b>AUC0-t</b>    | 2069.6 (53.3%)            | 83 | 2119.6 (37.3%)                 | 81 | 97.64   | (87.21, 109.31) |
| <b>AUC0-inf*</b> | 2235.7 (36.1%)            | 58 | 2186.6 (35.9%)                 | 48 | 102.24  | (91.31, 114.49) |

The units of Cmax and AUC are ng/mL and µg\*h/mL, respectively.

\* AUCinf was reported only where a well-characterized terminal phase was observed. A well-characterized terminal phase was defined as one with at least 3 data points,  $r^2 > 0.9$ , and AUCextrap% < 20.

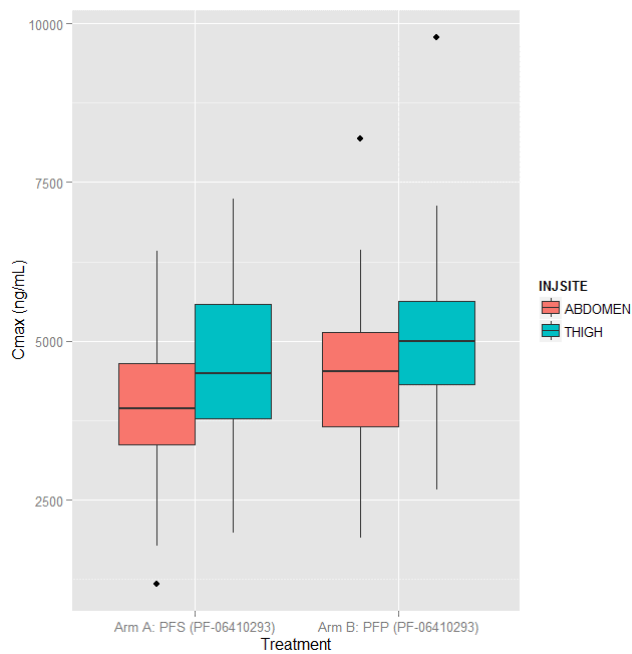
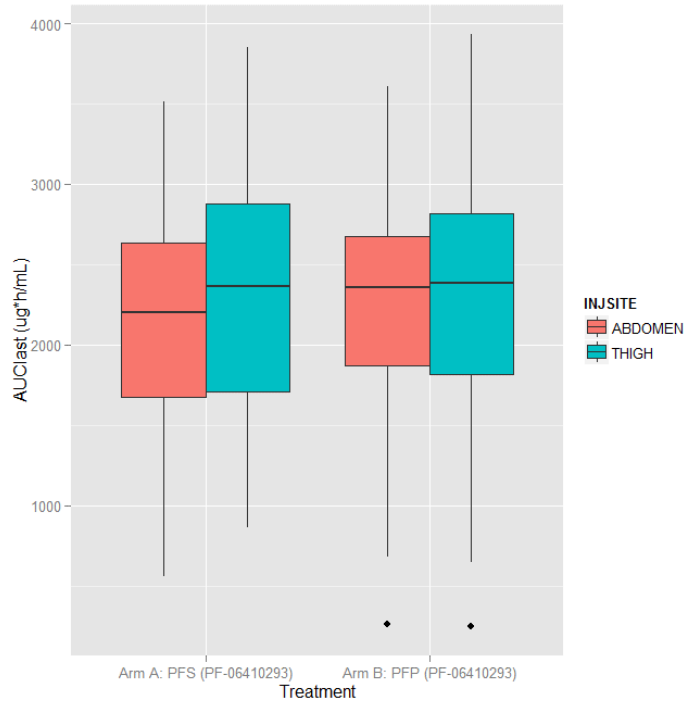
Source: FDA analysis

**Figure 4. PF-06410293 PK comparison using PFS and PFP in different weight groups (Study B5381005): Low weight (>50 kg but ≤60 kg, n=10 for PFS, n=10 for PFP), Average weight (>60 kg but ≤80 kg, n=38 for PFS, n=40 for PFP), High weight (>80 kg, n=33 for PFS, n=33 for PFP)**



Source: FDA analysis

**Figure 5. PF-06410293 PK comparison using PFS and PFP in different weight groups (Study B5381005): Low weight (>50 kg but ≤60 kg, n=10 for PFS, n=10 for PFP), Average weight (>60 kg but ≤80 kg, n=38 for PFS, n=40 for PFP), High weight (>80 kg, n=33 for PFS, n=33 for PFP)**



Source: FDA analysis

## PD Similarity Assessment

Not applicable.

## 6.4. Clinical Immunogenicity Studies

### Design Features of the Clinical Immunogenicity Assessment

ADA and NAb were evaluated in 4 studies (B5381001, B5381002, B5381005, and B5381007). Refer to **Table 3** for a summary of the studies. Immunogenicity was assessed in healthy subjects after a single dose, and in patients with RA after multiple doses including those who underwent a single transition to PF-06410293 or remained in the EU-Humira comparator arm during treatment period 2 (TP2).

### Immunogenicity Endpoints

Serum samples collected for immunogenicity assessment were first tested for ADA. Samples confirmed as positive for ADA were further tested for neutralizing antibodies (Nab).

### Immunogenicity Assay's Capability of Detecting the Antidrug Antibodies (ADA) in the Presence of Proposed Product, Reference Product, and Any Other Comparator Product (as applicable) in the Study Samples

The Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of expected levels of PF-06410293, US-Humira and EU-Humira. Refer to the OBP Immunogenicity review for more details.

### Adequacy of the Sampling Plan to Capture Baseline, Early Onset, and Dynamic Profile (Transient or Persistent) of ADA Formation

The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation.

- Study B5381001: Blood Samples for ADA assessment were collected at pre-dose on Day 1, and Day 15, Day 29, Day 43, Day 71, and at extended follow-up if applicable.
- Study B5381007: Blood Samples for ADA assessment were collected pre-dose on Day 1 and Day 15, Day 29, Day 43, Day 50, Day 71, and at extended follow-up if applicable.
- Study B5381002: Blood Samples for ADA assessment were collected pre-dose on day 1 and at weeks 2, 6, 12, 26 and weeks 30, 36, 52, 56, 66, 78, and 82.
- Study B5381005: Blood samples for ADA assessment were collected at predose, and day 15, 29, 43, and follow up visit.

## Incidence of ADA

### Immunogenicity in healthy subjects after single dose

The immunogenicity of PF-06410293 was comparable to that of US-Humira and EU-Humira in healthy adult subjects following a single 40 mg SC dose. **Table 13** and **Table 14** summarize the incidence of ADA and NAb by treatment group in study B5381007 and study B5381001, respectively, in healthy subjects.

**Table 13. Immunogenicity results for binding ADA and NAb in Study B5381007**

|             | N   | Anti-[drug] antibody |                   | Nab            |
|-------------|-----|----------------------|-------------------|----------------|
|             |     | Baseline             | Treatment-Induced |                |
| PF-06410293 | 121 | 1/121(0.8%)          | 91/119 (76.5%)    | 77/119 (64.7%) |
| US-Humira   | 119 | 0/119 (0%)           | 94/118 (79.7%)    | 74/118 (62.7%) |
| EU-Humira   | 119 | 6/119 (5.0%)         | 83/118 (70.3%)    | 71/118 (60.2%) |

Source: FDA summary based on **Table 18** and **Table 14.4.5.1.3**, CSR B5381007

**Table 14. Immunogenicity results for binding ADA and NAb in Study B5381001**

| Number (%) of Subjects                 | PF-06410293<br>(N=69) | Adalimumab-US<br>(N=71) | Adalimumab-EU<br>(N=70) |
|----------------------------------------|-----------------------|-------------------------|-------------------------|
| ≥1 incidence of positive ADA post-dose | 59 (85.5%)            | 67 (94.4%)              | 63 (90.0%)              |
| ≥1 incidence of positive NAb post-dose | 37 (53.6%)            | 47 (66.2%)              | 43 (61.4%)              |

Source: **Table 15**, CSR B5381001

In Study B5381005, ADA and NAb were only analyzed in 15 subjects experiencing injection site reaction (ISR) and/or rash and 15 randomly selected control subjects. The incidences of ADA and NAb in Study B5381005 are presented in **Table 15**.

**Table 15. ADA and NAb for ISR/Rash AE and Control Subjects by Visit (Study B5381005)**

| Number of Tested Subjects                                             | With<br>ISR/Rash AE<br>N = 15 | Without<br>ISR/Rash AE<br>N = 15 |
|-----------------------------------------------------------------------|-------------------------------|----------------------------------|
| <b>ADA at baseline (pre-dose)</b>                                     | 0                             | 0                                |
| <b>ADA post-dose</b>                                                  |                               |                                  |
| Number (%) of subjects tested positive on Day 15                      | 6 (40%)                       | 3 (20%)                          |
| Number (%) of subjects tested positive on Day 29                      | 7 (46.7%)                     | 4 (26.7%)                        |
| Number (%) of subjects tested positive on Day 43                      | 9 (60%)                       | 6 (40%)                          |
| Overall number (%) of subjects with at least 1 positive ADA post-dose | 11 (73.3%)                    | 7 (46.7%)                        |
| <b>NAb post-dose</b>                                                  |                               |                                  |
| Overall number (%) of subjects with at least 1 positive NAb post-dose | 7 (63.6%) <sup>a</sup>        | 5 (71.4%) <sup>a</sup>           |

Source: **Table 12**, CSR B5381005

### **Immunogenicity in RA subjects after multiple dose**

In Study B5381002, after multiple doses, the ADA incidence increased over time in all arms and was comparable between PF-06410293 and EU-Humira in patients with RA. In patients with RA, the percentage of patients with ADA at baseline was 3.4% and 3.7% for PF-06410293 and EU-Humira, respectively (**Table 16**). The overall incidence of ADA in treatment period 1 (TP1), defined as subjects with at least 1 post-dose positive ADA sample, was similar between the treatment arms at 44.4% and 50.5% for PF-06410293 and EU-Humira, respectively. Likewise, the overall incidence of NAb in TP1 was 13.8% and 14.0% in the PF-06410293 and EU-Humira arms, respectively. ADA/NAb results were balanced between treatment arms at all measured time points.

The ADA and NAb incidences after the single transition from EU-Humira to PF-06410293 are summarized in **Table 17**. At Week 26, prior to the first injection of study drug in TP2, 38.9%, 47.4% and 45.1% of the subjects in the safety population were ADA positive in the PF-06410293/PF-06410293, EU-Humira/EU-Humira, and EU-Humira/PF-06410293 groups, respectively.

Overall, the incidence of subjects with a positive ADA test result in TP2 was comparable among the 3 treatment groups, at 47.3%, 54.1% and 45.9% for the PF-06410293/PF-06410293, EU-Humira/EU-Humira, and EU-Humira/PF-06410293 groups, respectively. The majority of subjects with a positive ADA test result in TP2 were previously ADA positive in TP1. The overall TP1 + TP2 (1 year) incidence of a positive ADA test result in the TP2 safety population was 52.3%, 59.3% and 49.6% for the PF-06410293/PF-06410293, EU-Humira/EU-Humira, and EU-Humira/PF-06410293 groups, respectively.

**Table 16. Summary of ADA and NAb Incidence, Safety Population, TP1**

| Page 1 of 3                   |                     |                                 |                                   |
|-------------------------------|---------------------|---------------------------------|-----------------------------------|
| Visit                         | Criteria            | PF-06410293<br>(N=297)<br>n (%) | Adalimumab-EU<br>(N=299)<br>n (%) |
| Week 0 (Baseline)<br>(N1=595) | ADA positive        | 10 (3.4)                        | 11 (3.7)                          |
|                               | % of ADA+ Subjects  |                                 |                                   |
|                               | NAb positive        | 8 (80.0)                        | 5 (45.5)                          |
|                               | NAb negative        | 2 (20.0)                        | 6 (54.5)                          |
|                               | NAb not done        | 0                               | 0                                 |
|                               | % of Total Subjects |                                 |                                   |
|                               | NAb positive        | 8 (2.7)                         | 5 (1.7)                           |
|                               | NAb negative        | 2 (0.7)                         | 6 (2.0)                           |
|                               | NAb not done        | 0                               | 0                                 |
|                               | ADA negative        | 287 (96.6)                      | 287 (96.0)                        |
| ADA not done                  | 0                   | 1 (0.3)                         |                                   |
| Week 2 (N1=586)               | ADA positive        | 24 (8.1)                        | 26 (8.7)                          |
|                               | % of ADA+ Subjects  |                                 |                                   |
|                               | NAb positive        | 6 (25.0)                        | 3 (11.5)                          |
|                               | NAb negative        | 18 (75.0)                       | 23 (88.5)                         |
|                               | NAb not done        | 0                               | 0                                 |
|                               | % of Total Subjects |                                 |                                   |
|                               | NAb positive        | 6 (2.0)                         | 3 (1.0)                           |
|                               | NAb negative        | 18 (6.1)                        | 23 (7.7)                          |
|                               | NAb not done        | 0                               | 0                                 |
|                               | ADA negative        | 267 (89.9)                      | 269 (90.0)                        |
| ADA not done                  | 6 (2.0)             | 4 (1.3)                         |                                   |
| Week 6 (N1=587)               | ADA positive        | 40 (13.5)                       | 35 (11.7)                         |
|                               | % of ADA+ Subjects  |                                 |                                   |
|                               | NAb positive        | 19 (47.5)                       | 13 (37.1)                         |
|                               | NAb negative        | 21 (52.5)                       | 22 (62.9)                         |
|                               | NAb not done        | 0                               | 0                                 |
|                               | % of Total Subjects |                                 |                                   |
|                               | NAb positive        | 19 (6.4)                        | 13 (4.3)                          |
|                               | NAb negative        | 21 (7.1)                        | 22 (7.4)                          |
|                               | NAb not done        | 0                               | 0                                 |
|                               | ADA negative        | 254 (85.5)                      | 258 (86.3)                        |
| ADA not done                  | 3 (1.0)             | 6 (2.0)                         |                                   |
| Week 12 (N1=575)              | ADA positive        | 77 (25.9)                       | 91 (30.4)                         |
|                               | % of ADA+ Subjects  |                                 |                                   |
|                               | NAb positive        | 31 (40.3)                       | 20 (22.0)                         |
|                               | NAb negative        | 46 (59.7)                       | 71 (78.0)                         |
|                               | NAb not done        | 0                               | 0                                 |
|                               | % of Total Subjects |                                 |                                   |
|                               | NAb positive        | 31 (10.4)                       | 20 (6.7)                          |
|                               | NAb negative        | 46 (15.5)                       | 71 (23.7)                         |
|                               | NAb not done        | 0                               | 0                                 |
|                               | ADA negative        | 214 (72.1)                      | 193 (64.5)                        |
| ADA not done                  | 6 (2.0)             | 15 (5.0)                        |                                   |
| Week 26 (N1=557)              | ADA positive        | 112 (37.7)                      | 130 (43.5)                        |
|                               | % of ADA+ Subjects  |                                 |                                   |
|                               | NAb positive        | 29 (25.9)                       | 30 (23.1)                         |
|                               | NAb negative        | 83 (74.1)                       | 99 (76.2)                         |
|                               | NAb not done        | 0                               | 1 (0.8)                           |
|                               | % of Total Subjects |                                 |                                   |
|                               | NAb positive        | 29 (9.8)                        | 30 (10.0)                         |
|                               | NAb negative        | 83 (27.9)                       | 99 (33.1)                         |
|                               | NAb not done        | 0                               | 1 (0.3)                           |
|                               | ADA negative        | 173 (58.2)                      | 142 (47.5)                        |
| ADA not done                  | 12 (4.0)            | 27 (9.0)                        |                                   |

Source: Table 50, CSR B5381002

**Table 17. Summary of ADA and NAb Incidence, Safety Population, TP 2 (Study B5381002)**

| Page 1 of 3                    |                     |                                                  |                                                       |                                                    |
|--------------------------------|---------------------|--------------------------------------------------|-------------------------------------------------------|----------------------------------------------------|
| Visit                          | Criteria            | PF-06410293/<br>PF-06410293<br>(N1=283)<br>n (%) | Adalimumab-EU/<br>Adalimumab-EU/<br>(N1=135)<br>n (%) | Adalimumab-EU/<br>PF-06410293<br>(N1=133)<br>n (%) |
| Week 26 (N2=551)               | ADA positive        | 110 (38.9)                                       | 64 (47.4)                                             | 60 (45.1)                                          |
|                                | % of ADA+ Subjects  |                                                  |                                                       |                                                    |
|                                | NAb positive        | 28 (25.5)                                        | 15 (23.4)                                             | 13 (21.7)                                          |
|                                | NAb negative        | 82 (74.5)                                        | 49 (76.6)                                             | 47 (78.3)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | % of Total Subjects |                                                  |                                                       |                                                    |
|                                | NAb positive        | 28 (9.9)                                         | 15 (11.1)                                             | 13 (9.8)                                           |
|                                | NAb negative        | 82 (29.0)                                        | 49 (36.3)                                             | 47 (35.3)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | ADA negative        | 170 (60.1)                                       | 69 (51.1)                                             | 71 (53.4)                                          |
| ADA Not done                   | 3 (1.1)             | 2 (1.5)                                          | 2 (1.5)                                               |                                                    |
| Week 30 (N2=536)               | ADA positive        | 115 (40.6)                                       | 64 (47.4)                                             | 58 (43.6)                                          |
|                                | % of ADA+ Subjects  |                                                  |                                                       |                                                    |
|                                | NAb positive        | 27 (23.5)                                        | 9 (14.1)                                              | 11 (19.0)                                          |
|                                | NAb negative        | 88 (76.5)                                        | 55 (85.9)                                             | 47 (81.0)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | % of Total Subjects |                                                  |                                                       |                                                    |
|                                | NAb positive        | 27 (9.5)                                         | 9 (6.7)                                               | 11 (8.3)                                           |
|                                | NAb negative        | 88 (31.1)                                        | 55 (40.7)                                             | 47 (35.3)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | ADA negative        | 161 (56.9)                                       | 64 (47.4)                                             | 74 (55.6)                                          |
| ADA not done                   | 7 (2.5)             | 7 (5.2)                                          | 1 (0.8)                                               |                                                    |
| Week 36 (N2=519)               | ADA positive        | 114 (40.3)                                       | 64 (47.4)                                             | 57 (42.9)                                          |
|                                | % of ADA+ Subjects  |                                                  |                                                       |                                                    |
|                                | NAb positive        | 32 (28.1)                                        | 8 (12.5)                                              | 11 (19.3)                                          |
|                                | NAb negative        | 82 (71.9)                                        | 56 (87.5)                                             | 46 (80.7)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | % of Total Subjects |                                                  |                                                       |                                                    |
|                                | NAb positive        | 32 (11.3)                                        | 8 (5.9)                                               | 11 (8.3)                                           |
|                                | NAb negative        | 82 (29.0)                                        | 56 (41.5)                                             | 46 (34.6)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | ADA negative        | 153 (54.1)                                       | 60 (44.4)                                             | 71 (53.4)                                          |
| ADA not done                   | 16 (5.7)            | 11 (8.1)                                         | 5 (3.8)                                               |                                                    |
| Week 52 (N2=506)               | ADA positive        | 108 (38.2)                                       | 58 (43.0)                                             | 54 (40.6)                                          |
|                                | % of ADA+ Subjects  |                                                  |                                                       |                                                    |
|                                | NAb positive        | 27 (25.0)                                        | 11 (19.0)                                             | 12 (22.2)                                          |
|                                | NAb negative        | 80 (74.1)                                        | 47 (81.0)                                             | 42 (77.8)                                          |
|                                | NAb not done        | 1 (0.9)                                          | 0                                                     | 0                                                  |
|                                | % of Total Subjects |                                                  |                                                       |                                                    |
|                                | NAb positive        | 27 (9.5)                                         | 11 (8.1)                                              | 12 (9.0)                                           |
|                                | NAb negative        | 80 (28.3)                                        | 47 (34.8)                                             | 42 (31.6)                                          |
|                                | NAb not done        | 1 (0.4)                                          | 0                                                     | 0                                                  |
|                                | ADA negative        | 152 (53.7)                                       | 63 (46.7)                                             | 71 (53.4)                                          |
| ADA not done                   | 23 (8.1)            | 14 (10.4)                                        | 8 (6.0)                                               |                                                    |
| Overall TP2<br>(N2=550)        | ADA positive        | 134 (47.3)                                       | 73 (54.1)                                             | 61 (45.9)                                          |
|                                | % of ADA+ Subjects  |                                                  |                                                       |                                                    |
|                                | NAb positive        | 46 (34.3)                                        | 18 (24.7)                                             | 16 (26.2)                                          |
|                                | NAb negative        | 88 (65.7)                                        | 55 (75.3)                                             | 45 (73.8)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | % of Total Subjects |                                                  |                                                       |                                                    |
|                                | NAb positive        | 46 (16.3)                                        | 18 (13.3)                                             | 16 (12.0)                                          |
|                                | NAb negative        | 88 (31.1)                                        | 55 (40.7)                                             | 45 (33.8)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | ADA negative        | 149 (52.7)                                       | 61 (45.2)                                             | 72 (54.1)                                          |
| ADA not done                   | 0                   | 1 (0.7)                                          | 0                                                     |                                                    |
| Overall<br>TP1+TP2<br>(N2=551) | ADA positive        | 148 (52.3)                                       | 80 (59.3)                                             | 66 (49.6)                                          |
|                                | % of ADA+ Subjects  |                                                  |                                                       |                                                    |
|                                | NAb positive        | 51 (34.5)                                        | 23 (28.8)                                             | 20 (30.3)                                          |
|                                | NAb negative        | 97 (65.5)                                        | 57 (71.3)                                             | 46 (69.7)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | % of Total Subjects |                                                  |                                                       |                                                    |
|                                | NAb positive        | 51 (18.0)                                        | 23 (17.0)                                             | 20 (15.0)                                          |
|                                | NAb negative        | 97 (34.3)                                        | 57 (42.2)                                             | 46 (34.6)                                          |
|                                | NAb not done        | 0                                                | 0                                                     | 0                                                  |
|                                | ADA negative        | 135 (47.7)                                       | 55 (40.7)                                             | 67 (50.4)                                          |
| ADA not done                   | 0                   | 0                                                | 0                                                     |                                                    |

Source: Applicant **Table 50**, CSR B5381002

## Neutralizing Antibodies

A subgroup of subjects who developed binding ADA also developed neutralizing antibodies. The proportion of NAb-positive patients at any time, were similar between the PF-06410293 and EU-Humira treatment groups for the duration of the studies. Refer to **Table 13**, **Table 14**, and **Table 15** above for a summary of the neutralizing activity from Studies B5381007, B5381001 and B5381005 respectively . Refer to **Table 16** and **Table 17** above for a summary of the neutralizing activity from Study B5381002.

## Impact of ADA on the PK, PD, safety, and clinical outcomes of the proposed biosimilar product

### Impact of ADA and Nab on PK

With respect to the impact of ADA and Nab on PK in healthy subjects, in all three arms, the formation of ADA/NAb had minimal effect on C<sub>max</sub>, but had a noticeable impact on AUC<sub>t</sub> and AUC<sub>inf</sub>, demonstrating an accelerated elimination profile in ADA positive subjects ( **Table 18**, **Figure 6**, and **Figure 7**). In the single dose studies, the development of ADAs appears to increase clearance of all three products, and the impact of ADAs on PK was similar between the three treatment groups.

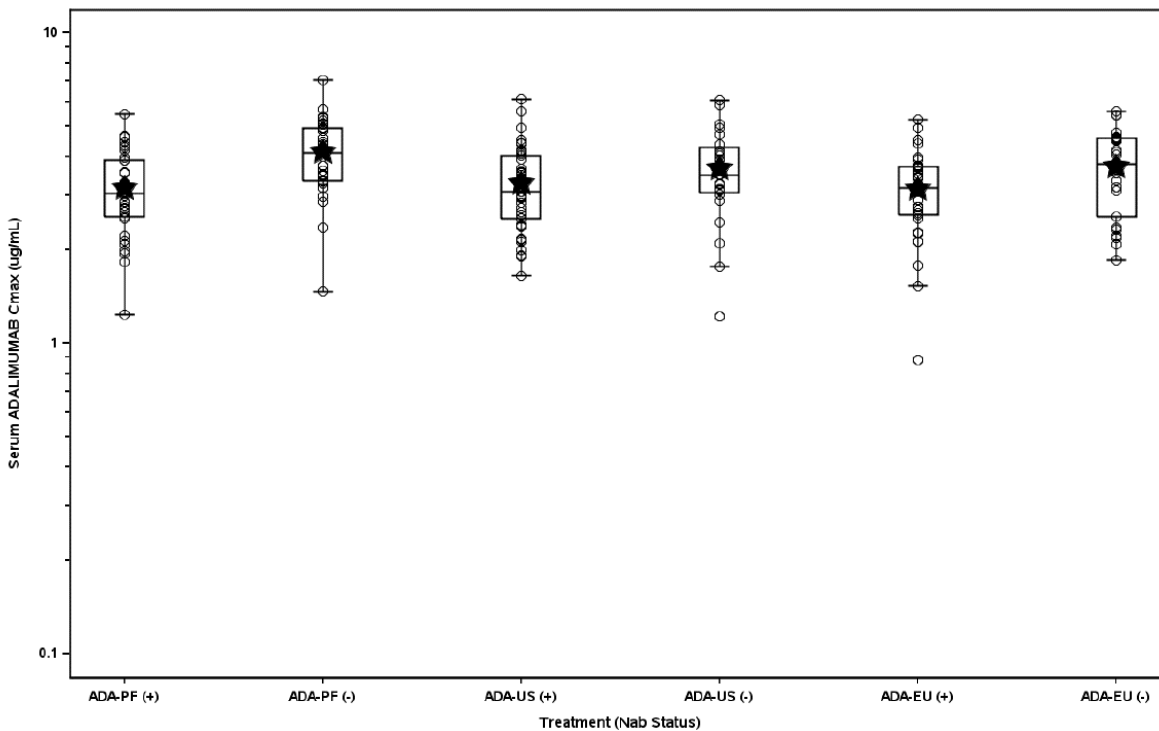
In the multiple dose study B5381002 with RA patients, the serum concentrations of PF-06410293 and EU-Humira were lower in ADA positive subjects compared to ADA negative subjects, and the impact of ADA on serum concentrations in ADA positive subjects was similar between treatment arms (**Table 10**; **Table 11**; **Figure 8**). With both products, NAb had a great impact on PK and further reduced the study drug exposure compared to binding ADAs, as shown in **Figure 9**.

**Table 18. Summary of PK Parameters in Study B5381007 by the binding ADA Status**

| Parameter           | Cmax<br>(ng/ml)<br>GM [n]<br>(GeoCV%) | AUClast<br>(µg.h/mL)<br>GM [n]<br>(GeoCV%) | AUCinf<br>(µg.h/mL)<br>GM [n]<br>(GeoCV%) |
|---------------------|---------------------------------------|--------------------------------------------|-------------------------------------------|
| <b>ADA positive</b> |                                       |                                            |                                           |
| <b>PF-06410293</b>  | 4257.7 [81]<br>(29.1%)                | 2318.3[81]<br>(41.4%)                      | 2598.8 [80]<br>(41.9%)                    |
| <b>US-Humira</b>    | 3813.8 [82]<br>(29.5%)                | 2098.8 [82]<br>(32.5%)                     | 2297.3 [82]<br>(33.4%)                    |
| <b>EU-Humira</b>    | 3919.8 [74]<br>(34.3%)                | 2200.6 [74]<br>(37.9%)                     | 2456.7 [73]<br>(36.0%)                    |
| <b>ADA negative</b> |                                       |                                            |                                           |
| <b>PF-06410293</b>  | 4635.0 [25]<br>(33.9%)                | 3579.7 [25]<br>(22.9%)                     | 4178.0 [25]<br>(24.2%)                    |
| <b>US-Humira</b>    | 4242.3[19]<br>(27.0%)                 | 3222.0 [19]<br>(27.2%)                     | 3873.1 [19]<br>(34.7%)                    |
| <b>EU-Humira</b>    | 3854.3 [30]<br>(32.6%)                | 3030.7 [30]<br>(23.1%)                     | 3650.0 [30]<br>(27.1%)                    |

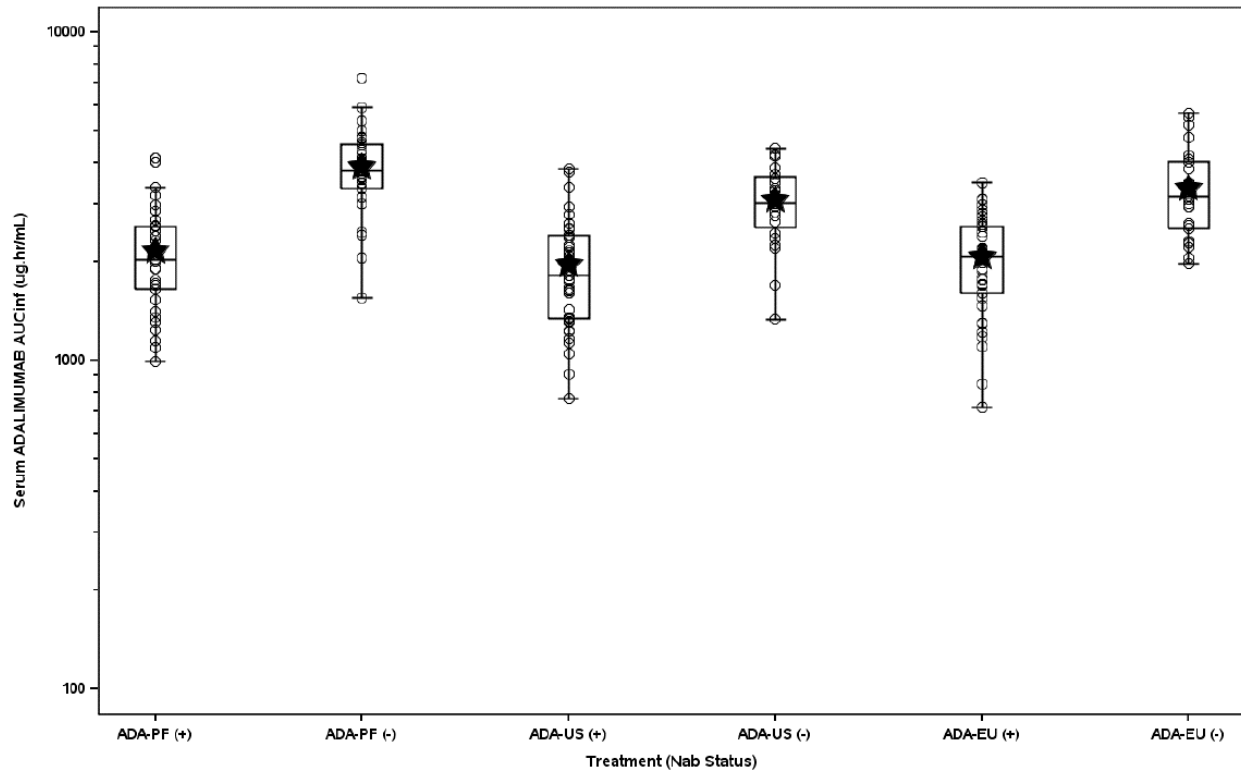
Source: FDA analysis

**Figure 6. Serum Cmax by Treatment and NAb Status (StudyB5381001)**



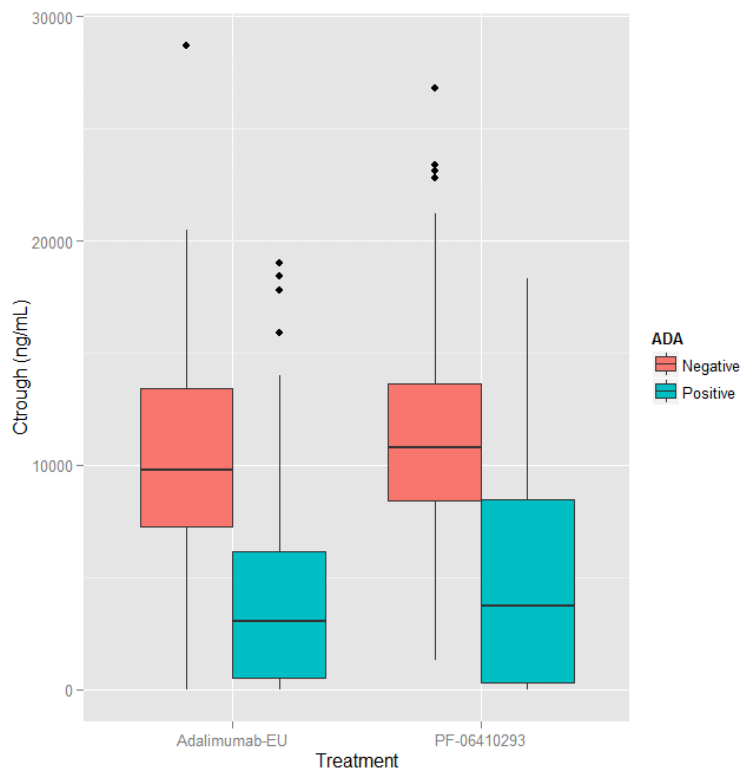
Source: Figure 14.4.3.2.3.2, CSR B5381001

**Figure 7. AUCinf by Treatment and NAb Status (StudyB5381001)**



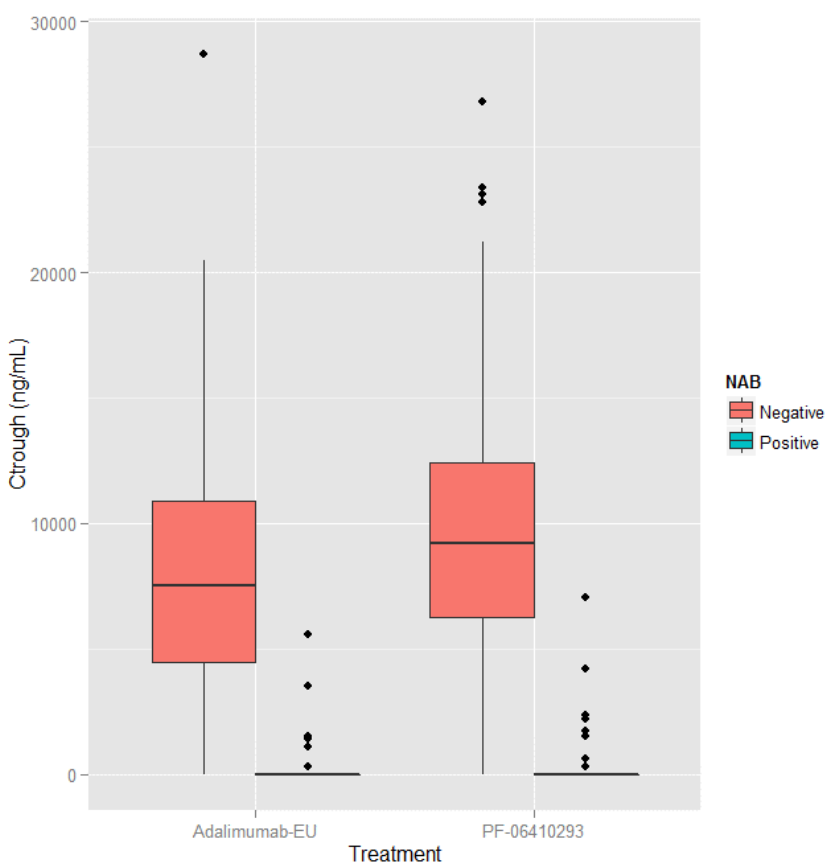
Source: Figure 14.4.3.2.2.2, CSR B5381001

**Figure 8. Serum Trough Concentrations by ADA Status at week 26 (StudyB5381002)**



Source: FDA analysis; Adalimumab-EU refers to EU-Humira

**Figure 9. Serum Trough Concentrations by NAb Status at week 26 (Study B5381002)**



Source: FDA analysis; Adalimumab-EU refers to EU-Humira

### Impact of ADA and Nab on efficacy

In Study B5381002, in patients who were ADA-negative,<sup>4</sup> the ACR20 response rates at Week 12 and 26 were comparable between PF-06410293 and EU-Humira. In patients who were ADA-positive,<sup>5</sup> ACR20 response rates at Week 12 were 64% (58/91) and 66% (69/105) for PF-06410293 and EU-Humira treatment groups respectively. In patients who were ADA-negative, ACR20 response rates at Week 12 were 71% (146/206) and 77% (149/193) for PF-06410293 and EU-Humira treatment groups respectively.

At Week 26, the ACR20 rates were numerically higher in the PF-06410293 than in the EU-Humira arm for both subgroups (but see paragraph below). Among patients identified as ADA-positive, the ACR20 rates were 82% (108/132) and 77% (117/151) for PF-06410293 and EU-

<sup>4</sup> A patient was considered to be ADA negative if at least one post-dose sample was negative and all remaining samples were negative up to the ACR20 week of assessment.

<sup>5</sup> A patient was evaluated as ADA positive so long as their post-dose sample was positive at any time-point up to the ACR20 week of assessment.

Humira treatment groups respectively. Among patients identified as ADA-negative, the ACR20 rates were 85% (140/165) and 80% (117/147) in the PF-06410293 and EU-Humira arm respectively.

Similarly, in the efficacy comparison by NAb status,<sup>6</sup> the ACR20 response rates at Week 26 are comparable between PF-06410293 (86%, 221/256) and EU-Humira (80%, 206/256) in NAb-negative subgroup. Among the NAb-positive subgroup, the ACR20 response rates were similar between PF-06410293 (66%, 27/41) and EU-Humira (67%, 28/42) in NAb-positive subgroup.

Overall, the impact of ADA and NAb on efficacy in Study B5381002, as assessed by ACR20 response, was similar between the treatment groups.

### **Impact of ADA on safety**

In Study B5381002, there was no increase in ISRs or immune-related safety events in subjects who developed ADA/NAb compared to subjects without ADA/NAb, within or across treatment arms. In addition, in Study B5381002 there was no increase in ADA or safety events following transition from EU-Humira to PF-06410293 in B5381002 compared to those that did not transition. Overall, no apparent impact of immunogenicity on safety was observed.

### **Authors:**

Jianmeng Chen, Ph.D.  
Clinical Pharmacology Reviewer

Ping Ji, Ph.D.  
Clinical Pharmacology Team Leader

---

<sup>6</sup> A patient is defined to be NAb positive if at least one post-dose NAb positive sample among ADA positive subjects up to ACR20 week of assessment. A patient is defined to be NAb non-positive if at least one post-dose sample is tested NAb negative among ADA positive patients and all ADA negative patients up to ACR20 week of assessment.

## 7. Statistical and Clinical Evaluation and Recommendations

---

### 7.1. Statistical and Clinical Executive Summary and Recommendations

**Comparative Efficacy:** Study B5381002 was a randomized, double-blind, two-arm parallel-group study to compare the efficacy, safety, population PK, and immunogenicity between PF-06410293 and EU-Humira in combination with methotrexate in patients with moderately to severely active RA who have had an inadequate response to methotrexate. The Applicant incorporated FDA advice on the study design through multiple BPD meetings during the clinical development. EU-Humira was used as a comparator in the study. The study included 52-week double-blind treatment followed by 26 weeks of open-label extension in which all subjects received PF-06410293.

The primary endpoint was ACR20 response at Week 12. At Week 12, 71.3% of the patients randomized to EU-Humira and 68.4% of the patients randomized to PF-0610293 were ACR20 responders who stayed on randomized treatment; the estimated difference on the absolute scale comparing PF-06410293 relative to EU-Humira was -2.98% (90% exact confidence interval (CI): -9.3%, 3.3%). The limits of the 90% CI were within the prespecified asymmetric margins of -12% and 15%, agreed upon with the Agency. At other time points, and for other ACR thresholds, individual components of change from baseline for ACR (swollen joint count out of 66 (SJC66), tender joint count out of 68 (TJC68), patient global assessment, physician global assessment, health assessment questionnaire-disability index (HAQ-DI), patient pain, and C-reactive protein (CRP)) and disease activity score-28 with four components based on CRP (DAS28(CRP)) were similar between the treatment arms.

**Comparative Safety and Immunogenicity:** The comparative safety evaluation plan of PF-06410293 reflected the known safety profile of US-Humira as described in the USPI and other published data. Given that the applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated with EU-Humira as the comparator, the submitted safety and immunogenicity data from B5381002 supported by the data from the single-dose PK studies, B5381007, B5381001, and B5381005, are adequate to support the demonstration of no clinically meaningful differences in safety and immunogenicity between PF-06410293 and US-Humira. The safety database submitted for PF-06410293 includes a total of 1,329 subjects who received at least one dose of study drug (733 healthy subjects and 596 patients with RA) and is adequate to provide a reliable descriptive comparison between the products. The safety risks identified are consistent with the known adverse event profile of US-Humira. There were no notable differences between PF-06410293 and EU-Humira in treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, adverse events leading to discontinuation, or development of anti-drug antibodies (ADA) between the treatment groups in B5381002. In addition, a single transition of non-treatment naïve patients to the proposed biosimilar, i.e., patients previously treated with EU-Humira to PF-06410293, did not result in an increase in immunogenicity or clinically significant adverse reactions.

Overall, the collective evidence from the comparative clinical study supports a demonstration of no clinically meaningful differences between PF-06410293 and US-Humira, as the Applicant provided adequate data to establish the scientific bridge between PF-06410293, US-Humira, and EU-Humira to justify the relevance of data generated with EU-Humira as the comparator to the assessment of biosimilarity.

### 7.1.1. Statistical and Clinical Residual Uncertainties Assessment

During this statistical review of Study B5381002, as described below, a few important statistical issues arose, and were adequately addressed.

Missing data can impact the validity of the study results. Therefore, we assessed the robustness of the results to missing data assumptions. The finding of no meaningful differences in efficacy between products based on ACR20 at Week 12 was maintained while varying plausible alternative assumptions regarding outcomes among patients with missing data. At Week 12, six (1%) patients had withdrawn from the study: Three patients (1%) from the PF-06410293 arm and three patients (1%) from the EU-Humira arm. Tipping point analyses conducted to explore the sensitivity of the results to violations in assumptions about the missing data showed that the confidence intervals for differences between PF-06410293 and EU-Humira arm were robust, ruling out meaningful differences in efficacy even under the assumption that outcomes among patients who dropped out on PF-06410293 were much worse or much better than outcomes among patients who dropped out on EU-Humira. Given the similar proportions of early withdrawal patients, similar distributions of reasons for early withdrawal, similar baseline characteristics between dropouts on the two treatment arms, and implausible differences between the outcomes among dropouts needed to tip results toward non-similarity, the observed results support similar efficacy.

To determine whether the proposed similarity margins are adequate to evaluate meaningful differences, we assessed and compared the conduct and patient population of the submitted study to historical studies (13.1) conducted with adalimumab.<sup>7</sup> This comparison can also be used to assess if the study was adequately designed to provide sensitivity to detect differences between the proposed biosimilar and EU-Humira, if such differences exist, i.e., assay sensitivity. Based on an evaluation of the CCS and the four historical, randomized, placebo-controlled clinical trials (**Table 19**) used to calculate the similarity margins, we concluded that: (1) there were relatively large and consistent treatment effects across the four historical studies; and (2) the design of the comparative study was largely similar to those of the historical trials from which the margin was calculated. In addition, the statistical reviewer did not identify issues of concern with study conduct, other than protocol deviations and minimal dropouts (addressed below in section 7.3.1), which could have affected the quality of study and bias the results towards similarity.

---

<sup>7</sup> References to unknown sources of adalimumab (e.g., based on historical studies) will use “adalimumab”.

Therefore, the study was sufficiently sensitive to allow a credible assessment of whether there are meaningful differences between PF-06410293 and EU-Humira. Further, the Applicant provided adequate data to establish the scientific bridge that justifies the relevance of comparative data generated using EU-Humira as the comparator to the assessment of biosimilarity.

## 7.2. Review Strategy

The evaluation of supportive evidence of no clinically meaningful differences between PF-06410293 and US-Humira centered on Study B5381002, which used EU-Humira as a comparator. The relevance of Study B5381002 data derived from EU-Humira was predicated on establishing a scientific bridge to US-Humira through appropriate pairwise comparisons of US-Humira, EU-Humira, and the proposed product.

The statistical reviewer analyzed the applicant's primary endpoint and key secondary endpoints and included additional analyses to evaluate the robustness of the results (Section 7.3). The key findings are presented and described in the tables and figures in the subsequent sections. After Week 26, because patients on EU-Humira arm are re-randomized to receive PF-06410293 or stay on EU-Humira, efficacy analyses are focused on the treatment period prior to re-randomization. This study is the primary contribution to the safety database. Though supplemental safety data from the other studies are also summarized by the Applicant, these studies were single-dose studies in healthy volunteers (B5381007, B5381001, and B5381005), and therefore, were not the primary focus of the safety review. A discussion of the safety evaluation is presented in **Section 7.4**.

## 7.3. Review of Comparative Clinical Studies with Statistical Endpoints

### 7.3.1. Study B5381002

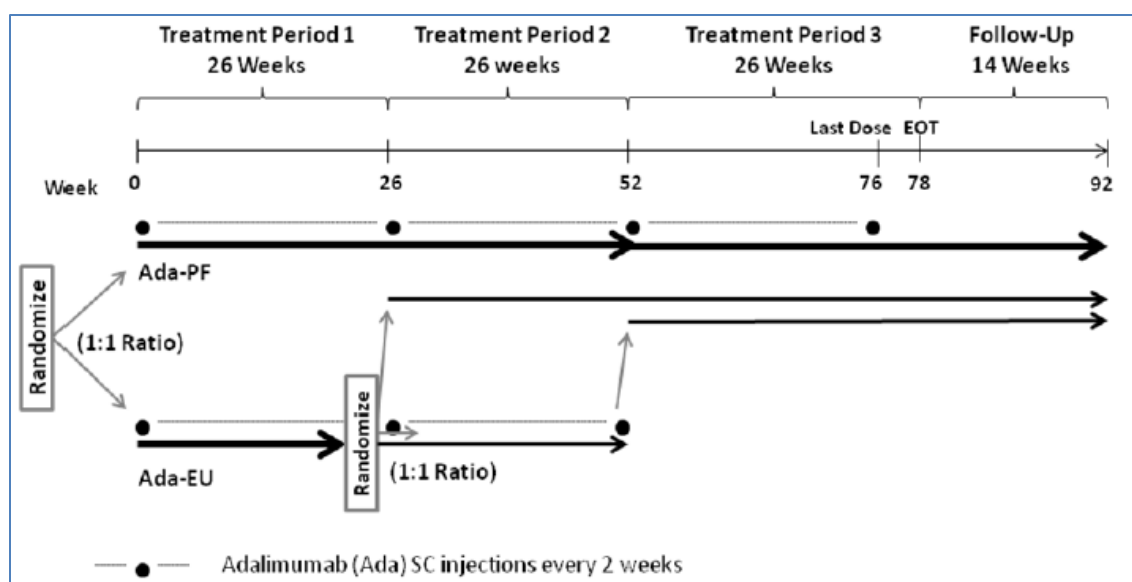
Study B5381002 was a multicenter, randomized, double-blind, parallel-group study designed to determine whether there are differences with respect to efficacy and safety between PF-0610293 and EU-Humira in patients with moderately to severely active rheumatoid arthritis who had an inadequate response to methotrexate therapy.

#### Study Design and Endpoints

The study design consisted of three treatment periods (**Figure 10**). During treatment period 1 (TP1), 597 patients were randomized in a 1:1 ratio at Week 0 to EU-Humira or PF-06410293. Randomization was stratified by geographic region (North America and Western Europe, Japan, South Korea and Taiwan, Latin America, and Rest of the World). TP1 ended with the completion of the Week 26 pre-dose assessment. Treatment period 2 (TP2) started from Week 26 and ended on Week 52 pre-dose assessment. During TP2, patients who completed Week 26 assessments and were initially randomized to EU-Humira were re-randomized in a 1:1 ratio to

EU-Humira or PF-06410293. Patients, who completed Week 26 assessments, initially randomized to PF-06410293 remained on their blinded assigned treatment until the completion of the Week 52 assessment. During treatment period 3 (TP3), all patients remaining on EU-Humira crossed over to receive PF-06410293 until Week 76, with an end of treatment assessment on Visit Week 78. Patients were then followed up for an additional 16 weeks after the last dose of study drug. All patients also received a stable dose of oral or parenteral MTX 10-25 mg/week (or 6-25 mg/week where 6 mg/week recommended initial dose by local guidance or standard of care) from four weeks prior to screening through Week 52.

**Figure 10. Study Design, B5381002**



Source: Applicant's Figure 1 in CSR B5381002ADA-EU refers to EU-Humira; ADA-PF refers to PF-06410293

The prespecified primary endpoint in this study was the proportion of patients achieving an ACR20 response at Week 12. ACR20 is a responder-type, multi-component endpoint defined by achieving at least 20% improvement from baseline in TJC68 and SJC66, with at least 20% or more improvement from baseline in 3 of the 5 additional measures of disease signs or symptoms: patient global assessment, physician global assessment, patient assessment of pain on a visual analog scale, HAQ-DI, and CRP. Patients with dose escalation were considered non-responders.

Other secondary endpoints included ACR50, ACR70, change from baseline in DAS28(CRP),<sup>8</sup> DAS28(CRP) < 2.6, European League Against Rheumatism (EULAR) response, ACR/EULAR

<sup>8</sup> DAS28(CRP) is a continuous outcome derived by combining tender joints counts out of 28 joints (TJC28), swollen joints out of 28 joints (SJC28), CRP (mg/L), and patient's global assessment of disease activity [GH] by the following equation:  $DAS28(CRP) = 0.56 \times TJC28 + 0.28 \times SJC28 + 0.36 \times \log_{10}(CRP + 1) + 0.014 \times GH + 0.96$ .

remission,<sup>9</sup> and change from baseline in individual components of ACR response. These endpoints were evaluated at Week 2, 4, 6, 8, 18, and 26.

**Study location:** This was a multi-national study. A total of 597 patients with RA were enrolled from 173 sites across 24 countries with approximately 13% from North America (US only), 6% from West Europe, 70% from east Europe and the rest from Asia and Latin America. The patients were randomized in a 1:1 ratio to receive either PF-06410293 (n=297) or EU-Humira (n=300). The randomization was stratified by five geographic regions (North America/Western Europe, Japan, South Korea/Taiwan, Latin America, and Rest of the World).

**Study subjects:** Patients with moderately to severely active RA disease and inadequate response to methotrexate were defined by the following criteria:

- Diagnosis of RA based on 2010 ACR/EULAR classification criteria for RA for at least a 4-month duration
- Class I-III of the ACR 1991 Revised Criteria for Global Functional Status in RA
- Moderately to severely active RA disease:
  - $\geq 6$  tender joints (of 68 assessed) at both screening and baseline, and
  - $\geq 6$  swollen joints (of 66 assessed) at both screening and baseline, and
  - hs-CRP  $> 8$  mg/L (0.8 mg/dL)
- Have received oral, SC, or intramuscular methotrexate for  $\geq 12$  weeks and been on a stable dose for  $\geq 4$  weeks prior to first dose of study drug.
- No current or prior treatment with adalimumab or lymphocyte depleting therapies, or washout for  $\geq 12$  weeks or 5 half-lives (whichever was longer) if having received up to two doses of one biologic therapy (any type), including an anti-TNF inhibitor biologic agent.
- Washout the following disease modifying anti-rheumatic drugs (DMARDs) with relevant intervals:
  - Immunosuppressive drugs, including alkylating agents (eg, cyclophosphamide and chlorambucil), mycophenolate mofetil, leflunomide, azathioprine, 6-mercaptopurine, tacrolimus, cyclosporine, gold therapy including auranofin or injectable gold (aurothioglucose or aurothiomalate), tofacitinib, D-penicillamine, sulfasalazine or anti-malarial drugs, and investigational treatments for RA

**Study treatments:** PF-06410293 or EU-Humira 40 mg q2-week, subcutaneously

- Administration by self-injection or a care-giver (for subjects who were not capable of or chose not to perform self-injection). The subjects, investigators, site staff, pharmacist, and Sponsor's personnel directly involved in the study conduct remained blinded to the treatment assignments in TP1 and TP2 throughout the study conduct.

---

<sup>9</sup> Either simplified disease activity index or SDAI  $\leq 3.3$ , sum of tender joint counts, swollen joint counts, patient global assessment, physician global assessment, and CRP or (tender joint counts, swollen joint counts, CRP, and patient global assessment) are all  $\leq 1$ .

- A single-use, 1-ml pre-filled glass syringe (PFS) containing 40 mg (0.8 ml) of PF-06410293 or EU-Humira.
- The injection site at a lower quadrant of the abdominal wall or the upper front thighs.
- The first injection was performed at the study site under the supervision of the investigator or designee. All subjects and care-givers received Instruction for Use and a proper training for the administration procedure prior to the first injection.

**Concomitant medications:** The following medications at stable dose were allowed during the study

- Methotrexate: stable regimen of oral or intramuscular methotrexate (6-25 mg/week based on standard of care (SOC) in geographic regions)
- Folic acid: oral folate ( $\geq 1$  mg/week) or oral folinic acid supplementation ( $\geq 5$  mg/week)
- Corticosteroid: oral stable dose of  $\leq 10$  mg/day of prednisone equivalent. Tapering or discontinuation of any corticosteroid treatment was only allowed after Week 52 unless required for toxicity
- NSAIDs: oral or topical dose of one NSAID
- Low dose aspirin for cardiovascular protection
- Stable doses ( $\geq 2$  weeks prior to Day 1) of only 1 immediate-release opioids (tramadol, codeine, hydrocodone, oxycodone, or propoxyphene) and/or acetaminophen 2-3 g/day (according to local guidance).

**Rescue treatment for RA:**

- Analgesics: To increase dose of allowed analgesics (as described above) or to replace with a new analgesic (morphine, hydromorphone or meperidine). Only one opioid agent (immediately-release) at a time was allowed
- Intra-articular corticosteroids:  $\leq 40$  mg methylprednisolone or its equivalent per injection to up to 2 joints at and after the Week 12 assessments
- Arthrocentesis without intra-articular medication: up to 2 joints after Week 12
- Oral corticosteroids: one course of oral dose (but not IM or IV) at  $\leq 20$  mg/day of prednisone equivalent lasting  $\leq 7$  days after Week 26 for treatment of RA flare
- Non-pharmacologic treatment: including application of heat and cold, massage, physical therapy, splinting, or ultrasound was allowed

**Statistical Methodologies**

The protocol-defined primary endpoint, ACR20 response while remaining on study treatment at Week 12, was analyzed for similarity using an exact binomial test, with the null hypothesis of non-similarity rejected if the 90% confidence bounds for the difference in ACR20 response probabilities at Week 12 were within the pre-specified similarity margins. The limits of the 90% confidence interval were obtained based on score statistics using the method of Farrington-

Manning [Chan and Zhang, 1999]. A planned supportive analysis used the unconditional approach based on Santner and Snell [Santner and Snell, 1980].

Based upon discussion with the Agency, the Applicant prespecified an asymmetric margin for the CCS. If an adequate bridge could be established to justify the relevance of data generated with EU-Humira as a comparator to the assessment of biosimilarity, the results from study B5381002 would provide additional evidence to support a demonstration of no clinically meaningful differences where the 2-sided 90% confidence interval (or 1-sided 5% Type 1 error rate) for the difference in the two treatment groups would fall within the asymmetric margin of (-12%, +15%). The margin interval includes the two bounds.

The Applicant included an additional supportive analysis for the primary endpoint using a binomial regression model with an identity link, adjusted for treatment group and geographic region. In addition, the Applicant reported the mean change from baseline for the individual components of ACR across time, along with the 95% CI.

Binary responder-type endpoints, ACR20, ACR50, ACR70, EULAR response, DAS remission rate, ACR/EULAR remission rate at all scheduled visits (Weeks 2, 4, 6, 8, 12, 18, and 26) were summarized using counts and percentage by arm.

The continuous components of ACR, namely, joint counts, patient's and physician's global assessment (visual analog scale), and HAQ-DI at all scheduled visits were summarized using descriptive statistics, i.e., unadjusted differences in means and standard deviations. A generalized estimating equation model using the binomial family with identity link was fit to evaluate ACR20 in all patients, regardless of adherence to treatment, from Week 2 up to Week 26, adjusting for treatment arm, categorical visit, treatment by visit interaction, and geographical region. An autoregressive correlation with visit lag of one was assumed for the variance structure. Estimated differences in proportion comparing PF-06410293 with EU-Humira at each visit, respective 95% and 90% CIs, were reported from the regression model.

A linear mixed-effects repeated measure model was fit to the change from baseline in DAS28(CRP), adjusting for treatment, categorical visit, treatment and visit interaction, categorical geographical regions, baseline value of the DAS28(CRP) and interaction of continuous DAS28(CRP) with categorical visit. Within-subject variation across visits was accounted using an unstructured variance-covariance structure, and Kenward-Roger approximation was used to estimate degrees of freedom for pairwise comparisons. The estimated differences, and respective 95% CI and 90% CI, in the adjusted mean change from baseline in DAS28(CRP) comparing PF-06410293 with EU-Humira at each visit were reported from this model.

The above statistical analyses were carried out in both intent-to-treat (ITT) and per-protocol (PP) population. The ITT population included all randomized patients. The PP population included all patients who were randomized correctly and received treatment as planned up to

Week 12; had an ACR measurement; and did not have major protocol deviations. Major protocol deviations specified in the SAP included failure to meet key inclusion and exclusion criteria, deviations that impact primary and key secondary efficacy endpoints, issues with respect to investigational product, use of disallowed medications that can affect efficacy, and major deviations in study procedures. Additional factors considered to be major protocol deviations include an assessment out of window by more than 2 weeks for the Week 12 visit, and patients who discontinued or reduced their methotrexate dose for more than 2 consecutive weeks up to Week 12.

Subgroup analyses evaluated treatment differences, assuming MAR, according to age (18-44, 45-64,  $\geq 65$  years), sex (male/female), race (white, black, Asian, others), geographic region (North America and Western Europe, Japan, South Korea + Taiwan, Latin America, and rest of the world), as well as important RA disease characteristics including baseline corticosteroid use (yes/no), baseline MTX dose (<15, 15-20,  $\geq 20$  mg/week), duration of prior use of MTX (< 1 year, 1 year to < 3 years, and  $\geq 3$  years).

For each subgroup, point estimates and two-sided 95% CIs based on the normal approximation were reported for the difference in ACR20 at week 12 between the two treatment arms. The statistical reviewer included cumulative responder curves by computing the probability of ACR response at all thresholds at all study visit weeks to assess for departures from similarity between PF-06410293 and EU-Humira for probability of ACR response. In addition, post hoc comparisons between PF-06410293 and EU-Humira for each ACR response threshold were computed based on differences in proportions, with 95% CI based on a normal approximation of the differences in proportions using unpooled standard deviations.

For evaluation of key continuous secondary efficacy endpoints such as DAS28(CRP), the Applicant considered the use of mixed models repeated measures for the analysis method. However, the presence of missing data presented additional issues because the proposed statistical model relies on strong and unverifiable assumptions about the missingness mechanism, in addition to assumptions of constant variance and normality across treatment arms. Thus, as supportive analyses, the statistical reviewer reported the observed means, standard deviations, and number of patients available, for the change from baseline in DAS28(CRP) analysis based on all observed data. The statistical reviewer further fit the change from baseline in DAS28(CRP) at each scheduled visit using a linear regression with Huber-White sandwich errors, allowing for heteroskedasticity, adjusting for continuous baseline DAS28(CRP), treatment group, geographical region. Additionally, cumulative distribution curves at Week 12 were computed for observed DAS28(CRP) to descriptively assess for potential departures of similarity based on the entire observed distribution regardless of adherence to treatment.

The statistical reviewer carried out all key analyses in all randomized patients to evaluate mean differences between treatment groups at key time points in all randomized patients regardless of adherence to the treatment or to the protocol (i.e., the intention-to-treat or de facto estimand). The statistical reviewer also carried out analyses in the PP population to evaluate

mean differences between treatment groups at key time points in the subset of patients who tolerate and adhere, corresponding to a different estimand. The FDA guidance<sup>10</sup> and ICH guidelines<sup>11</sup> indicate that the evaluation of both estimands is important in the context of a study designed to compare treatments. The de facto evaluation is critical because, unlike the per-protocol evaluation, it preserves the integrity of randomization and therefore guarantees reliable inference regarding possible differences in effects of the treatment strategies (if there are no missing data). There is also value in the per-protocol analysis. Because this analysis is restricted to the subset of patients who adhere, differences in the per-protocol effect may be larger and easier to detect in the presence of true differences between treatments.

The Agency had recommended that the Applicant conduct additional analyses to more systematically and comprehensively explore the space of plausible missing data assumptions. The Applicant conducted two sensitivity analyses to address missing data assumptions for ACR20 and DAS28-CRP at Week 12. They included (1) an analysis of all observed data collected regardless of adherence to randomized treatment without any imputation (i.e., patients with missing data at Week 12 were excluded), and (2) a tipping point sensitivity analysis based on pattern mixture approach with multiple imputation. The tipping point analysis results presented by the Applicant evaluated a specific missing not at random assumption depending on the history of the ACR20 and evaluated a limited tipping point parameter space. Thus, the statistical reviewer included an additional tipping point analysis that relaxes the dependence on the history of ACR20 collected post baseline. In this tipping point analyses, the statistical reviewer computed confidence intervals based on a normal approximation for the difference in ACR20 responses at Week 12. Then, the statistical reviewer varied the potential outcomes of the dropouts on both arms independently to completely explore the tipping space. This allows for a follow-up discussion of the plausibility of those assumptions under which the conclusions change.

### Margin Selection

The similarity margin for study B5381002 was determined based on several discussions with the Agency and the Applicant. During the BPD2 meeting on May 6, 2014, the Agency agreed with the Applicant's proposed similarity margin of  $\pm 14\%$  absolute difference in the probability of ACR20 response at Week 12 to comparatively evaluate PF-06410293 and EU-Humira with respect to efficacy using a 95% CI.

In a later communication, April 9, 2015, the Agency recommended a  $\pm 12\%$  similarity margin using a 90% CI, which was based on meta-analyses of historical effects of adalimumab and discussions with clinicians weighing the clinical importance of different losses in effect against the feasibility of different study sizes. The studies and the meta-analyses that the Agency based their recommendation on are shown below in **Table 19**. The  $\pm 12\%$  margin was selected as it

---

<sup>10</sup> Food and Drug Administration. Draft guidance for industry: Non-inferiority clinical trials, 2010.

<sup>11</sup> International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. E9: Statistical principles for clinical trials, 1998.

will preserve at least half of the effect of US-Humira. The Agency also stated that a relaxed upper bound, as part of an asymmetric margin, could be used if adequate scientific justification was provided.

Subsequently, the Applicant agreed to use -12% as the lower margin and proposed to use a relaxed upper margin of +15%. The Applicant included the following arguments, based on the dose-response curve and the likelihood of dose-related effects, to justify the use of a relaxed upper bound.

As stated by the Applicant, with the proposed design specification for study B5381002, the hypothesized ACR20 response rate for PF-06410293 (68.2%) and EU-Humira (60%), a difference of +8.2%, would result in a 90% CI of the treatment difference of (0.85%, 14.92%). Based on the dose-ranging results from the ARMADA trial (Weinblatt et al 2003), the hypothesized difference of +8.2% is smaller than 20% and 30% of the Week 12 effect size comparing adalimumab 40 mg every other week vs placebo (66% - 23%=43%) and adalimumab 20 mg every other week vs placebo (53% - 23%=30%) respectively. Therefore, this +8.2% difference would preserve at least 80% of the effect size observed for the approved dose of 40 mg every other week and at least 70% of the non-approved 20 mg dose. Based on this reasoning, the +15% relaxed upper margin for this CCS would be appropriate to evaluate meaningful differences in efficacy.

The Applicant stated that results from the ARMADA trial (Weinblatt et al 2003) suggested that the approved 40 mg every other week (EOW) dose is at the plateau of the dose-response efficacy curve; there was little evidence that doubling the dose to 80 mg EOW provided greater benefit. Therefore, according to the Applicant, based on their stepwise approach to collect data to support biosimilarity, a 100% increase in potency for their proposed biosimilar was unlikely to impact the ACR20 response rates at Weeks 12 and 24.

In a written communication dated September 16, 2015, the Agency agreed with the applicant's proposed margin of -12% and +15%. The above justifications to use a relaxed upper bound are appropriate.

**Table 19 Summary of the Four Historical Randomized Clinical Studies of Adalimumab in Patients with Active RA with Inadequate Response to MTX**

| Study                                                           | Week | MTX + Placebo |            | MTX + Adalimumab |            | Difference in % Response |
|-----------------------------------------------------------------|------|---------------|------------|------------------|------------|--------------------------|
|                                                                 |      | N             | % Response | N                | % Response |                          |
| Keystone 2004 [1]                                               | 12   | 200           | 25%        | 207              | 57%        | 32%                      |
| Weinblatt 2003 [2]                                              | 12   | 62            | 23%        | 67               | 66%        | 43%                      |
| Kim 2007 [3]                                                    | 12   | 63            | 25%        | 65               | 57%        | 32%                      |
| Chen 2009 [4]                                                   | 12   | 12            | 33%        | 35               | 54%        | 21%                      |
| Meta-Analysis (fixed effects): Difference (95% CI) <sup>1</sup> |      |               |            |                  |            | 34.0% (27.1%, 40.8%)     |
| Meta-Analysis (fixed effects): Difference (95% CI) <sup>2</sup> |      |               |            |                  |            | 34.1% (27.3%, 41.0%)     |
| Heterogeneity p-value                                           |      |               |            |                  |            | 0.54                     |

1: Based on Mantel-Haenszel weights

2: Based on DerSimonian-Laird approach

Abbreviations: MTX=methotrexate; RA=rheumatoid arthritis; CI=confidence intervals

[Source: Statistical Reviewer]

### Subject Disposition

At Week 26, approximately 95% of the randomized patients completed the study (Table 20). The study discontinuation rates were numerically higher on the EU-Humira arm. By the end of Week 26 (i.e., last dose at Week 24), 93% of the patients completed randomized treatment. By Week 12, 2% and 4% of the patients from the PF-06410293 and EU-Humira arm discontinued treatment respectively. The reasons for discontinuation from treatment (Table 21) or discontinuation from study (Table 22) for both treatment groups were numerically similar. There was one death from EU-Humira reported during TP1. These minor differences observed between treatment arms in the disposition of patients do not impact the conclusions.

**Table 20 Disposition of Patients during TP1, B5381002**

|                                                      | PF-06410293 | EU-Humira               | Total                 |
|------------------------------------------------------|-------------|-------------------------|-----------------------|
| <b>Total Randomized (N) <sup>a</sup></b>             | 297         | 300                     | 597                   |
| <b># received at least 1 dose of drug</b>            | 297 (100%)  | 299 (100%) <sup>c</sup> | 596 (100%)            |
| <b># completed follow-up by Week 26 <sup>b</sup></b> | 286 (96%)   | 273 (91%)               | 559 (95%)             |
| <b># completed treatment by Week 26</b>              | 283 (95%)   | 268 (89%)               | 551 (93%)             |
| <b># Discontinued treatment by Week 26</b>           | 14 ( 4%)    | 32 ( 9%) <sup>c</sup>   | 46 ( 8%) <sup>c</sup> |
| <b># Discontinued treatment by Week 12</b>           | 5 ( 2%)     | 12 ( 4%)                | 17 ( 3%)              |

a: Counts and percentages were computed relative to row.

b: Includes patients who completed study visits regardless of discontinuation of randomized treatments

c: Patient <sup>(b) (6)</sup> was listed as treatment discontinuation even though the patient was randomized and withdrew informed consent prior to receiving the first dose of study drug.

TP1 is from randomization until Week 26.

[Source: Statistical Reviewer]

**Table 21 Summary of Reasons for Discontinuation from Treatment Prior to Week 26, B5381002**

|                                            | PF-06410293<br>(N=297)<br>Counts (%) <sup>@</sup> | EU-Humira<br>(N=300)<br>Counts (%) <sup>@</sup> | Total<br>(N=597)<br>Counts (%) |
|--------------------------------------------|---------------------------------------------------|-------------------------------------------------|--------------------------------|
| <b>Number who discontinued treatment</b>   | 14 ( 5%)                                          | 32 (10%) <sup>2</sup>                           | 46 ( 8%)                       |
| <i>Adverse event: Related to drug</i>      | 6 ( 2%)                                           | 9 ( 3%)                                         | 15 ( 3%)                       |
| <i>Death</i>                               | -                                                 | 1 (<1%)                                         | 1 (<1%)                        |
| <i>Insufficient clinical response</i>      | 2 ( 1%)                                           | 6 ( 2%)                                         | 8 ( 1%)                        |
| <i>Lost to follow-up</i>                   | -                                                 | 1 (<1%)                                         | 1 (<1%)                        |
| <i>Non-compliance with study treatment</i> | -                                                 | 1 (<1%)                                         | 1 (<1%)                        |
| <i>Other</i>                               | 3 ( 1%)                                           | 3 ( 1%)                                         | 6 ( 1%)                        |
| <i>Protocol violation</i>                  | 1 (<1%)                                           | 3 ( 1%)                                         | 4 ( 1%)                        |
| <i>Withdrawal by subject</i>               | -                                                 | 2 ( 1%)                                         | 2 (<1%)                        |
| <i>Withdrawn consent</i>                   | 2 ( 1%)                                           | 6 ( 2%)                                         | 8 ( 1%)                        |

<sup>@</sup>: Counts and percentages were computed relative to N.

1: One (1) subject <sup>(b) (6)</sup> in the PF-06410293 arm was incorrectly recorded as discontinuation from treatment due to an AE; the correct reason was insufficient clinical response.

2: Patient <sup>(b) (6)</sup> was randomized, did not start randomized treatment and withdraw informed consent prior to receiving study drug was treated as treatment discontinuation. Reason was stated as "Other."

[Source: Statistical Reviewer]

**Table 22 Summary of Reasons for Discontinuation from Study Prior to Week 26, B5381002**

|                                                       | PF-06410293<br>(N=297)<br>Counts (%) <sup>@</sup> | EU-Humira<br>(N=300)<br>Counts (%) <sup>@</sup> | Total<br>(N=597)<br>Counts (%) |
|-------------------------------------------------------|---------------------------------------------------|-------------------------------------------------|--------------------------------|
| <b>Number who discontinued study prior to Week 26</b> | 6 ( 2%)                                           | 16 ( 5%)                                        | 21 ( 4%)                       |
| <i>Adverse event: Related to drug</i>                 | 2 ( 1%)                                           | 2 ( 1%)                                         | 4 ( 1%)                        |
| <i>Death</i>                                          | -                                                 | 1 (<1%)                                         | 1 (<1%)                        |
| <i>Insufficient clinical response</i>                 | -                                                 | 1 (<1%)                                         | 1 (<1%)                        |
| <i>Lost to follow-up</i>                              | -                                                 | 2 ( 1%)                                         | 2 (<1%)                        |
| <i>Non-compliance with study treatment</i>            | -                                                 | 1 (<1%)                                         | 1 (<1%)                        |
| <i>Other</i>                                          | 1 (<1%)                                           | 1 (<1%)                                         | 1 (<1%)                        |
| <i>Withdrawal by subject</i>                          | 2 ( 1%)                                           | 2 ( 1%)                                         | 4 ( 1%)                        |
| <i>Withdrawn consent</i>                              | 1 (<1%)                                           | 6 ( 2%)                                         | 7 ( 1%)                        |

<sup>@</sup>: Counts and percentages were computed relative to N.

1: Patient (b) (6) was randomized, did not start randomized treatment and withdraw informed consent prior to receiving study drug was treated as treatment discontinuation.

2: Patients (b) (6) “withdrawn consent” to be randomized into treatment period 2 after completing Week 26 assessments. Patient (b) (6) was flagged as “Non-compliant” and withdrawn from study but completed study assessments.

[Source: Statistical Reviewer]

### Protocol Deviations

During TP1 and TP2, the most commonly-reported protocol deviations were study procedure/tests (such as time to collect blood sample for laboratory samples, including those for PK and ADA), drug administration (such as dosing schedule error), and visit schedules (such as “Visit performed but not per protocol”). The proportion of deviations appears comparable among treatment arms.

A total of 13% of the patients were excluded from the per-protocol population based on data collected up to Week 12, the time of the primary efficacy endpoint (Table 23). The reasons for exclusion were generally balanced across the two arms. The most common reason for being excluded from the per-protocol population was not receiving complete doses up to Week 12.

**Table 23 Reasons for being Excluded from the Per-Protocol Population, B5381002**

|                                                   | PF-06410293<br>(N=297)<br>Counts (%) <sup>@</sup> | EU-Humira<br>(N=300)<br>Counts (%) <sup>@</sup> | Total<br>(N=597)<br>Counts (%) |
|---------------------------------------------------|---------------------------------------------------|-------------------------------------------------|--------------------------------|
| <b>Patients excluded from PP based on Week 12</b> | 30 (10%)                                          | 46 (15%)                                        | 76 (13%)                       |
| <i>Incorrectly randomized</i>                     | -                                                 | 1 (<1%)                                         | 1 (<1%)                        |
| <i>Did not meet inclusion/exclusion</i>           | 8 (3%)                                            | 14 (5%)                                         | 22 (4%)                        |
| <i>Fail to complete dosing</i> <sup>1</sup>       | 16 (5%)                                           | 34 (11%)                                        | 50 (8%)                        |
| <i>No joint counts evaluated at Week 12</i>       | 1 (<1%)                                           | -                                               | 1 (<1%)                        |
| <i>Concomitant medications prior to Week 12</i>   | 6 (2%)                                            | 8 (3%)                                          | 14 (2%)                        |

<sup>@</sup>: Counts and percentages were computed relative to N.

Patients can have more than one reasons for being excluded.

1: A total of six and 13 patients on PF-06410293 and EU-Humira respectively missed more than five doses of study drug.

Abbreviations: PP=per protocol.

[Source: Statistical Reviewer]

### Demographics and Baseline Characteristics

Patient demographics and anthropometric variables were similar across the two treatment arms (Table 24). Patients were on average 53 years of age, more frequently female, more frequently white, and neither Hispanic nor Latino. The majority of the randomized patients were enrolled from regions of the world other than North America, Western Europe, Japan, South Korea, or Latin America. Thirteen percent of the randomized patients were from the U.S.

**Table 24 Baseline Characteristics for All Randomized Patients,<sup>a</sup> B5381002**

|                                              | PF-06410293<br>(N=297) | EU-Humira<br>(N=300) | Total<br>(N=597) |
|----------------------------------------------|------------------------|----------------------|------------------|
| <b>Age (years)</b>                           | 51.5 (13.6)            | 53.5 (12.9)          | 52.5 (13.2)      |
| <b>Female</b>                                | 241 (81%)              | 229 (76%)            | 470 (79%)        |
| <b>Race</b>                                  |                        |                      |                  |
| <i>White</i>                                 | 261 (88%)              | 256 (85%)            | 517 (87%)        |
| <i>Black</i>                                 | 6 (2%)                 | 9 (3%)               | 15 (3%)          |
| <i>Asian</i>                                 | 16 (5%)                | 17 (6%)              | 33 (6%)          |
| <i>Other</i>                                 | 14 (5%)                | 18 (6%)              | 32 (5%)          |
| <b>Geographical Location</b>                 |                        |                      |                  |
| <i>North America/<br/>    Western Europe</i> | 57 (19%)               | 57 (19%)             | 114 (19%)        |
| <i>US patients</i>                           | 36 (12%)               | 39 (13%)             | 75 (13%)         |
| <i>Japan</i>                                 | 8 (3%)                 | 9 (3%)               | 17 (3%)          |
| <i>South Korea + Taiwan</i>                  | 5 (2%)                 | 6 (2%)               | 11 (2%)          |
| <i>Latin America</i>                         | 19 (6%)                | 20 (7%)              | 39 (7%)          |
| <i>Rest of the world</i>                     | 208 (70%)              | 208 (69%)            | 416 (70%)        |
| <b>Ethnicity</b>                             |                        |                      |                  |
| <i>Hispanic/Latino</i>                       | 25 (8%)                | 29 (10%)             | 54 (9%)          |
| <i>Not (Hispanic/Latino)</i>                 | 272 (92%)              | 271 (90%)            | 543 (91%)        |
| <b>Weight (kg)</b>                           | 74.7 (17.5)            | 76.2 (20.8)          | 75.4 (19.2)      |
| <b>Height (cm)</b>                           | 164.6 (9.0)            | 164.4 (9.0)          | 164.5 (9.0)      |
| <b>Body Mass Index (kg/m<sup>2</sup>)</b>    | 27.5 (6.1)             | 28.1 (7.3)           | 27.8 (6.7)       |

Counts (percentages relative to N) or means (standard deviation) are presented.

[Source: Statistical Reviewer]

Baseline RA disease characteristics were generally comparable across the two treatment arms (Table 25). The average RA disease duration was 6.8 years. A similar proportion of patients in each treatment group were seropositive (PF-06410293: 81.5%, EU-Humira: 81.7%). Patients had an average of 16 swollen joints, 25 tender joints, and HAQ-DI of 1.6. The average weekly MTX dose was approximately 15 mg/week in each treatment group. The proportion of patients with prior use of biologic drugs was 2%.

**Table 25 Baseline Disease Characteristics for all Randomized Patients,<sup>a</sup> B5381002**

|                                                                 |                       | PF-06410293<br>(N=297) | EU-Humira<br>(N=300) | Total<br>(N=597) |
|-----------------------------------------------------------------|-----------------------|------------------------|----------------------|------------------|
| RA disease duration                                             | (years)               | 6.8 (7.1)              | 6.8 (6.9)            | 6.8 (7.0)        |
| Replaced and/or fused joint                                     |                       | 19 ( 6%)               | 22 ( 7%)             | 41 ( 7%)         |
| Swollen joint counts                                            | (out of 66)           | 15.4 (7.8)             | 17.0 (9.8)           | 16.2 (8.9)       |
| Tender joint counts                                             | (out of 68)           | 24.3 (12.3)            | 26.7 (14.8)          | 25.5 (13.6)      |
| Swollen joint counts                                            | (out of 28)           | 11.6 (4.8)             | 12.4 (5.6)           | 12.0 (5.3)       |
| Tender joint counts                                             | (out of 28)           | 15.4 (6.1)             | 16.4 (6.3)           | 15.9 (6.3)       |
| Patient global assessment                                       | (0 – 100mm)           | 64.4 (19.3)            | 68.2 (19.5)          | 66.3 (19.5)      |
| Physician global assessment                                     | (0 – 100mm)           | 65.0 (15.2)            | 66.7 (15.8)          | 65.8 (15.5)      |
| Patient pain assessment                                         | (0 – 100mm)           | 63.7 (18.4)            | 65.9 (19.6)          | 64.8 (19.0)      |
| HAQ-DI                                                          | (0 – 3 scale)         | 1.5 (0.6)              | 1.7 (0.6)            | 1.6 (0.6)        |
| CRP                                                             | (mg/L)                | 21.3 (22.7)            | 22.8 (25.2)          | 22.1 (24.0)      |
| <b>Duration of MTX use</b>                                      |                       |                        |                      |                  |
|                                                                 | < 1 year              | 163 (55%)              | 151 (50%)            | 314 (53%)        |
|                                                                 | ≥ 1 year to < 3 years | 72 (24%)               | 77 (26%)             | 149 (25%)        |
|                                                                 | ≥ 3 years             | 62 (21%)               | 71 (24%)             | 133 (22%)        |
| Methotrexate (MTX) dose                                         | (mg/week)             | 15.2 (4.4)             | 15.2 (4.5)           | 15.2 (4.4)       |
| Prior and current non-biologic DMARDs<br>(inc MTX) <sup>a</sup> |                       | 1.5 (1.0)              | 1.5 (0.9)            | 1.5 (0.9)        |
| Prior use of 1 biologic drugs <sup>b</sup>                      |                       | 8 ( 3%)                | 5 ( 2%)              | 13 ( 2%)         |
| Use of cortisone (Yes)                                          |                       | 164 (55%)              | 170 (57%)            | 334 (56%)        |

Counts (percentages relative to N) or means (standard deviation) are presented.

<sup>a</sup>: Patients reported previous use of auranofin, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sodium aurothiomalate, sulfasalazine, tofacitinib.

<sup>b</sup>: Patients reported previous use of adalimumab, tocilizumab, certolizumab pegol.

Abbreviations: CRP=C-reactive protein; anti-CCP=anti-cyclic citrullinated peptide; DMARDs=disease modifying anti-rheumatic drugs; HAQ-DI=health assessment questionnaire-disability index; MTX=methotrexate; RA=rheumatoid arthritis; RF=rheumatoid factor

[Source: Statistical Reviewer]

### Analysis of Primary Clinical Endpoint(s)

The 90% confidence limits on differences between treatments were within the pre-specified asymmetric margin of -12% and +15% (Table 26). At Week 12, 71.3% of the randomized patients on EU-Humira and 68.4% of the randomized patients on PF-06410293 remained in the study and achieved ACR20 response at Week 12, with an estimated absolute response rate of 2.98% lower (90% exact CI: -9.3%, 3.3%) on the PF-06410293 arm compared to the EU-Humira arm. Additional supportive analysis based on all observed data analysis provided similar findings. The per protocol analysis with non-responder imputation or all observed data collected similarly ruled out the asymmetric margin.

**Table 26 Differences in ACR20 Responses at Week 12**

|                                   | EU-Humira<br>(N=300) |             | PF-06410293<br>(N=297) |             | Difference in<br>Response<br>(%) | 90% CI<br>Lower<br>(%) | 90% CI<br>Upper<br>(%) |
|-----------------------------------|----------------------|-------------|------------------------|-------------|----------------------------------|------------------------|------------------------|
|                                   | N                    | Count (%)   | N                      | Count (%)   |                                  |                        |                        |
| <b>ITT: NRI</b>                   | 300                  | 214 (71.3%) | 297                    | 203 (68.4%) | -2.98                            | -9.25                  | 3.28                   |
| <b>ITT: Observed <sup>1</sup></b> | 293                  | 218 (74.4%) | 291                    | 204 (70.1%) | -4.30                            | -10.44                 | 1.85                   |
| <b>PP: Observed</b>               | 254                  | 191 (75.2%) | 267                    | 189 (70.8%) | -4.14                            | -10.60                 | 2.46                   |

1: Observed analysis included all efficacy data collected regardless of adherence to study treatment.

NRI: Patients who discontinued the study treatment or withdraw from the study were imputed as non-responder.

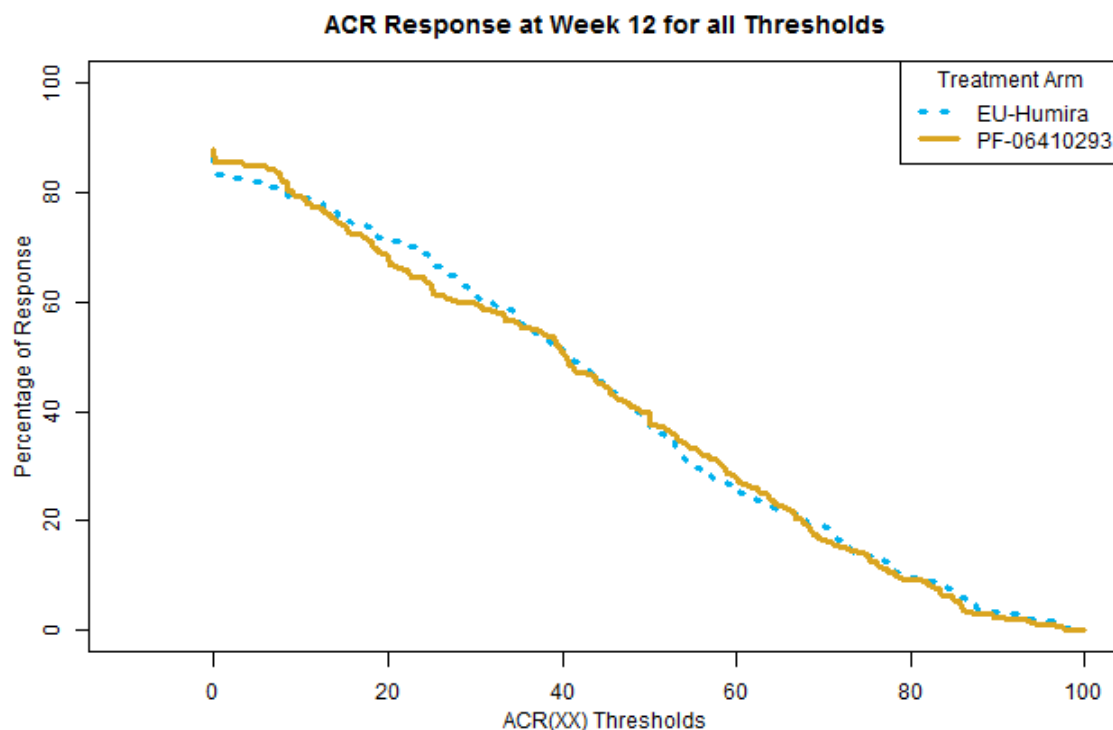
Abbreviations: ACR=American College of Rheumatology; CI=confidence intervals; ITT=intent to treat; NRI=non-responder imputation; PP=per protocol

[Source: Statistical Reviewer]

The cumulative distribution curves for EU-Humira and PF-06410293 at Week 12 were similar, with a slight trend toward greater efficacy of PF-06410293 at higher ACR thresholds (**Figure 11**), regardless of adherence to study treatment. However, the numerical trend towards greater efficacy of PF-06410293 at higher ACR thresholds observed at Week 12 did not persist at later weeks.

Supportive analyses for ACR20 at other weeks, not accounting for multiplicity but otherwise analyzed using the primary analysis method, did not show notable differences in efficacy (**Table 54**).

**Figure 11 ACR Responder Curve, Regardless of Adherence to Study Treatment for Various Thresholds at Week 12**



ACR Response(%)

|             |             |             |            |
|-------------|-------------|-------------|------------|
| EU-Humira   | 214 (71.3%) | 118 (39.3%) | 57 (19.0%) |
| PF-06410293 | 203 (68.4%) | 118 (39.7%) | 49 (16.5%) |

Patients without ACR data at Week 12 had their outcome imputed as non-response

Counts and percentage in parenthesis are presented.

Abbreviations: ACR=American College of Rheumatology

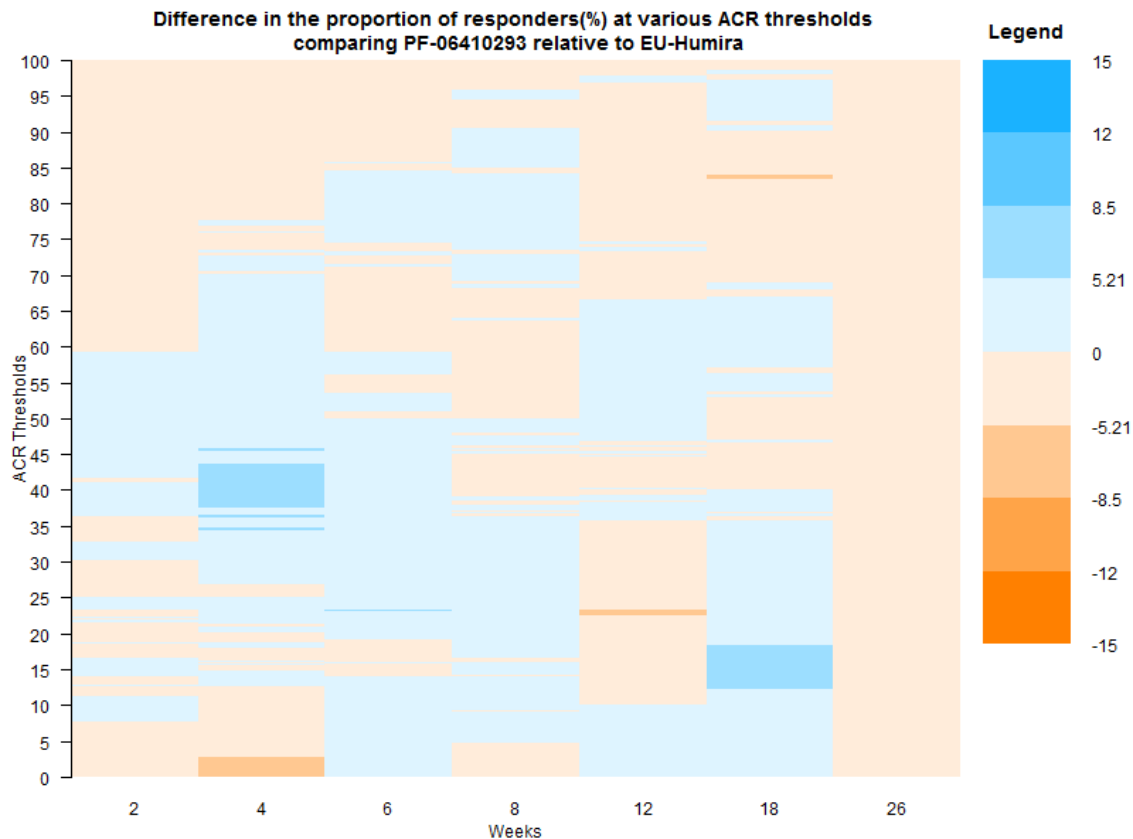
[Source: Statistical Reviewer]

In **Figure 12**, the difference in response comparing PF-06410293 relative to EU-Humira using all possible ACR thresholds at all study visits up to Week 26 was in general similar and PF-06410293 did not exhibit gains or losses in efficacy compared to EU-Humira.

Summary measures based on all observed data for the individual components of ACR, i.e., SJC66, TJC68, patient global, physician global, patient pain, HAQ-DI, and CRP were numerically similar (**Table 55** and **Table 56**).

In summary, improvements in ACR20, other thresholds of ACR, and individual components of ACR at protocol-defined primary week of analysis as well as other study weeks were similar between PF-06410293 and EU-Humira.

**Figure 12 Differences in ACR Response Comparing PF-06410293 vs EU-Humira Using all Possible ACR Thresholds Across Different Study Visits up to Week 26, Regardless of Adherence to Study Treatment**



Abbreviations: ACR=American College of Rheumatology  
[Source: Statistical Reviewer]

### Potential Effects of Missing Data

In the primary analysis based on the ITT set, patients who discontinued randomized treatment were considered non-responders, thus the primary endpoint was a composite measure of treatment success defined by adherence to the treatment through Week 12 and achieving an ACR20 response at Week 12. Comparing treatments with respect to this composite measure of treatment success may confound differences between treatments in efficacy with differences in tolerability or adherence. The composite measure could fail to identify meaningful differences in efficacy, for example, if the proposed biosimilar was better tolerated than the comparator but had lesser efficacy in the subset of patients who adhere. Therefore, it is important to evaluate differences in the components of the composite primary endpoint.

The statistical reviewer included an evaluation of ACR20 at Week 12 in all randomized patients regardless of adherence (an evaluation of the de facto or intention-to-treat estimand), in

addition to de facto evaluations of the components of ACR20. Such evaluations are subject to some missing data (because patients who discontinued treatment were not followed up for assessment) and rely on strong and unverifiable assumptions, such as the assumption that outcomes in patients who withdrew early are missing (completely) at random.

The statistical reviewer requested tipping point analyses from the Applicant to explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing-not-at-random assumptions). The reviewer also performed his own tipping point analyses. Specifically, in **Table 26**, at Week 12, 13 (2%) patients did not have any ACR data: 6 patients (2%) from the PF-06410293 treatment group and 7 patients (2%) from the EU-Humira treatment group. In the tipping point analyses conducted by the statistical reviewer, all points evaluated were within the similarity margins, i.e., ruled out an absolute loss of greater than 12% in probability of ACR20 response comparing PF-06410293 and EU-Humira (**Figure 17**) and ruled out an absolute gain of greater than a 15% (**Figure 18**). These results were consistent with the Applicant's analyses.

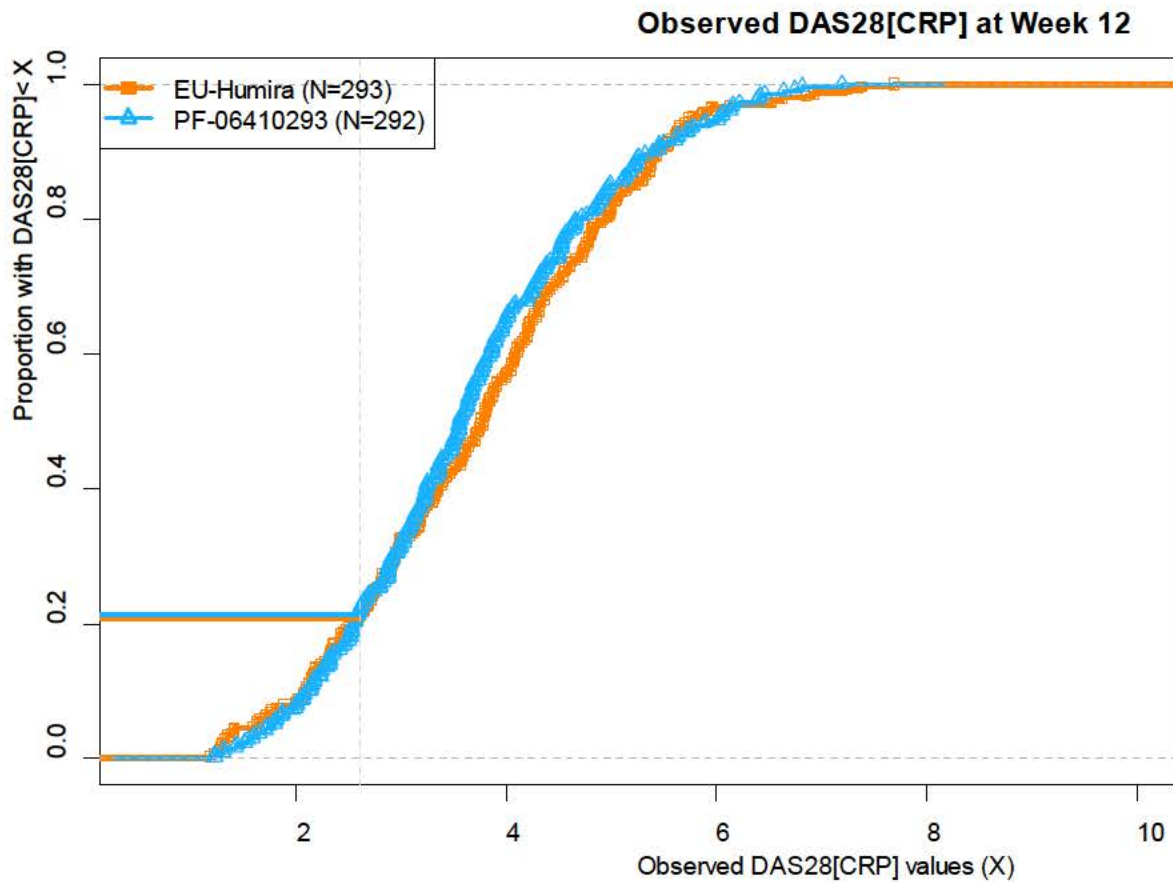
In summary, the efficacy of EU-Humira was similar to that of PF-06410293 for the primary endpoint, ACR20 at Week 12 notwithstanding missing data. There were relatively small proportions of dropouts at week 12, similar distributions of reasons for early withdrawal on the two treatment arms, and large differences between the outcomes in dropouts on the two arms based on the tipping point analyses seemed implausible (**Figure 17** and **Figure 18**). As a point of reference, the response probabilities among completers on PF-06410293 and EU-Humira were 70% and 74%, respectively. Therefore, the tipping point sensitivity analyses supported the findings of similar efficacy in the two treatment arms in Study B5381002.

### **Analysis of DAS28 (CRP)**

The cumulative distribution curves for all observed DAS28(CRP) at Week 12 were in general similar for the two treatments (**Figure 13**).

The adjusted change from baseline in DAS28(CRP) among all randomized patients regardless of adherence to study treatment and per-protocol population at each visit week were in general similar across study weeks for the two products (**Table 27**).

Figure 13. Cumulative Distribution Curves for Patients with Observed DAS28(CRP) at Week 12



Vertical dotted gray line represents DAS28(CRP) < 2.6.  
[Source: Reviewer]

**Table 27. Regression Analysis of the Change from Baseline in DAS28(CRP) Based on all Patients Regardless of Adherence to Study Treatment and PP Dataset**

|                   | Week     | PF-06410293<br>(N=297)<br>Mean (SD); n | EU-Humira<br>(N=300)<br>Mean (SD); n | Estimated<br>difference<br>(90% Robust CI) <sup>a</sup> | Estimated<br>difference<br>(90% CI) <sup>b</sup> |
|-------------------|----------|----------------------------------------|--------------------------------------|---------------------------------------------------------|--------------------------------------------------|
| ITT<br>(Observed) | Baseline | 5.9 (0.9); 297                         | 6.1 (0.9); 299                       |                                                         |                                                  |
|                   | 2        | 4.8 (1.1); 289                         | 4.9 (1.2); 289                       | -0.06 (-0.18, 0.06)                                     | -0.06 (-0.18, 0.06)                              |
|                   | 4        | 4.4 (1.1); 292                         | 4.5 (1.2); 291                       | -0.01 (-0.14, 0.12)                                     | -0.03 (-0.16, 0.11)                              |
|                   | 6        | 4.0 (1.2); 295                         | 4.2 (1.3); 293                       | -0.06 (-0.22, 0.10)                                     | -0.07 (-0.23, 0.09)                              |
|                   | 8        | 3.9 (1.2); 291                         | 3.9 (1.3); 292                       | 0.05 (-0.11, 0.21)                                      | 0.03 (-0.13, 0.19)                               |
|                   | 12       | 3.7 (1.2); 290                         | 3.8 (1.3); 293                       | 0.01 (-0.15, 0.17)                                      | 0.00 (-0.16, 0.16)                               |
|                   | 18       | 3.4 (1.2); 292                         | 3.5 (1.4); 286                       | 0.04 (-0.12, 0.20)                                      | 0.00 (-0.16, 0.17)                               |
|                   | 26       | 3.2 (1.1); 288                         | 3.3 (1.3); 276                       | -0.01 (-0.17, 0.15)                                     | -0.04 (-0.20, 0.12)                              |
| PP                | Baseline | 5.9 (0.9); 267                         | 6.0 (0.9); 254                       |                                                         |                                                  |
|                   | 2        | 4.8 (1.1); 262                         | 4.9 (1.1); 246                       | -0.04 (-0.16, 0.09)                                     | -0.05 (-0.18, 0.08)                              |
|                   | 4        | 4.3 (1.1); 263                         | 4.5 (1.2); 251                       | -0.02 (-0.16, 0.12)                                     | -0.04 (-0.18, 0.11)                              |
|                   | 6        | 4.0 (1.2); 267                         | 4.2 (1.3); 252                       | -0.09 (-0.25, 0.08)                                     | -0.09 (-0.25, 0.08)                              |
|                   | 8        | 3.8 (1.2); 266                         | 3.9 (1.3); 253                       | -0.03 (-0.19, 0.14)                                     | -0.02 (-0.19, 0.14)                              |
|                   | 12       | 3.6 (1.2); 265                         | 3.7 (1.3); 254                       | -0.03 (-0.20, 0.14)                                     | -0.02 (-0.19, 0.15)                              |
|                   | 18       | 3.4 (1.2); 266                         | 3.4 (1.3); 251                       | 0.01 (-0.15, 0.18)                                      | 0.00 (-0.17, 0.17)                               |
|                   | 26       | 3.2 (1.1); 264                         | 3.2 (1.3); 243                       | 0.01 (-0.16, 0.17)                                      | -0.02 (-0.18, 0.15)                              |

<sup>a</sup>: Linear regression model with Huber-White sandwich errors to the change from baseline in DAS28(CRP) at each week, adjusting for baseline DAS28(CRP), categorical geographic region, and treatment

<sup>b</sup>: MMRM model fit to the change from baseline in DAS28(CRP) adjusting for baseline continuous DAS28(CRP), categorical geographic region, categorical treatment group, categorical scheduled visit week, categorical scheduled visit week and treatment interaction, and continuous baseline DAS28(CRP) and categorical scheduled visit week interaction, with an unstructured covariance matrix. Kenward-Roger approximation was used to estimate the denominator degrees of freedom.

Abbreviations: DAS28(CRP)= Disease Activity Score-28, 4 components based on CRP; MMRM= mixed-effects model repeat measures; ITT=intent-to-treat; PP=per protocol; SD=standard deviation; CI=confidence intervals

[Source: Reviewer]

### Additional Analyses

In reviewing this CCS, it is important to understand the similarity of the study design to the historical studies used in setting the similarity margin (Table 19). Therefore, the statistical reviewer compared the key characteristics of the four historical, randomized, double-blind, parallel-group, placebo-controlled clinical trials of adalimumab used to calculate the similarity margin, along with study B5381002.

In summary, the key characteristics were generally similar, albeit some differences in the designs of these studies existed (Table 28). All patients in the studies included in Table 28 had

active RA despite treatment with methotrexate. The main difference between this study and the previous studies was that this study allowed patients to enroll who had prior exposure to TNF inhibitors other than US-Humira or non-U.S.-licensed adalimumab. However, very few randomized patients actually had prior experience with biologics (about 2%), and therefore, the anticipated impact of prior anti-TNF inhibitor treatment is minimal. There were also several minor differences in the inclusion criteria in Study B5381002 compared to the other studies. In Study B5381002, the inclusion criteria for eligibility based on the number of tender joints was at least six rather than 9 compared to historical studies. ESR was part of the inclusion criteria in Study B5381002 but not in historical studies. Study B5381002 was conducted in a much wider range of geographic locations (and only 13% of the randomized patients were from US). Only two of the four historical studies were conducted in US. Despite these differences, there was no observable effect of these changes on the enrolled population and these studies are sufficiently similar to maintain the assay sensitivity.

Study quality can impact the clinical study results. Conduct issues such as violations in eligibility criteria, poor adherence, cross-over between arms, or missing data tend to bias results toward the alternative hypothesis of similarity. In this study, 3% of the patients discontinued treatment at Week 12 and, on both arms, 7% discontinued treatment prior to Week 24. The protocol continued follow-up of patients after study treatment discontinuation reduced the missing data to approximately 5% on each arm. The number of protocol deviations was similar across treatment groups and potential violations in eligibility criteria were limited. The review of the DMC minutes for the open and closed sessions submitted by the Applicant did not identify major issues with study conduct. In summary, the study conduct was acceptable and did not raise any concerns that could impact the results.

In order to further assess assay sensitivity, the statistical reviewer also examined whether the within-group responses in the comparative clinical study were similar to those observed in previous placebo-controlled trials. The ACR20 response rate of 71% on EU-Humira in Study B5381002 at Week 12 is numerically higher than the historical rates, which ranged from 54% to 67%. Among US patients, the ACR rates were 54% and 59% at Weeks 12 and 26 respectively and comparable to historical rates albeit the small patient population. As previously noted, the study conduct was acceptable and there were high retention rates compared to historical studies. Given the higher adherence and retention rates due to good study conduct, there is sufficient assurance that, despite the higher observed ACR rates compared to historical rates, the study had adequate assay sensitivity.

In summary, although there were minor differences in terms of disease characteristics, including lack of biologic agents historically compared to current SOC, and a wider range of geographic regions, any concerns about study design and conduct in the submitted trial impacting assay sensitivity were sufficiently addressed. Further, even though observed higher ACR20 rates were noted in study B5381002 compared to historical studies differences, rates were consistent within the US patient population despite small numbers, and the good study conduct in B5381002 provided sufficient assurance on the results and conclusions from study

B5381002. Therefore, the available information addresses concerns regarding assay sensitivity of B5381002.

**Table 28. Comparison of Key Characteristics of Historical Randomized, Placebo-Controlled Clinical Trials of Adalimumab<sup>1</sup> in RA and Comparative Clinical Study B5381002**

|                                              | Keystone, et al., 2004                          | Weinblatt, et al., 2003                        | Kim, et al., 2007                             | Chen, et al., 2009                            | B5381002                                                                                               |
|----------------------------------------------|-------------------------------------------------|------------------------------------------------|-----------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Selected inclusion/exclusion criteria</b> | SJ≥6, TJ≥9, CRP >1 mg/dL, RF+, ≥1 joint erosion | SJ≥6, TJ≥9                                     | SJ≥6, TJ≥9                                    | SJ≥6, TJ≥9                                    | SJ≥6, TJ≥6, CRP≥0.8 mg/dL                                                                              |
| <b>Anti-TNF allowed?</b>                     | No                                              | No                                             | No                                            | No                                            | Allowed exposure to ≤ 2 doses of biologic agents other than US-Humira or non-U.S.-licensed adalimumab. |
| <b>Concomitant DMARDs</b>                    | Stable MTX, corticosteroids, NSAIDs             | Stable MTX, corticosteroids, NSAIDs            | Stable MTX                                    | Stable MTX                                    | Stable MTX, corticosteroids, NSAIDs                                                                    |
| <b>Region/Country</b>                        | US & Canada                                     | US & Canada                                    | Korea                                         | Taiwan                                        | US, Europe, Japan, Taiwan, South Korea, Latin America                                                  |
| <b>Baseline characteristics<sup>2</sup></b>  | SJ: 19;<br>TJ: 27;<br>dur: 11 yrs;<br>HAQ: 1.5  | SJ: 17;<br>TJ: 28;<br>dur: 12 yrs;<br>HAQ: 1.6 | SJ: 12;<br>TJ: 19;<br>dur: 6 yrs;<br>HAQ: 1.4 | SJ: 22;<br>TJ: 33;<br>dur: 6 yrs;<br>HAQ: 1.7 | SJ: 16;<br>TJ: 25;<br>dur: 7 yrs;<br>HAQ: 1.6                                                          |
| <b>Time of ACR20 Evaluation</b>              | Week 24                                         | Week 24                                        | Week 24                                       | Week 12                                       | Week 12                                                                                                |
| <b>ACR20 response on adalimumab</b>          | 63%                                             | 67%                                            | 62%                                           | 54%                                           | Overall<br>71% @ Week 12<br>77% @ Week 26<br>US only<br>54% @ Week 12<br>59% @ Week 26                 |
| <b>Withdrawal Rates</b>                      | 22% (Week 52)                                   | 7% (Week 16)                                   | 9%                                            | NA                                            | 3% @ week 12<br>6% @ week 26                                                                           |

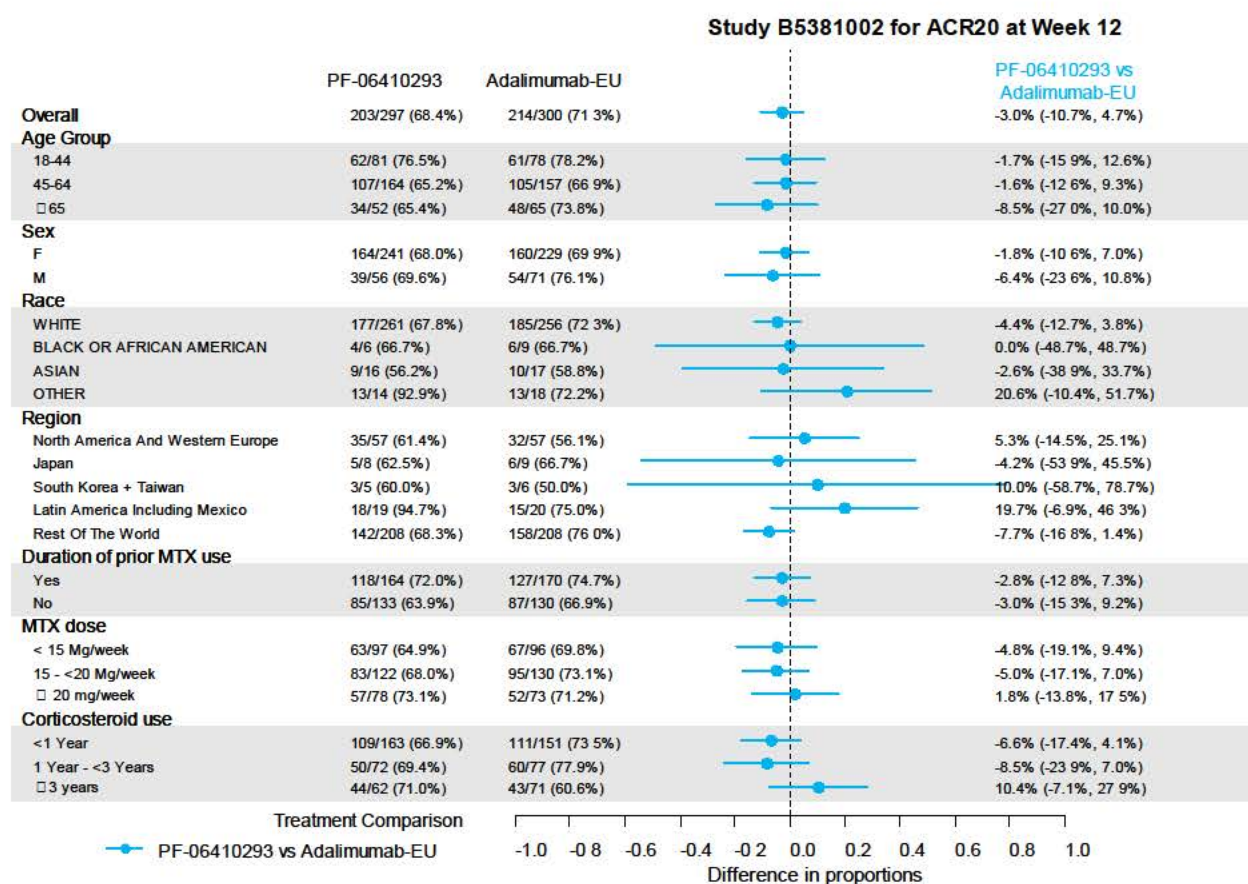
<sup>1</sup>: References to unknown sources of adalimumab (e.g., based on historical studies) will use "adalimumab."

<sup>2</sup>: Means or medians, depending on what was reported in publication; Abbreviations: ACR=American College of Rheumatology; SJ=swollen joint count; YRS=years; ESR=erythrocyte sedimentation rate; DUR=disease duration; CRP=C-reactive protein; HAQ=health assessment questionnaire-disability index; MTX=methotrexate; TJ=tender joint count; ULN=upper limit of normal; RF=rheumatoid factor; NSAIDs=non-steroidal anti-inflammatory drugs; DMARDs=disease modifying anti-rheumatic drugs [Source: Statistical Reviewer]

### Subgroup Analysis

There were no notable efficacy trends favoring EU-Humira or PF-06410293 based on subgroup analyses by sex, race, age, geographical region, as well as protocol-defined key RA baseline characteristics (Figure 14). Of note, subgroup results based on anti-drug antibody and neutralizing antibody, which were determined after randomization, were not presented. In summary, there were no notable trends of differences between products.

**Figure 14. Subgroup Analysis in the Probability of ACR20 Response at Week 12 and on Randomized Treatment**



Difference in proportions and respective 95% CI based on normal approximation difference in proportions are presented. The applicant presented subgroup analysis based on all observed data collected regardless of adherence to treatment.

Abbreviations: F=female; M=male; ACR=American College of Rheumatology; MTX=methotrexate

[Source: Statistical Reviewer]

**Authors:**

William Koh, PhD  
 Statistical Reviewer

Rebecca Rothwell, PhD  
 Statistical Team Leader

Jin Chen, MD, PhD  
 Clinical Reviewer

Rachel Glaser, MD  
 Clinical Team Leader

**7.3.2. Sub-Study B5381002**

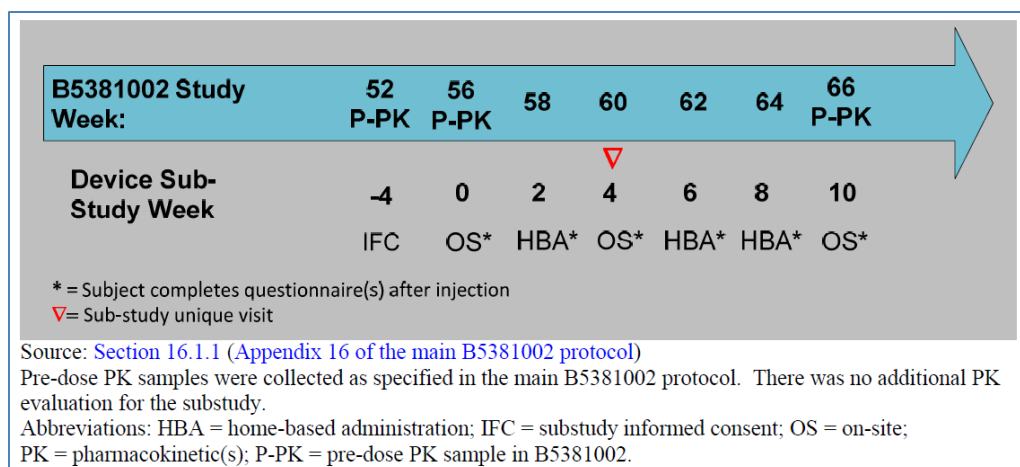
**Study Title:** “An Open-Label, Single Arm, Prefilled Pen Sub-Study in a Subset of Subjects Participating in Protocol B5381002”

**Study design:** This was an open-label, single arm study for subset (n=50) of RA patients enrolled in Study B5381002 to determine whether the patients or their non-healthcare professional caregivers could safely and effectively administer PF-06410293 with the pre-filled pen (PFP) device (**Figure 15**).

**Subjects:** N= 50

- Had completed Week 52 (TP1 and TP2) in Study B5381002 and moving into open-label extension period (TP3)
- Understood English for PFP administration instructions
- Was self-injecting the study drug or had a non-healthcare professional caregiver performing their injection during TP1 and TP2

**Figure 15. Substudy B5381002 Schema**



Source: Applicant’s Figure 1 in the CSR of Substudy B5381002

**Treatment:**

- PF-06410293 40 mg SC q2-week with single-use PFP device
- The PFP strength and dosage were the same as the PFS used in the main study
- A total of duration of treatment: 10 weeks (6 injections)

**Injection training:**

- Subjects and/or their non-healthcare professional caregivers were trained in using the PFP by trained local site personnel
- The first, third, and sixth injections were performed at the site under the supervision of the investigator or designated observer
- If the investigator or designated observer determined that the subject or their non-healthcare professional caregiver was not able to correctly administer an injection by PFP, the original training was to be repeated

**PFP injection success evaluations:**

- Delivery system success rate (DSSR):
  - Investigator/Designated Observer Performance Assessment: The investigator or observer observed the PFP injection, inspected the window on the PFP at the first, third, and sixth injections at the study site, and recorded the success of injection using the PFP Observer Assessment Tool (OAT questionnaire, see **Figure 19** in Appendix 16.5.3).
  - Participant Performance Assessment: The actual PFP users (subject or non-healthcare caregiver) injected, inspected the window on the PFP and recorded the success using the Participant Assessment Tool (PAT questionnaire, see in
  - 
  - **Figure 20** Appendix 16.5.3).
- Characterization of unsuccessful PFP injections
- A determination, by inspection, of the correct mechanical function of returned PFP devices. A portion of used PFPs were to be visually inspected centrally and undergo an industrial computed tomography (CT) scan to assess PFP function and correct operation.
- Medical Device Complaint Reporting Requirements: all medical device complaints including failure of the PFP to perform, regardless of whether the medical device complaint was associated with an AE, were to be recorded on the applicable Medical Device Complaint pages.

**Statistical Methodologies**

**Sample size:** The 50 subject sample size would allow description of the success of a projected  $\leq 300$  PFP injections. The Applicant did not specify how the subset of subjects was selected from the 505 subjects who were eligible to entering to the TP3 (**Figure 10**).

**Statistical analyses:** No formal statistical hypothesis was tested. All data were summarized using descriptive statistics. The percent variables calculated at each PFP injection visit were based on the number of subjects who attempted an injection at the visit.

**Primary endpoint:** The DSSR was defined as the percentage of subjects who achieved delivery success for an attempted injection at each of the 6 PFP injections during the 10-week study. The delivery success was based on:

- “Yes” for injection success on the OAT (**Figure 19**)
- Lack of injection failure on the PAT (
- 
- **Figure 20**)

**Primary endpoint analyses:**

- DSSR at each visit was accompanied by an exact, 2-sided 95% confidence interval (CI), using the Clopper-Pearson method.
- Overall DSSR (across all visits) and the 95% CI were to be obtained from a clustered binomial analysis using a generalized estimating equation (GEE) binomial model with logit link and working correlation structure of independence.

**Secondary endpoints and analysis:**

- Characterization of unsuccessful PFP injections was descriptive and correlated with the inspection of returned PFPs.
- Determination of the correct function of returned PFP devices was described by visual inspection and an industrial CT scan, and summarized in an inspection report

## Subject Disposition

A total of 63 subjects were screened and 50 subjects entered the substudy and received PFP treatment. One subject discontinued the substudy and main study due to withdrawal of consent, the remaining 49 (98.0%) subjects completed the study, and 47 (95.9%) of them selected the PFP device for continued B5381002 study treatment.

## Demographics and Baseline Characteristics

Overall demographics of the 50 subjects were consistent with the main study, except the geographic distribution included more subjects from the US (28% vs. 12% in the main study). The remaining subjects were from Poland (38%), Czech Republic (20%) and Lithuania (14%).

The baseline RA disease characteristics (at Week 52, the end of TP2) show improvement of all disease activity measurements compared to the main study day 1 baseline.

The majority of the subjects (92.0%) were right handed. No subject had finger joint hyperextension or ulnar deviation at metacarpophalangeals (MCPs). Approximately 6% (n=3) of subjects had previous tendon injury or procedure history on the dominant hand (right hand).

None of the 50 subjects had experience in use of an autoinjector or injection pen prior to participation in this substudy.

### **Treatment Compliance**

Full compliance (received all 6 doses) was 92% (n=46). Of the four subjects who did not full compliance, 3 missed one dose and 1 missed 3 doses. No subjects required a second attempt with the use of a second PFP.

### **Analysis of Primary Clinical Endpoint(s)**

The Delivery System Success Rate (DSSR) based on participant (the actual PFP user) and observer observations was 100% (95% CI: 92%-100%).

- Observer Assessment Tool (OAT): For the three injection visits, the OAT observers recorded all injections as successful. However, four subjects had difficulty pressing the button in a few injections, which were resolved after verbal help from the observer.
- Participant Assessment Tool (PAT): 96% (n=48) performed self-injection and the remaining 2 subjects had help from non-professional caregiver. No actual PFP User switched from subject to non-healthcare professional caregiver, or vice versa during the study. All actual users responded to all PAT questions to indicate injection success. Five subjects responded "I forgot to hold for 5 seconds" across the 6 injections.

### **Analysis of Secondary Clinical Endpoint(s)**

- Inspection of used PFP device: a total of 292 used PFP devices were returned and inspected. All showed complete injection. A bent needle was documented in 5 (1.7%) used PFPs on CT scan.
- No medical device complaints

### **Safety evaluation**

The AE profile was consistent with that reported during TP3 of the main study. No new safety signals were observed and no injection site reactions events were reported.

In summary, all actual PFP Users were able to successfully administer each of the injection attempts by the PFP. The majority of subjects (95.9%) opted to continue use of the PFP injections for the remainder of B5381002 study treatment.

**Authors:**

---

Jin Chen, MD, PhD  
Clinical Reviewer

---

Rachel Glaser, MD  
Clinical Team Leader

## **7.4. Review of Safety Data**

### **7.4.1. Methods**

To evaluate comparative safety, adverse events, laboratory examination, vital signs, hypersensitivity, and immunogenicity were reviewed. The primary study used to evaluate comparative safety was the comparative clinical study, B5381002, as it provided comparisons between EU-Humira and PF-06410293 in patients with RA for up to 78 weeks. Additionally, a portion of patients in B5381002 who received EU-Humira were transitioned to PF-06410293 in order to assess for potential safety issues after transitioning from EU-Humira to PF-06410293. Safety data from the 3 PK studies in healthy volunteers (B5381007, B5381001, and B5381005), were reviewed as supportive of the primary safety assessment.

US-Humira is an immunosuppressant drug with a well characterized safety profile. Black box warnings on the US-Humira prescribing information include serious infections and malignancy. Additional warnings and precautions include invasive fungal infections, anaphylaxis or serious allergic reactions, Hepatitis B reactivation, demyelinating diseases, cytopenias including pancytopenia, and Lupus-like syndrome. The most common adverse reactions are infections, injection site reactions, headache, and rash.

### **Clinical Studies Used to Evaluate Safety**

The Applicant collected safety data from four clinical studies, as listed in **Table 3** and summarized below. In all studies, subjects received 40 mg of subcutaneous study drug. Three of the studies were PK similarity studies; these studies had limited follow-up and were conducted in healthy subjects. Therefore, only limited safety information could be obtained from these three studies.

Study B5381007 was a randomized, double-blind, three-arm parallel group single dose study in healthy subjects to compare the PK of SC PF-06410293, US-Humira, and EU-Humira. There were 362 subjects (119-121 subjects/arm) who received at least one dose of investigational product.

Study B5381001 was a randomized, double-blind, single-dose, three-arm parallel group single dose study to compare the PK of SC PF-06410293, US-Humira, and EU-Humira in healthy subjects. Sixty-nine subjects received PF-06410293, 71 subjects received US-Humira, and 70 subjects received EU-Humira.

Study B5381005 was a randomized, open-label, two-arm parallel group single dose PK study to compare the PK of PF-06410293 administered SC via a prefilled syringe versus a prefilled pen. Eighty-one subjects received a single dose of PF-06410293 via PFS and 83 received a single dose of PF-06410293 via PFP. There were no comparisons to US-Humira in this study.

The primary safety data were derived from the comparative clinical study, B5381002, a 78-week, randomized, double-blind, parallel group, active-controlled study in patients with moderate to severe RA despite methotrexate therapy. The safety population included 596 patients. At week 26, patients who were on EU-Humira were randomized to continue on EU-Humira or transition to PF-06410293. The transition was used to assess potential risks in safety and immunogenicity as a result of transitioning from EU-Humira to PF-06410293. Study B5381002 included a substudy in 50 patients to evaluate the usability and safety of the prefilled pen. Additional details of the study design are described in Section 7.3.1 and Section 7.3.2 above.

**Extent of exposure:** The safety database included a total of 1329 subjects who received at least one dose of study drug. The number of subjects allocated to PF-06410293 or the comparator arms (EU-Humira or US-Humira) and duration of treatment are adequate to support a comparative safety assessment.

- Healthy subjects: N=733 received a single dose of 40 mg/0.8ml study product SC with 6-10 weeks of post-dosing safety follow-up
  - PF-06410293: N=354
  - US-Humira: N=190
  - EU-Humira: N=189
- Patients with RA: N=596 received at least one dose of 40 mg/0.8ml SC q2-week for up to 76 weeks with safety follow-up to up to 16 weeks after the last dose. One randomized patient did not receive study drug and was not included in the safety population. The number of patients with the median treatment durations were summarized in **Table 29** and **Table 58**:
  - PF-06410293: N=297 for 24 weeks; 283 of them for 52 weeks and 258 of them for 74 weeks (TP2+TP3)
  - EU-Humira: N=299 for 24 weeks; 135 of them for 52 weeks and 120 of them for 74 weeks (TP2+TP3)
  - EU-Humira switched to PF-06410293: N=133 for 52 weeks (TP2+TP1+TP3)

The median duration of treatment and median number of doses was similar in each treatment group, PF-06410293, EU-Humira, and the patients who transitioned from EU-Humira to PF-06410293, through each treatment period. The proportion of patients with any missed doses was numerically greatest in the group originally randomized to EU-Humira across each treatment period.

**Table 29. Extent of exposure during TP1 in B5381002**

|                                             | PF-06410293<br>N=297 | EU-Humira<br>N=299 | Total<br>N=596 |
|---------------------------------------------|----------------------|--------------------|----------------|
| Duration of Treatment                       |                      |                    |                |
| Median (range) (weeks)                      | 24.1 (0-26)          | 24.1 (0-28)        | 24.1 (0-28)    |
| Median (range) (days)                       | 169 (1-184)          | 169 (1-197)        | 169 (1-197)    |
| Total Number of Doses                       |                      |                    |                |
| Median (range)                              | 13 (1-14)            | 13 (1-14)          | 13 (1-14)      |
| Mean (SD)                                   | 13 (1.5)             | 12 (2.2)           | 13 (1.9)       |
| Subjects with any missed dose, <i>n</i> (%) | 29 (9.8)             | 51 (17.1)          | 80 (13.4)      |

Source: Applicant's **Tables 54 and 55** in CSR of Study B5381002 (Week 52).

### Population Demographics

The baseline demographics of patients in Study B5381002 are summarized in **Table 24** and the baseline disease characteristics are found in **Table 25**. In general, the baseline characteristics of the patients in Study B5381002 are representative of a RA population with moderate to severely active disease, and was similar between PF-06410293 and EU-Humira treatment groups.

The three PK studies enrolled healthy subjects. The demographics of subjects in the PK studies are presented in **Table 30**. Within each study, the demographics were similar across treatment arms.

**Table 30. Demographics in three comparative PK studies**

|                                   | Study B5381001  | Study B5381007 | Study B5381005   |
|-----------------------------------|-----------------|----------------|------------------|
| Primary Objective                 | PK similarity   | PK similarity  | PK comparability |
| Sample Size                       | 210             | 359            | 164              |
| Gender (M)                        | 209 (99.5%)     | 226 (63%)      | 82 (50%)         |
| Age (years)                       |                 |                |                  |
| 18-45                             | 80%             | 100%           | 75%              |
| >45                               | 20%             | 0%             | 25%              |
| Race                              |                 |                |                  |
| White                             | 62%             | 54%            | 79%              |
| Black                             | 26%             | 43%            | 18%              |
| Body Weight (kg)<br>Mean $\pm$ SD | 81.1 $\pm$ 11.4 | 76.7 $\pm$ 9.7 | 75.8 $\pm$ 12.4  |
| BMI (kg/m <sup>2</sup> )          | 25.8 $\pm$ 3.0  | 25.7 $\pm$ 2.6 | 27.0 $\pm$ 3.2   |

Source: Applicant's **Tables 4 and 5** of SCS, and datasets "ADSL" of individual study reports

† The remaining 60% subjects in Study B5381001 were enrolled from Belgium

### Categorization of Adverse Events

A treatment-emergent adverse event (TEAE) TEAE was defined as any adverse event (AE) that occurred after the beginning of the study treatment or any pre-existing AE that worsened after the beginning of the study drug treatment during the study (until the last visit). AEs of specific interest were defined based on the known risks associated with treatment with US-Humira and other TNF inhibitors.

The TEAEs were coded based on the MedDRA versions that were most current at the time of the data base lock in each of 4 studies: MedDRA versions from 16.1, 18, 19 to 20 for Study B5381001, Study B5381007, Study B5381005 and Study B5381002, respectively.

The severity of AEs was graded with Grades 1-5 (from mild, moderate, severe, life-threatening to death) according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Causality of AE, or treatment-related AEs, were primarily assessed by the investigators.

### Safety Analyses

All subjects randomized and treated with at least 1 dose of study drug, defined the safety population, and were included in the safety analyses. The Applicant did not plan and perform any integrated (pooling) analysis of the AE data across the four clinical studies due to inherent differences in the study design. This is consistent with the discussion during the pre-BLA (BPD4) meeting.

AEs, treatment-related AEs, and SAEs were summarized by SOC and PT according to MedDRA terminology with descriptive comparisons between PF-06410293 and EU-Humira and, where applicable, US-Humira.

For the comparative clinical Study B5381002, the Applicant pre-specified the following safety endpoints and analyses:

- Safety measures characterized by type, incidence, severity, timing, seriousness and relatedness of adverse events (AEs) and laboratory abnormalities.
- Incidence and titers of anti-drug antibodies (ADA) and neutralizing antibodies (NAb). Transient ADA response was defined as Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which ought to be considered persistent unless shown to be undetectable at a later time) or Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.
- Standard 3-tier adverse events reporting approach was employed:
  - *Tier-1 events*: The specified events of interest, including injection site reactions (ISRs), anaphylaxis/angioedema/urticaria, and opportunistic infections (including tuberculosis). The Tier-1 events were identified by the medical team on an ongoing basis and the final list of events were determined before database lock. Frequency and percentage of subjects with each treatment group, risk difference (RD), 95% CI on RD and p-values were calculated for each event group.
  - *Tier-2 events*: The events occurred in  $\geq 5\%$  patients in at least one treatment group, expressed as the frequency and percentage of subjects, RD and 95% CI of RD.
  - *Tier-3 events*: All other events that are neither Tier-1 nor Tier-2. Only frequency and percentage of subjects were presented.
- Targeted medical events (TMEs) were identified by the medical team on an ongoing basis and the final list of events were determined before database lock. TME categories include Hypersensitivity Standardized MedDRA Query (SMQ, broad and narrow), Anaphylactic reactions SMQ (broad and narrow) and High-Level Group Terms (HLGT) Immunology and allergy investigations, Neoplasms, Infections, Hypersensitivity, Blood/lymphatic Events, Demyelinating Conditions, Cardiovascular Events, Gastrointestinal/Hepatic Events, and Other. Frequency and percentage of subjects with each treatment group, risk difference (RD), 95% CI on RD and p-values will be provided for each TME category.

The following comparisons for each AE in Tier-1, Tier-2 and TME are primary focus:

- Between PF-06410293 and EU-Humira (TP1)
- Between PF-06410293/PF-06410293 and EU-Humira/EU-Humira (TP2)
- Between EU-Humira-transitioned-to-PF-06410293 and EU-Humira/EU-Humira (TP2)

## 7.4.2. Major Safety Results

### Relevant Characteristics of the Population Evaluated for Safety

The safety database submitted for assessment of comparative safety between PF-06410293, US-Humira and EU-Humira included four clinical studies (three single-dose comparative PK studies and one comparative clinical study) as summarized above. Due to differences in clinical study design and study population, no pooled analyses by demographic subgroups were performed. The comparative clinical study, Study B5381002, was conducted in active RA patients, who are representative of the target patient population. The study design was not powered for any subgroup analyses of safety.

### Overall AE profile:

A summary of AEs observed in Study B5381002 is presented below. No new safety signals were identified in the PF-06410293 treatment arm compared with the known adverse event profile of US-Humira. The overall all-causality AE profile in the RA study was comparable between PF-06410293 and EU-Humira during the first 26 weeks of double-blind treatment (TP1, **Table 31**), and between PF-06410293, EU-Humira and in patients who transition from EU-Humira to PF-06410293 (EU-Humira/PF-06410293) during the second 26 weeks of double-blind treatment (TP2, **Table 32**). During the 26-week open-label extension treatment (TP3) with PF-06410293, the safety profile was comparable between the 3 treatment groups based on the treatment received in the previous TP2 (**Table 58**). Overall, there were no major differences in deaths, SAEs, TEAEs, AEs leading to discontinuation, and AESI between the treatment groups. In addition, the safety observed in the single-dose PK studies in healthy subjects further support the comparable safety profile between PF-06410293 and US-Humira.

The following discussion concerns various AEs. Overall, AEs were comparable between the two treatment arms. While there were some minor numerical differences in AEs, the small number of events and the inconsistent trends are likely due to chance alone and do not indicate meaningful differences between the two treatment arms.

**Table 31. Overall AE profile during the TP1 in Safety Population in Study B5381002**

|                                        | All-Causality AEs             |                             |
|----------------------------------------|-------------------------------|-----------------------------|
|                                        | PF-06410293<br>N=297<br>n (%) | EU-Humira<br>N=299<br>n (%) |
| Number of AE                           | 343                           | 379                         |
| Subjects with AE                       | 143 (48.1)                    | 143 (47.8)                  |
| Subjects with SAE                      | 12 (4.0)                      | 13 (4.3)                    |
| Subjects with Grade 3 AE               | 15 (5.1)                      | 16 (5.4)                    |
| Subjects with Grade 4 AE               | 2 (0.7)                       | 4 (1.3)                     |
| Subjects with Grade 5 AE               | 0                             | 1 (0.3)                     |
| Death                                  | 0                             | 1 (0.3)                     |
| AE-Related Discontinuation             |                               |                             |
| Temporary discontinuation <sup>†</sup> | 17 (5.7)                      | 29 (9.7)                    |
| Discontinuation from treatment         | 11 (3.7)                      | 14 (4.7)                    |
| Discontinuation from study             | 8 (2.7)                       | 9 (3.0)                     |

Source: Applicant's **Tables 14.3.1.2.1.1.1 and 14.3.1.3.1.1.1** in SCR of Study B5381002 (Week 52)

<sup>†</sup> Treatment was temporarily discontinued at the discretion of the investigator in case of AE and resumed later.

<sup>‡</sup> Causality of an AE (treatment-related AE) was adjudicated by investigators. No specified adjudication criteria and procedure were provided in the study report nor in the final study protocol.

**Table 32. Overall AE profile during the TP2 in Safety Population in Study B5381002**

|                             | All-Causality AEs             |                             |                                            |
|-----------------------------|-------------------------------|-----------------------------|--------------------------------------------|
|                             | PF-06410293<br>N=283<br>n (%) | EU-Humira<br>N=135<br>n (%) | EU-Humira to PF-06410293<br>N=133<br>n (%) |
| Number of AE                | 243                           | 112                         | 100                                        |
| Subjects with AE            | 123 (43.5)                    | 60 (44.4)                   | 51 (38.3)                                  |
| Subjects with SAE           | 4 (1.4)                       | 6 (4.4)                     | 3 (2.3)                                    |
| Subjects with Grade 3 AE    | 7 (2.5)                       | 5 (3.7)                     | 4 (3.0)                                    |
| Subjects with Grade 4 AE    | 0                             | 2 (1.5)                     | 0                                          |
| Subjects with Grade 5 AE    | 0                             | 0                           | 0                                          |
| Death                       | 0                             | 0                           | 0                                          |
| AE-related Discontinuation  |                               |                             |                                            |
| Temporary discontinuation   | 16 (5.7)                      | 8 (5.9)                     | 5 (3.8)                                    |
| Discontinued from treatment | 6 (2.1)                       | 8 (5.9)                     | 2 (1.5)                                    |
| Discontinued from study     | 5 (1.8)                       | 8 (5.9)                     | 1 (0.8)                                    |

Source: Applicant's **Table 14.3.1.2.1.1.2** in CSR of Study B5381002 report (Week 52)

## Deaths

Two deaths were reported during the clinical development program, both reported in the comparative clinical study, Study B5381002. Neither death was determined to be related to study treatment by the investigator. One death due to coronary heart disease occurred on Study Day 132 in a 66 year old female receiving EU-Humira the day following an SAE of myocardial infarction for which the patient underwent percutaneous angioplasty. The death was not considered by the investigator to be related to study treatment.

In addition, a 73 year old female (Subject (b) (6)) died on Study Day 474 due to SAEs of anemia, upper GI hemorrhage, shock, aspiration pneumonia, and respiratory failure. She received EU-Humira in TP1 and TP2, and PF-06410293 in TP3 until the onset of the event when she presented with dark red stools, hypotension, and decreased mental status with a hemoglobin of 6.2 g/dL (reference 12-14 g/dL). Upper digestive endoscopy showed erosive gastropathy. She had continued clinical worsening despite support with fluids, blood products, tranexamic acid, pressors, and ventilator support. The investigator assessed the events as related to concomitant meloxicam.

There were no deaths reported in the healthy subjects in the PK studies, B5381001, B5381007, and B5381005.

Deaths observed in the PF-06410293 clinical program were few, and balanced by treatment group. Based on review of the submitted narratives, the deaths were not likely to be related to study treatment. These findings support the similar safety profiles between PF-06410293 and EU-Humira.

### Serious Adverse Events (SAEs)

**Patients with RA (n=596):** In Study B5381002, the total number of subjects who experienced an SAE was 25 (4.2%) during TP1 (**Table 31**), 13 (2.4%) during TP2 (**Table 32**) and 21 (4.2%) during TP3 (**Table 59**) in Study B5381002. During TP1, SAEs were reported by similar proportions of patients in the PF-06410293 arm and the EU-Humira arm (4.0% and 4.3%, respectively). SAEs within the Infections and Infestations SOC were reported most frequently, and were reported by 3 subjects in each treatment arm. The most frequently reported SAE by PT were pneumonia/pneumocystic jirovecci pneumonia, reported by 1 subject (0.3%) in the PF-06410293 arm and 2 subjects (0.7%) in the EU-Humira arm.

During TP2, SAEs were generally comparable across treatment groups, specifically SAEs were reported by 4 subjects (1.4%) in the PF-06410293/PF-06410293 arm, 6 subjects (4.4%) in the EU-Humira/EU-Humira arm, and 3 subjects (2.3%) in the EU-Humira/ PF-06410293 arm. The SOC with the highest proportion of subjects was Infections and infestations (0.4%, 2.2%, and 0 in the PF-06410293/PF-06410293, EU-Humira/EU-Humira, and PF-06410293/EU-Humira arms, respectively). SAEs were singular by PT in TP2.

During TP3, SAEs were reported by fewer subjects who received PF-06410293/PF-06410293/ PF-06410293 (3.5%) and EU-Humira/PF-06410293/PF-06410293 (2.4%), than in subjects who received EU-Humira/EU-Humira/PF-06410293 (7.5%). SAEs within the Infections and Infestations SOC were reported most frequently, and reported by a similar proportion of subjects in the PF-06410293/PF-06410293/ PF-06410293 arm and the EU-Humira/ PF-06410293/PF-06410293 arm. SAEs were singular by PT except for tonsillitis, which was reported by 2 subjects (0.8%) in the PF-06410293/PF-06410293/PF-06410293 arm, and rheumatoid arthritis which was reported in 1 subject each in the PF-06410293/PF-06410293/PF-06410293 arm and the EU-Humira/EU-Humira/ PF-06410293 arm.

The SAEs (by PT) were sporadically across all SOCs reported from all treatment periods (**Table 33** and **Table 34**, TP3 data not shown). There were no meaningful differences in the types and frequencies of SAEs among PF-06410293, EU-Humira and EU-Humira- -to-PF-06410293 groups during up to 76 weeks of treatment. These findings support the similar safety profiles between EU-Humira and PF-06410293.

**Table 33. All-causality Serious Adverse Events (SAEs) reported during TP1 in Study B5381002**

| SOC and PT                                             | PF-06410293<br>N=297<br>n (%) | EU-Humira<br>N=299<br>n (%) | Total<br>N=596<br>n (%) |
|--------------------------------------------------------|-------------------------------|-----------------------------|-------------------------|
| <b>Blood and lymphatic system disorders</b>            | 2 (0.7)                       | 0                           | 2 (0.3)                 |
| Anaemia                                                | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| Pancytopenia                                           | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| <b>Cardiac disorders</b>                               | 0                             | 2 (0.7)                     | 2 (0.3)                 |
| Atrial fibrillation                                    | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Myocardial infarction                                  | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| <b>Gastrointestinal disorders</b>                      | 3 (1.0)                       | 1 (0.3)                     | 4 (0.7)                 |
| Ileus                                                  | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Abdominal pain                                         | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| Haemorrhoids                                           | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| Pancreatitis chronic                                   | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| Rectal haemorrhage                                     | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| <b>Infections and infestations</b>                     | 3 (1.0)                       | 3 (1.0)                     | 6 (1.0)                 |
| Bronchitis                                             | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Gastroenteritis                                        | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Pneumonia                                              | 0                             | 2 (0.7)                     | 2 (0.3)                 |
| Gastroenteritis viral                                  | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| Pneumocystis jirovecii pneumonia                       | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| Pyelonephritis acute                                   | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| Urosepsis                                              | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| <b>Injury, poisoning and procedural complications</b>  | 0                             | 2 (0.7)                     | 2 (0.3)                 |
| Foot fracture                                          | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Spinal compression fracture                            | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| <b>Metabolism and nutrition disorders</b>              | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Dehydration                                            | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Hypokalaemia                                           | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| <b>Neoplasms benign, malignant and unspecified</b>     | 1 (0.3)                       | 2 (0.7)                     | 3 (0.5)                 |
| Adenocarcinoma of colon                                | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Papillary thyroid cancer                               | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Fibroadenoma of breast                                 | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| <b>Nervous system disorders</b>                        | 0                             | 2 (0.7)                     | 2 (0.3)                 |
| Cerebrovascular accident                               | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Seizure                                                | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| <b>Psychiatric disorders</b>                           | 1 (0.3)                       | 1 (0.3)                     | 2 (0.3)                 |
| Panic attack                                           | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Intentional self-injury                                | 1 (0.3)                       |                             | 1 (0.2)                 |
| <b>Renal and urinary disorders</b>                     | 1 (0.3)                       | 1 (0.3)                     | 2 (0.3)                 |
| Pelvi-ureteric obstruction                             | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Ureterolithiasis                                       | 1 (0.3)                       |                             | 1 (0.2)                 |
| <b>Respiratory, thoracic and mediastinal disorders</b> | 1 (0.3)                       | 2 (0.7)                     | 3 (0.5)                 |
| Chronic obstructive pulmonary disease                  | 0                             | 2 (0.7)                     | 2 (0.3)                 |
| Hypoxia                                                | 0                             | 1 (0.3)                     | 1 (0.2)                 |
| Interstitial lung disease                              | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| <b>Skin and subcutaneous tissue disorders</b>          | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| Toxic skin eruption                                    | 1 (0.3)                       | 0                           | 1 (0.2)                 |

| SOC and PT                | PF-06410293<br>N=297<br>n (%) | EU-Humira<br>N=299<br>n (%) | Total<br>N=596<br>n (%) |
|---------------------------|-------------------------------|-----------------------------|-------------------------|
| <b>Vascular disorders</b> | 1 (0.3)                       | 0                           | 1 (0.2)                 |
| Hypertensive crisis       | 1 (0.3)                       | 0                           | 1 (0.2)                 |

Source: Applicant's dataset "adae" of Study B5381002 report (Week 52)

**Table 34. All-causality Serious Adverse Events during TP2 in Study B5381002**

| SOC and PT                                                                 | PF-06410293<br>N=283<br>n (%) | EU-Humira<br>N=135<br>n (%) | EU-Humira/PF-06410293<br>N=133<br>n (%) |
|----------------------------------------------------------------------------|-------------------------------|-----------------------------|-----------------------------------------|
| <b>Any AEs</b>                                                             | 4 (1.4)                       | 6 (4.4)                     | 3 (2.3)                                 |
| <b>Cardiac disorders</b>                                                   | 1 (0.4)                       | 1 (0.7)                     | 0                                       |
| Acute myocardial infarction                                                | 1 (0.4)                       | 0                           | 0                                       |
| Myocardial infarction                                                      | 0                             | 1 (0.7)                     | 0                                       |
| <b>Gastrointestinal disorders</b>                                          | 1 (0.4)                       | 0                           | 1 (0.8)                                 |
| Gastrointestinal inflammation                                              | 0                             | 0                           | 1 (0.8)                                 |
| Irritable bowel syndrome                                                   | 1 (0.4)                       | 0                           | 0                                       |
| <b>General disorders and Administration</b>                                | 1 (0.4)                       | 0                           | 0                                       |
| Chest pain                                                                 | 1 (0.4)                       | 0                           | 0                                       |
| <b>Infections and infestations</b>                                         | 1 (0.4)                       | 3 (2.2)                     | 0                                       |
| Bronchopulmonary aspergillosis                                             | 0                             | 1 (0.7)                     | 0                                       |
| Ear infection                                                              | 1 (0.4)                       | 0                           | 0                                       |
| Gastroenteritis salmonella                                                 | 0                             | 1 (0.7)                     | 0                                       |
| Pneumonia                                                                  | 0                             | 1 (0.7)                     | 0                                       |
| <b>Injury, poisoning and procedural Complications</b>                      | 0                             | 1 (0.7)                     | 1 (0.8)                                 |
| Fall                                                                       | 0                             | 1 (0.7)                     | 0                                       |
| Upper limb fracture                                                        | 0                             | 0                           | 1 (0.8)                                 |
| <b>Musculoskeletal and connective tissue disorders</b>                     | 1 (0.4)                       | 0                           | 0                                       |
| Rheumatoid arthritis                                                       | 1 (0.4)                       | 0                           | 0                                       |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> | 0                             | 1 (0.7)                     | 0                                       |
| <b>Respiratory, thoracic and Mediastinal</b>                               | 1 (0.4)                       | 0                           | 1 (0.8)                                 |
| Paranasal cyst                                                             | 1 (0.4)                       | 0                           | 0                                       |
| Pneumothorax spontaneous                                                   | 0                             | 0                           | 1 (0.8)                                 |
| <b>Vascular disorders</b>                                                  | 0                             | 1 (0.7)                     | 0                                       |
| Venous thrombosis limb                                                     | 0                             | 1 (0.7)                     | 0                                       |

Source: Applicant's **Table 92** in Study B5381002 report (Week 52)

Two subjects were unblinded by Sponsor's personnel during TP1 for suspected unexpected serious adverse reactions (SUSARs); one subject (PF-06410293 arm) who had SAE of viral

gastroenteritis and 1 subject (PF-06410293 arm) with a history of chronic pancreatitis who had SAE of chronic pancreatitis. Both SUSARs were subsequently downgraded. Two subjects were also unblinded during TP2. One 69 year old female subject in the EU-Humira/EU-Humira group experienced an SAE of right femoral vein thrombosis on Study Day 227. The subject was discontinued from the study and subsequently diagnosed with lymphoma on Study Day 283. One 54 yo female in the PF-06410293/PF-06410293 experienced an SAE of paranasal cyst, considered treatment-related by the investigator. The outcome of the event cyst was reported resolved as on Study Day 358. Unblinded information was only accessible to safety personnel involved in safety reporting; therefore, the unblinding did not lead to subjects' exclusion from any safety analyses.

**Healthy subjects (n=733):** In total, two subjects experienced an SAE in the three single-dose PK studies. In B5381001, one subject in the EU-Humira arm had upper abdominal pain requiring hospitalization, who was found to have H. pylori. In B5381005, one subject in the PF-006410293 PFS arm had ovarian cyst rupture with anemia, requiring hospitalization. Both events were considered unrelated to study drug by the investigator.

#### **Treatment-emergent adverse events (TEAEs)**

**Patients with RA:** Overall TEAEs were comparable between PF-06410293 and EU-Humira and before/after EU-Humira transition to PF-06410293. It was also comparable in the AE profile during the open-label extension (TP3) based on the treatment arms received during TP2. No new safety signals were identified in B5381002.

In TP1, the type, incidences and severity of all-causality TEAEs by SOC or PT were comparable between PF-06410293 and EU-Humira. **Table 35** shows all-causality TEAEs experienced by  $\geq 2\%$  subjects.

The TEAEs by SOC reported by the greatest number of subjects (top 3), PF-06410293 vs. EU-Humira:

- Infections and infestations: 24.9% vs. 25.1%
- Musculoskeletal and connective tissue disorders: 10.4% vs. 8.7%
- Investigations: 8.8% vs. 7.7%

The most commonly reported TEAEs by PT ( $\geq 2\%$  subjects), PF-06410293 vs. EU-Humira:

- Viral upper respiratory tract infection: 7.1% vs. 6.0%
- Headache: 3.4% vs. 2.7%
- Anaemia: 3.0% vs. 0.7%
- ALT increased: 2.7% vs. 4.3%
- Hypertension: 2.7% vs. 4.3%

Pneumonia was the only TEAE of Grade 3 or higher with an incidence of  $\geq 1\%$  in any treatment arm. Pneumonia of Grade 3 was reported by 3 (1.0%) of subjects in the EU-Humira arm and 0 subjects in the PF-06410293 arm.

**Table 35. All-causality TEAEs (by ≥2% Subjects) during TP1 in Study B5381002**

| SOC and PT                                                  | PF-06410293<br>N=297<br>n (%) | EU-Humira<br>N=299<br>n (%) | All<br>N=596<br>n (%) |
|-------------------------------------------------------------|-------------------------------|-----------------------------|-----------------------|
| <b>Any AEs</b>                                              | 143 (48.1)                    | 143 (47.8)                  | 286 (48.0)            |
| <b>Blood and lymphatic system disorders</b>                 | 19 (6.4)                      | 13 (4.3)                    | 32 (5.4)              |
| Anaemia                                                     | 9 (3.0)                       | 2 (0.7)                     | 11 (1.8)              |
| <b>General disorders and administration site conditions</b> | 10 (3.4)                      | 22 (7.4)                    | 32 (5.4)              |
| Injection site reaction                                     | 5 (1.7)                       | 6 (2)                       | 11 (1.8)              |
| <b>Infections and infestations</b>                          | 77 (25.9)                     | 79 (26.4)                   | 156 (26.2)            |
| Bronchitis                                                  | 3 (1.0)                       | 6 (2.0)                     | 9 (1.5)               |
| Upper respiratory tract infection                           | 6 (2)                         | 14 (4.7)                    | 20 (3.4)              |
| Viral upper respiratory tract infection                     | 22 (7.4)                      | 19 (6.4)                    | 41 (6.9)              |
| <b>Investigations</b>                                       | 26 (8.8)                      | 25 (8.4)                    | 51 (8.6)              |
| Alanine aminotransferase increased                          | 8 (2.7)                       | 13 (4.3)                    | 21 (3.5)              |
| Aspartate aminotransferase increased                        | 7 (2.4)                       | 7 (2.3)                     | 14 (2.3)              |
| <b>Musculoskeletal and connective tissue disorders</b>      | 33 (11.1)                     | 28 (9.4)                    | 61(10.2)              |
| Arthralgia                                                  | 6 (2.0)                       | 1 (0.3)                     | 7 (1.2)               |
| Back pain                                                   | 5 (1.7)                       | 7 (2.3)                     | 12 (2)                |
| <b>Nervous system disorders</b>                             | 13 (4.4)                      | 21 (7.0)                    | 34 (5.7)              |
| Headache                                                    | 10 (3.4)                      | 8 (2.7)                     | 18 (3)                |
| <b>Vascular disorders</b>                                   | 12 (4.0)                      | 18 (6.0)                    | 30 (5.0)              |
| Hypertension                                                | 8 (2.7)                       | 15 (5.0)                    | 23 (3.9)              |

Source: Based on the Applicant's database "adae" for TP1 in CSR of Study B5381002 (Week 52)

In TP2, the type, incidence and severity of all-causality TEAEs by SOC or PT were comparable among the three treatment groups, PF-06410293/PF-06410293, EU-Humira/EU-Humira and EU-Humira/PF-06410293 (Table 36). The most commonly reported TEAEs by SOC (top 3) among three groups (PF-06410293/PF-06410293, EU-Humira/EU-Humira and EU-Humira/PF-06410293):

- Infections and infestations: 17.3%, 17% and 21%
- Investigations: 7.8%, 9.6% and 7.5%
- Musculoskeletal and connective tissue: 7.4%, 9.6% and 7.5%

The most commonly reported TEAEs by PT ( $\geq 2\%$  subjects) among three groups (PF-06410293/PF-06410293, EU-Humira/EU-Humira and EU-Humira/PF-06410293):

- Viral upper respiratory tract infection: 5.3%, 3.7% and 4.5%
- Upper respiratory tract infection: 1.4%, 3.7% and 4.5%
- Urinary tract infection: 1.1%, 0.7% and 3.8%

Grade 3 or higher TEAEs were reported in 2.5%, 5.2%, and 3.0% of subjects in the PF-06410293/PF-06410293, EU-Humira/EU-Humira and EU-Humira/PF-06410293 groups, respectively. Grade 3 or higher events were most frequently reported in the Infections and Infestations SOC (0.4%, 1.5%, and 0.8%) and Vascular disorders SOC (0.4%, 1.5%, and 0) of subjects in the PF-06410293/PF-06410293, EU-Humira/EU-Humira and EU-Humira/PF-06410293 groups, respectively. All Grade 3 or higher TEAEs were singular by PT.

**Table 36. All-causality TEAEs (by ≥2% Subjects) during TP2 in Study B5381002**

| SOC and PT                                            | PF-06410293/PF-06410293<br>N=283<br>n (%) | EU-Humira/EU-Humira<br>N=135<br>n (%) | EU-Humira/PF-06410293<br>N=133<br>n (%) |
|-------------------------------------------------------|-------------------------------------------|---------------------------------------|-----------------------------------------|
| <b>Any AEs</b>                                        | <b>123 (43.5)</b>                         | <b>60 (44.4)</b>                      | <b>51 (38.3)</b>                        |
| <b>Blood and lymphatic system disorders</b>           | <b>9 (3.2)</b>                            | <b>7 (5.2)</b>                        | <b>2 (1.5)</b>                          |
| Neutropenia                                           | 2 (0.7)                                   | 4 (3.0)                               | 2 (1.5)                                 |
| <b>Infections and infestations</b>                    | <b>49 (17.3)</b>                          | <b>23 (17.0)</b>                      | <b>28 (21.1)</b>                        |
| Bronchitis                                            | 1 (0.4)                                   | 0                                     | 4 (3.0)                                 |
| Upper respiratory tract infection                     | 4 (1.4)                                   | 5 (3.7)                               | 6 (4.5)                                 |
| Urinary tract infection                               | 3 (1.1)                                   | 1 (0.7)                               | 5 (3.8)                                 |
| Viral upper respiratory tract infection               | 15 (5.3)                                  | 5 (3.7)                               | 6 (4.5)                                 |
| <b>Injury, poisoning and procedural complications</b> | <b>12 (4.2)</b>                           | <b>3 (2.2)</b>                        | <b>5 (3.8)</b>                          |
| Fall                                                  | 4 (1.4)                                   | 1 (0.7)                               | 4 (3.0)                                 |
| <b>Investigations</b>                                 | <b>22 (7.8)</b>                           | <b>13 (9.6)</b>                       | <b>10 (7.5)</b>                         |
| Blood creatinine increased                            | 1 (0.4)                                   | 3 (2.2)                               | 0                                       |
| Alanine aminotransferase increased                    | 5 (1.8)                                   | 4 (3.0)                               | 4 (3.0)                                 |
| Aspartate aminotransferase increased                  | 3 (1.1)                                   | 4 (3.0)                               | 1 (0.8)                                 |
| <b>Musculoskeletal and connective tissue</b>          | <b>21 (7.4)</b>                           | <b>13 (9.6)</b>                       | <b>10 (7.5)</b>                         |
| Rheumatoid arthritis                                  | 4 (1.4)                                   | 2 (1.5)                               | 3 (2.3)                                 |
| <b>Nervous system disorders</b>                       | <b>14 (4.9)</b>                           | <b>1 (0.7)</b>                        | <b>5 (3.8)</b>                          |
| Headache                                              | 9 (3.2)                                   | 1 (0.7)                               | 2 (1.5)                                 |
| <b>Vascular disorders</b>                             | <b>12 (4.2)</b>                           | <b>5 (3.7)</b>                        | <b>3 (2.3)</b>                          |
| Hypertension                                          | 8 (2.8)                                   | 3 (2.2)                               | 3 (2.3)                                 |

Source: Applicant's **Table 81** in CSR of Study B5381002 (Week 52)

In TP3, in which all subjects received PF-06410293, and the follow-up period, a similar proportion of subjects experienced TEAEs in the PF-06410293/PF-06410293/PF-06410293 arm (42.6%) and the EU-Humira/PF-06410293/PF-06410293 (37%), while a numerically greater proportion of subjects had TEAEs in the EU-Humira/EU-Humira/PF-06410293 arm (50.8%). The most commonly reported TEAEs by SOC (top 3) among the three groups (PF-06410293/PF-

06410293/PF-06410293, EU-Humira/EU-Humira/PF-06410293 and EU-Humira/PF-06410293/PF-06410293):

- Infections and Infestations: 20.2%, 19.2% and 20.5%
- Musculoskeletal and Connective Tissue Disorders: 10.9%, 17.5% and 10.2%
- Investigations: 5.0%, 9.2% and 5.5%

The most commonly reported TEAEs by PT among the three groups (PF-06410293/PF-06410293/PF-06410293, EU-Humira/EU-Humira/PF-06410293 and EU-Humira/PF-06410293/PF-06410293):

- Rheumatoid arthritis: 5.0%, 9.2%, and 3.9%
- Nasopharyngitis: 5.0%, 2.5% and 7.9%
- Hypertension: 1.6%, 1.7% and 3.9%
- Upper respiratory tract infection: 0.8%, 1.7% and 4.7%
- Anaemia: 1.9%, 3.3% and 0.8%

Grade 3 or higher TEAEs were most frequently reported by subjects in the EU-Humira/EU-Humira/PF-06410293 treatment group (9.2%) as compared to the PF-06410293/PF-06410293/PF-06410293 (5.4%), and EU-Humira/PF-06410293/PF-06410293 (2.4%). Grade 3 or higher TEAEs occurred most commonly in the Infections and Infestations, Musculoskeletal and Connective tissue disorders, and Vascular disorders SOCs. Differences between treatment groups were due to small numbers of subjects. All were singular within treatment group by preferred term.

Overall, there were generally small numerical differences between groups, and there were no new safety signals identified in Study B5381002. The type, incidence and severity of all-causality TEAEs were generally comparable between treatment arms during each treatment period. There was no increase in TEAEs in the subjects who underwent a single transition from EU-Humira to PF-06410293 in TP2. These findings support the similar safety profiles between EU-Humira and PF-06410293.

**Healthy subjects:** The frequency of TEAEs reported from two single-dose comparative PK studies (Studies B5381001 and B5381007) in healthy subjects was comparable among PF-06410293, US-Humira and EU-Humira. In the comparative PK study to assess PFS vs. PFP of PF-06410293 (Study B5381005), the AE profile was similar between the two devices and was also consistent with the other two comparative PK studies. The majority of the AEs were mild to moderate in severity (CTCAE Grade 1 and 2).

The most commonly reported AEs in the healthy subjects across the PK studies by System Organ Class (SOC) were Infections and Infestations, Nervous System Disorders and Gastrointestinal Disorders (**Table 37**).

**Table 37. Incidence of AEs by System Organ Class (SOC) in healthy subjects from two comparative single-dose PK studies**

| SOC*                                                 | Study B5381001   |                |                | Study B5381007    |                 |                 |
|------------------------------------------------------|------------------|----------------|----------------|-------------------|-----------------|-----------------|
|                                                      | PF-06410293 N=69 | US-Humira N=70 | EU-Humira N=70 | PF-06410293 N=121 | US-Humira N=119 | EU-Humira N=119 |
| Any AEs                                              | 46.4%            | 53.5%          | 62.9%          | 57.0%             | 47.1%           | 40.3%           |
| Infections and Infestations                          | 20.3%            | 18.3%          | 28.6%          | 10.7%             | 8.4%            | 7.6%            |
| Nervous system disorders                             | 8.7%             | 15.5%          | 21.4%          | 15.7%             | 15.1%           | 10.1%           |
| gastrointestinal disorders                           | 13.0%            | 19.7%          | 20.0%          | 12.4%             | 8.4%            | 4.2%            |
| Respiratory, Thoracic and Mediastinal Disorders      | 7.2%             | 5.6%           | 7.1%           | 18.2%             | 14.3%           | 13.4%           |
| Investigations                                       | 0%               | 1.4%           | 4.3%           | 13.2%             | 9.2%            | 8.4%            |
| General disorders and administration site conditions | 5.8%             | 12.7%          | 7.1%           | 9.1%              | 10.1%           | 4.2%            |

Source: **Table 18** of CSR in Study B5381001; **Table 21** of CSR in Study B5381007

\* SOC: System Organ Class

The most frequently reported AEs in the healthy subjects across the PK studies by preferred term (PT), were headache, influenza, nasopharyngitis, nausea and fatigue. These events were generally mild in severity and transient. The small numerical differences and inconsistent trends are likely due to chance and do not indicate meaningful differences across the study products.

### Dropouts and/or Discontinuations

**Patients with RA** (Study B5381002): Overall AE-related discontinuations, either from the study drug or from the study, were comparable between treatment groups in TP1 (**Table 31**). In TP1, AEs leading to discontinuation from the treatment or from the study was comparable, (3.7% and 2.7%, respectively in PF-06410293 arm vs. 4.7% and 3.0% in EU-Humira arm). The SOC with the highest proportion of subjects with AEs leading to treatment discontinuations was Infections and Infestations, which were greater in the PF-06410293 group than in the EU-Humira group, 2.7% (n=8) vs. 1% (n=3). Latent TB was the most frequently reported AE leading to treatment discontinuation by PT, (1.7% (n=5) on PF-06410293 and 0.3% (n=1) on EU-Humira). Other AEs leading to treatment discontinuation were singular by PT in TP1.

In TP2, AEs leading to treatment discontinuation and study discontinuation more frequently in the EU-Humira/EU-Humira arm (5.9% and 5.9%), than the PF-06410293/PF-06410293 arm (2.1% and 1.8%), and the EU-Humira/PF-06410293 arm (1.5% and 0.8%). The most frequently

reported AEs leading to treatment discontinuation occurred in the Infections and infestations, Musculoskeletal and connective tissue disorders, and investigations SOC and were generally balanced by treatment group. The most frequently reported PT leading to treatment discontinuation was latent TB occurring in 2 subjects each in the PF-06410293/PF-06410293 and the EU-Humira/EU-Humira arms, and in 1 subject in the EU-Humira/PF-06410293 arm. Other AEs leading to treatment discontinuation were singular by PT in TP2.

In TP3, overall AE-related discontinuations were low and there were no meaningful differences across treatment groups corresponding to treatment assignment (in the TP2) prior to the open-label extension. In TP3, AE-related discontinuation from treatment occurred in 2.2% (n=11) of subjects, including 2.3%, 2.5% and 1.6% in the PF-06410293/PF-06410293/PF-06410293, EU-Humira/EU-Humira/PF-06410293, and EU-Humira/PF-06410293/PF-06410293 groups, respectively. AEs leading to discontinuation from study occurred in 1.6%, 2.5%, and 0.8%, respectively.

While there are numerical differences in the proportions of subjects with AEs leading to discontinuation with the greatest numbers in the EU-Humira/EU-Humira group, the observed differences are generally due to differences in a small number of subjects, and do not cluster by PT or SOC. No new safety signals were identified. These findings support the similar safety profiles between EU-Humira and PF-06410293.

**Healthy subjects** (Studies B5381001, B5381007, or B5381005): There were no discontinuations due to AEs in three comparative PK studies in healthy subjects.

### **Product Specific Safety Concerns**

The Adverse Events of Specific Interest (AESI) for anti-TNF $\alpha$  class, including adalimumab products, as defined by the Applicant include

- injection site reactions (ISRs)
- opportunistic infections
- urticaria/angioedema/anaphylactic reactions
- malignancies

Overall, the type, frequencies and severity of AESIs reported in the safety database are comparable and without meaningful differences between PF-06410293 and US-Humira and/or EU-Humira in healthy subjects and between PF-06410293 and EU-Humira in patients with RA.

The AESIs from the RA study (Study B5381002) are summarized in **Table 38** for TP1, **Table 39** for TP2 and **Table 58** for TP3.

**Table 38. Adverse Events of Special Interest (AESI) during TP1 in Study B5381002**

| <b>AESI (PT)</b>                                   | <b>PF-06410293<br/>N=297<br/>n (%)</b> | <b>EU-Humira<br/>N=299<br/>n (%)</b> |
|----------------------------------------------------|----------------------------------------|--------------------------------------|
| <b>Injection site reactions</b>                    | <b>5 (1.7)</b>                         | <b>6 (2.0)</b>                       |
| Injection site reaction                            | 5 (1.7)                                | 6 (2.0)                              |
| <b>Opportunistic infections</b>                    | <b>7 (2.4)</b>                         | <b>5 (1.7)</b>                       |
| Herpes zoster                                      | 1 (0.3)                                | 3 (1.0)                              |
| Latent tuberculosis                                | 5 (1.7)                                | 1 (0.3)                              |
| Oral candidiasis                                   | 0                                      | 1 (0.3)                              |
| Pneumocystis jirovecii pneumonia                   | 1 (0.3)                                | 0                                    |
| <b>Urticaria/angioedema/ anaphylactic reaction</b> | <b>0</b>                               | <b>2 (0.7)</b>                       |
| Urticaria                                          | 0                                      | 2 (0.7)                              |
| <b>Total</b>                                       | <b>11 (3.7)</b>                        | <b>12 (4.0)</b>                      |

Source: Applicant's Table 65 in Study B5381005 Week 52 report

**Table 39. Adverse Events of Special Interest (AESI) during TP2 in Study B5381002**

| AESI (PT)                                         | PF-06410293<br>N=283<br>n (%) | EU-Humira<br>N=135<br>n (%) | EU-Humira/<br>PF-06410293<br>N=133<br>n (%) |
|---------------------------------------------------|-------------------------------|-----------------------------|---------------------------------------------|
| <b>Injection site reaction</b>                    | <b>1 (0.4)</b>                | <b>0</b>                    | <b>1 (0.8)</b>                              |
| Injection site reaction                           | 1 (0.4)                       | 0                           | 1 (0.8)                                     |
| <b>Opportunistic infections</b>                   | <b>3 (1.1)</b>                | <b>4 (3.0)</b>              | <b>1 (0.8)</b>                              |
| Bronchopulmonary aspergillosis                    | 0                             | 1 (0.7)                     | 0                                           |
| Gastroenteritis salmonella                        | 0                             | 1 (0.7)                     | 0                                           |
| Herpes zoster                                     | 1 (0.4)                       | 0                           | 0                                           |
| Latent tuberculosis                               | 2 (0.7)                       | 2 (1.5)                     | 1 (0.8)                                     |
| <b>Urticaria/angioedema/anaphylactic reaction</b> | <b>0</b>                      | <b>0</b>                    | <b>0</b>                                    |
| <b>Total</b>                                      | <b>4 (1.4)</b>                | <b>4 (3.0)</b>              | <b>2 (1.5)</b>                              |

Source: Applicant's **Table 85** in Study B5381005 Week 52 report ; including all new AEs, and ongoing AEs at the start of TP2 that worsened, on or after the first injection of study drug in TP2.

**Injection Site Reactions (ISRs):** ISRs were defined by the symptoms (e.g., swelling, redness, itching) at the injection sites (abdomen or thigh) with severity grading based on the NCI-CTCAE toxicity scale.

**ISRs in healthy subjects:** In two single-dose comparative PK studies in healthy subjects (Studies B5381001 and B5381007), approximately 2.5% (n=14) of subjects experienced at least one ISR. Differences between groups were related to small differences in the number of subjects with ISR. In B5381001, ISR occurred in 1.4%, 7.0%, and 0 subjects in the PF-06410293, US-Humira, and EU-Humira groups, respectively, while in B5381007, ISR occurred in 0, 5.0%, and 1.7% of subjects in the PF-06410293, US-Humira, and EU-Humira groups, respectively. There was a single Grade 2 ISR in the US-Humira arm of B5381001; all other ISRs were Grade 1 in severity.

In Study B5381005, a comparative PK study of two delivery devices (PFS vs. PFP), the ISR incidence was comparable with PF-06410293 delivered by PFS vs. PFP (**Table 40**). All ISR were of t Grade 1 or 2 severity.

**Table 40. Injection Site Reactions of PF-06410293 delivered by PFS vs. PFP in Study B5381005**

| Injection Site Reaction (ISR)  | PFP<br>N=83<br>n (%) | PFS<br>N=81<br>n (%) |
|--------------------------------|----------------------|----------------------|
| <b>Total Subjects with ISR</b> | 7 (8.4%)             | 7 (8.7%)             |
| Erythema                       | 4 (4.8%)             | 3 (3.7%)             |
| Pruritus                       | 4 (4.8%)             | 2 (2.5%)             |
| Haematoma                      | 1 (1.2%)             | 0                    |
| Edema                          | 1 (1.2%)             | 4 (4.9%)             |
| Rash                           | 1 (1.2%)             | 0                    |
| Bruising                       | 0                    | 1 (1.2%)             |

Source: **Table 14.3.1.2.2.1** of Study B5381005 report (Week 52)

**ISR in patients with RA:** During the TP1, incidences of ISRs were low (<2%) in both treatment group and comparable between PF-06410293 and EU-Humira (**Table 41**), predominately at the abdominal location. There was one subject in the PF-06410293 arm with a Grade 2 ISR; all other ISRs in both groups were Grade 1. The most commonly reported symptom of ISRs was redness. In the patients with positive ADA, the ISR incidences on or after the first positive test for ADA were comparable between PF-06410293 (1 subject, 0.8%) and EU-Humira (2 subjects, 1.3%) groups.

**Table 41. Injection Site Reactions in TP1 (Study B5381002)**

| Injection Site Reaction (ISR)  | PF-06410293<br>(N=297)<br>n (%) | EU-Humira<br>(N=299)<br>n (%) |
|--------------------------------|---------------------------------|-------------------------------|
| <b>Total subjects with ISR</b> | 5 (1.7)                         | 6 (2.0)                       |
| Redness                        | 3 (1.0)                         | 2 (0.7)                       |
| Ecchymosis                     | 1 (0.3)                         | 0                             |
| Pain                           | 1 (0.3)                         | 1 (0.3)                       |
| Swelling                       | 1 (0.3)                         | 1 (0.3)                       |
| Tingling                       | 1 (0.3)                         | 0                             |
| Burning sensation              | 0                               | 1 (0.3)                       |
| Erythema                       | 0                               | 1 (0.3)                       |
| Fever                          | 0                               | 1 (0.3)                       |
| Itching                        | 0                               | 1 (0.3)                       |
| Rash                           | 0                               | 1 (0.3)                       |

Source: Applicant's **Table 14.3.1.2.4.2.1**

During TP2, a single subject experienced a new ISR in the PF-06410293/ PF-06410293 and EU-Humira/PF-06410293 groups, while there were no reported ISR in the EU-Humira/EU-Humira treatment group. The events were Grade 1 itching and erythema. No ISRs were observed in subjects that occurred on or after the first ADA positive test during TP2.

During TP3, a total of 2 subjects experienced ISRs, both in the PF-06410293/ PF-06410293/PF-06410293 group. The reported reactions were pruritus (Grade 1) and eczema (Grade 1). The symptoms were resolved without treatment. Only one subject with ISR (eczema) had positive ADA prior to entering TP3. The majority of subjects who developed ADA did not have ISR.

Overall, the incidence of injection site reactions in the PF-06410293 treatment group was similar to the incidence in the EU-Humira treatment group throughout Study B5381002. The incidence of ISR was similar or lower in ADA positive patients as the overall study population and comparable across PF-06410293 and EU-Humira, although assessment of ADA impact is limited by the low incidence of ADA. There was no notable increase in ISR following transition from EU-Humira to PF-06410293.

**Opportunistic Infections:** Opportunistic infections, including herpes zoster, latent TB, oral candidiasis, pneumocystis, were reported by 2.4% of subjects in the PF-06410293 arm and 1.7% in the EU-Humira arm. Latent TB was more frequently reported in PF-06410293 (1.7%) than EU-Humira (0.3%). There were no cases of active TB. All patients with latent TB had negative QuantiFERON-TB tests at screening. Countries where latent TB was reported include: Germany, Poland, Ukraine (2), and Spain. Diagnosis of latent TB was made by study investigators in consultation with pulmonary or infectious disease specialists, and based on positive QuantiFERON-TB test, with some subjects undergoing additional testing. While a greater number of patients in the PF-06410293 arm had AEs of latent TB, the percentage of subjects who became QuantiFERON-TB test positive over TP1 was balanced between the 2 arms (5.6% vs. 4.9%).

Herpes zoster was reported more frequently in the subjects on EU-Humira (1.0%) than PF-06410293 (0.3%), and there was 1 subject each with oral candidiasis (EU-Humira) and pneumocystic jirovecii pneumonia (PF-06410293).

During TP2, opportunistic infections were reported by 3 (1.1%) subjects in the PF-06410293/PF-06410293 group, 3.0% in the EU-Humira/EU-Humira group, and 0.8% in the EU-Humira/PF-06410293 group. In TP2, latent TB was reported by a greater proportion of subjects in the EU-Humira/EU-Humira group, as compared to the PF-06410293/PF-06410293 and EU-Humira/PF-06410293 groups:

Latent TB reported during TP2: n=5

- PF-06410293/PF-06410293: n=2 (0.7%)
- EU-Humira/EU-Humira: n=2 (1.5%)
- EU-Humira/PF-06410293: n=1 (0.8%)

In addition during TP2, there was 1 subject with herpes zoster (PF-06410293/PF-06410293), and 1 subject each with bronchopulmonary aspergillosis and gastroenteritis salmonella (EU-Humira/EU-Humira).

During the TP3, 1 subject (PF-06410293/PF-06410293/PF-06410293) developed an opportunistic infection of latent TB. There were no other opportunistic infections reported during TP3.

Overall, subjects with opportunistic infections were generally balanced between the treatment groups in B5381002. A numerical increase in AEs of latent TB was observed in the PF-06410293 arm during TP1, however, the percentage of subjects who became QuantiFERON-TB test positive during TP1 was similar between the treatment arms, and the incidence of AEs of latent TB was lower in the PF-06410293/PF-06410293 arm in TP2. Other opportunistic infections were infrequently reported, and similar by treatment group.

**Hypersensitivity:** Hypersensitivity events were identified by Hypersensitivity Standardized MedDRA Query (SMQ, broad and narrow), Anaphylactic reactions SMQ (broad and narrow) and High-Level Group Terms (HLGT) Immunology and allergy investigations based on MedDRA version 20.0 or later search criteria.

During the TP1, the incidences and severity (mostly Grade 1-2) of hypersensitivity events (mostly cough, erythema, or rash) were generally comparable between PF-06410293 and EU-Humira.

- PF-06410293: n=13 (4.4%) with 23 AEs; n=5 (3.8%) with positive ADA
- EU-Humira: n= 25 (8.4%) with 33 events; n=7 (4.6%) with positive ADA

There were 2 cases of urticaria reported in the EU-Humira group. No cases of angioedema or anaphylactic reaction were reported in either group. Both urticaria cases were considered non-serious, Grade 2 and transient, and appear confounded by other factors. The study drug was not interrupted due to the event.

In addition, serious interstitial lung disease and toxic skin eruption were reported by 1 subject each in the PF-06410293 group. One 64-year-old female experienced serious, Grade 3, interstitial lung disease considered related to study drug by the investigator. The subject was permanently discontinued from the study drug and the event resolved. One 45-year-old female developed Grade 1 pityriasis rosea on Study Day 72, which was confirmed as toxic skin eruption by skin biopsy, and considered related to study drug by the investigator. The patient discontinued from the study drug on Study Day 86 due to the event (late corrected as Lack of Efficacy).

Overall reported frequency of hypersensitivity events was low and comparable between the two treatment arms.

During TP1, hypersensitivity AEs were reported in similar proportions of ADA positive subjects in the PF-06410293 and EU-Humira arms (3.8% and 4.6%, respectively). Two subjects (1.5%) in the PF-06410293 arm reported Grade 3 AEs, both were SAEs, including interstitial lung disease and toxic eruption (discussed above). One subject (0.8%) in the PF-06410293 arm discontinued treatment and the study due to a hypersensitivity TEAE.

During TP2, no subjects experienced urticaria, angioedema or anaphylactic reactions. The incidence and severity (grade 1-2) of hypersensitivity events based on SMQ analysis were comparable among the three treatment arms:

- PF-06410293/PF-06410293: n=10 (3.5%)
- EU-Humira/EU-Humira: n=6 (4.4%)
- EU-Humira/PF-06410293: n=5 (3.8%)

In the ADA positive population, of the 126, 69, and 64 TP2 subjects with a post-dose ADA first identified in TP1, 7 (5.6%), 3 (4.3%), and 3 (4.7%) of subjects experienced hypersensitivity TEAEs in TP2 in PF-06410293/PF-06410293, EU-Humira/EU-Humira, and EU-Humira/PF-06410293. The most frequently reported hypersensitivity TEAEs were cough, rash, and allergic rhinitis. No action was taken with study drug. Of the subjects who developed ADA in TP1 or TP2, the majority of subjects in TP1 (95.0%) and all subjects in TP2, had no hypersensitivity events in TP2.

In TP3, two subjects (EU-Humira/PF-06410293/PF-06410293) experienced urticaria. The events were non-serious, Grade 1 or 2, and considered not related to study drug (confounded potential food allergy). There was also one subject (Subject (b) (6) EU-Humira/EU-Humira/PF-06410293) who reported serious AE of shock, with multiple medical conditions including aspiration pneumonia, Upper Gastrointestinal Bleeding, and Acute Anemia. This subject is discussed further under deaths.

Adverse events of hypersensitivity based on SMQ analysis were lower in the PF-06410293 treatment group in TP1 and similar in TP2. There was no increase in hypersensitivity AEs in subjects who underwent a transition from EU-Humira to PF-06410293. Urticaria was reported rarely and without increase in the PF-06410293 treatment group. There were no events of anaphylaxis.

**Neoplasms:** During TP1, a total of 10 cases of neoplasms were reported, including 3 malignancies. The overall incidences were balanced between the two treatment arms.

- PF-06410293: n=5, including 1 malignancy: basal cell carcinoma
- EU-Humira: n=5, including 2 malignancies: adenocarcinoma of colon and papillary thyroid cancer

Non-malignant neoplasms included uterine leiomyoma (N=3), fibroadenoma of the breast, benign breast neoplasm, acrochordon, and seborrheic keratosis.

During TP2, a total of 8 events of neoplasms were reported in 5 subjects:

- PF-06410293/PF-06410293: n=4 (1.4%), including 2 malignancies (squamous cell carcinoma and basal cell carcinoma)
- EU-Humira/EU-Humira: n=1 (0.7%) lymphoma
- EU-Humira/PF-06410293: n=0

Non-malignant neoplasms included kidney angiomyolipoma, melanocytic nevus, and seborrheic keratosis.

During TP3, 4 cases (including 2 SAEs) of neoplasms were reported: 2 cases each in the PF-06410293/PF-06410293/PF-06410293 (paraproteinemia and uterine leiomyoma) and EU-Humira/EU-Humira/PF-06410293 groups (breast cancer stage II and endometrial adenocarcinoma).

In Study B5381002, there was no clustering by type of malignancy and the incidence of malignancies was low.

### **Targeted Medical Events (TME)**

TME categories included Neoplasms, Infections, Hypersensitivity, Blood/Lymphatic Events, Demyelinating Conditions, Cardiovascular Events, Gastrointestinal/Hepatic Events, and Other. Neoplasms and hypersensitivity are discussed under AESI above, and infections are described under TEAEs above.

**Blood and Lymphatic System:** The most frequently reported Blood and Lymphatic AEs were anemia, neutropenia and leukopenia during TP1, TP2 and TP3. In TP1, the incidence of anemia was greater in the PF-06410293 group compared to the EU-Humira group (3% vs. 0.7%), while the incidence of leukopenia was higher in the EU-Humira arm than PF-06410293 (1.3% vs. 0.3%). Neutropenia was reported by similar numbers of subjects in each group. None of the 9 subjects with anemia in the PF-06410293 arm was assessed as related to study drug; causality was attributed to underlying disease, concomitant medication, iron deficiency, menstruation, and alimentary genesis. None of the events of anemia in either arm resulted in action being taken with study drug. One subject in the PF-06410293 arm had SAEs of anemia, hemorrhoids, and rectal hemorrhage (Grade 4). The events resolved after 13 days without action taken with study drug. In addition, 1 subject (PF-06410293) experienced pancytopenia and pneumocystis jirovecii pneumonia.

In TP2, anemia was similar between treatment groups (1.1% PF-06410293/PF-06410293 vs. 1.5% EU-Humira/EU-Humira. Neutropenia was numerically lower in the PF-06410293/PF-06410293 and EU-Humira/PF-06410293 arms than the EU-Humira/EU-Humira, however neutrophil count decreased was numerically lower in the EU-Humira/EU-Humira group.

While there were numerical differences in anemia between treatment groups in TP1, AEs were generally attributed to other causes and did not require interruption or discontinuation of study drug.

### **Demyelinating Conditions**

There were no Demyelinating conditions TMEs reported in Study B5381002.

### **Cardiovascular Events**

In TP1, the Cardiovascular TMEs were reported more frequently in subjects on EU-Humira (5.4%) as compared those receiving PF-06410293 (3.0%). The most frequently reported Cardiovascular TME was hypertension (2.7% PF-06410293, 4.3% EU-Humira). Other Cardiovascular TMEs were reported by single subjects in any arm and included 1 subject in each arm with peripheral edema, and 1 EU-Humira treated subject each with cerebrovascular accident and myocardial infarction. The AEs of cerebrovascular accident and myocardial infarction were SAEs with fatal outcomes and are discussed under deaths above. In addition, an SAE of Grade 3 hypertensive crisis was reported in 1 subject on PF-06410293. The event resolved without action with study drug.

In TP2, the most frequently reported Cardiovascular TME was hypertension, reported in similar proportions of subjects in each treatment group (2.8%, 2.2%, and 2.3% in PF-06410293/PF-06410293, EU-Humira/EU-Humira, and EU-Humira/PF-06410293. There were 2 cardiovascular SAEs: 1 subject (PF-06410293/PF-06410293) with chest pain who underwent angiography with stent placement and 1 subject (EU-Humira/EU-Humira) with myocardial infarction who also underwent angiography with stent placement.

Overall, cardiovascular TMEs and SAEs were similar across the treatment groups in TP1 and TP2 in Study B5381002.

### **Gastrointestinal/Hepatic Events**

Gastrointestinal/Hepatic TMEs in TP1 were generally comparable in the PF-06410293 and EU-Humira treatment groups (3.7% vs. 4.7%, respectively). The most frequently reported Gastrointestinal/Hepatic TMEs were ALT increased and AST increased, reported in 2.7% and 2.4% of subjects on PF-06410293 and 4.3% and 2.3% of subjects on EU-Humira. All other Gastrointestinal/Hepatic TMEs were reported by a single subject in any arm. None were reported as SAEs. In TP2, Gastrointestinal/Hepatic TMEs were reported in similar proportions of subjects on PF-06410293/PF-06410293, EU-Humira/EU-Humira, and EU-Humira/PF-06410293 (2.8%, 4.4%, and 3.0%, respectively). The most frequently reported TMEs were ALT increased (1.8%, 3.0%, and 3.0%, respectively) and AST increased (1.1%, 3.0%, and 0.8%) on PF-06410293/PF-06410293, EU-Humira/EU-Humira, and EU-Humira/PF-06410293. None of the Gastrointestinal/Hepatic TMEs were SAEs.

While there are numerical differences observed in Gastrointestinal/Hepatic TMEs between the treatment groups, slightly higher in the EU-Humira group, the differences are small in magnitude and there were no SAEs observed. The small number of events are likely due to chance alone and do not indicate meaningful differences between PF-06410293 and EU-Humira.

### 7.4.3. Additional Safety Evaluations

Not applicable.

#### Authors:

---

Jin Chen, MD, PhD  
Clinical Reviewer

---

Rachel Glaser, MD  
Clinical Team Leader

---

William Koh, PhD  
Statistical Reviewer

---

Rebecca Rothwell, PhD  
Statistical Team Leader

### 7.5. Clinical Conclusions on Immunogenicity

The immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (from single dose PK studies) and in patients with RA (multiple dose up to 76 weeks), and an assessment of the impact of ADA on PK, efficacy and safety. It is concluded that PF-06410293 was similar to US-Humira and/or EU-Humira in the production of ADA/NAb and their impact on PK, efficacy and safety. Refer to section 6.4 *Clinical Immunogenicity Studies* for results of the immunogenicity assessments.

### 7.6. Extrapolation to Support Licensure of Non-Studied Indications

Given the scientific bridge was established (based on the three-way analytical and PK comparisons between PF-06410293, US-Humira, and EU-Humira) to justify the relevance of data generated with EU-Humira as the comparator, the collective evidence from the comparative clinical study supports a demonstration of no clinically meaningful differences between PF-06410293 and US-Humira in the studied indication (RA). In addition to the RA indication, the Applicant is seeking licensure for following 6 indications, for which US-Humira has been previously approved and for which PF-06410293 has not been directly studied:

1. Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age and older
2. Psoriatic Arthritis (PsA)
3. Ankylosing Spondylitis (AS)
4. Adult Crohn's Disease (CD)
5. Ulcerative Colitis (UC)
6. Plaque Psoriasis (Ps)

The Applicant provided a justification for extrapolation of data and information submitted in

the application to support licensure of PF-06410293 as a biosimilar for each indication for which licensure is sought and for which US-Humira has been previously approved.

First, the Applicant's extensive analytical characterization data support a demonstration that PF-06410293 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components. In addition, the data support a demonstration there are no clinically meaningful differences between PF-06410293 and US-licensed Humira in terms of safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in RA.

Further, the additional points considered in the scientific justification for extrapolation of data and information to support licensure of PF-06410293 for the treatment of JIA in patients 4 years of age and older, PsA, AS, adult CD, UC, and PsO, as referenced in Section 7.6.1 and Section 7.6.2, include:

- Similar PK was demonstrated between PF-06410293 and US-Humira as discussed in the section on Clinical Pharmacology. Importantly, PF-06410293 was demonstrated to be highly similar to US-Humira, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between PF-06410293 and US-Humira in the indications sought for licensure. Thus, a similar PK profile would be expected between PF-06410293 and US-Humira in patients across all the indications being sought for licensure.
- In general, immunogenicity of US-Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used.<sup>12</sup> As stated elsewhere in this document, the Agency has concluded that there are sufficient data to support similar immunogenicity between PF-06410293 and EU-Humira with repeat dosing in patients with RA, and between PF-06410293, EU-Humira, and US-Humira after a single dose in healthy subjects. Accordingly, given that an adequate scientific bridge was established, similar immunogenicity would be expected between PF-06410293 and US-Humira in patients with JIA, PsA, AS, adult CD, UC, and PsO.
- The Applicant demonstrated that there are no clinically meaningful differences between PF-06410293 and US-Humira in patients with RA, and between PF-06410293, EU-Humira, and US-licensed Humira following single doses in healthy subjects. Additionally, in controlled clinical studies of US-Humira submitted to support its approval, as described in the approved labeling, the types of adverse events and their rates were similar across indications. The foregoing, coupled with the demonstration of analytical and PK similarity between PF-06410293 and US-Humira, support the conclusion that a

---

<sup>12</sup> FDA-approved US-Humira labeling

similar safety profile would be expected between PF-06410293 and US-Humira in patients with JIA, PsA, AS, adult CD, UC, and PsO.

- Pfizer addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that PF-06410293 and US-licensed Humira have the same mechanisms for each of the sought indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Therefore, based on the above considerations, DPARP, DDDP, and DGIEP review teams have concluded (see also Section 0 and Section 0) that the Applicant has provided adequate data and information to support licensure of PF-06410293 for each of the following indications for which US-licensed Humira has been previously licensed and for which Pfizer is seeking licensure of PF-06410293: RA, JIA in patients 4 years and older, PsA, AS, PsO, adult CD, and UC.

**Authors:**

---

Jin Chen, MD, PhD  
Clinical Reviewer

---

Rachel Glaser, MD  
Clinical Team Leader

### 7.6.1. Division of Gastroenterology and Inborn Error Products

#### Proposed Indications

Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.

Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.

Adult Crohn's Disease (adult CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab products.

Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis (PsO): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

#### Executive Summary

The Division of Gastroenterology and Inborn Errors Products concludes that the Applicant provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (rheumatoid arthritis), to support licensure of PF-06410293 as a biosimilar to US-licensed Humira, under section 351(k) of the PHS Act, for the inflammatory bowel disease indications (ulcerative colitis and adult Crohn's disease<sup>13</sup>).

---

<sup>13</sup> The Applicant did not provide a scientific justification for extrapolation for pediatric Crohn's disease and is not requesting licensure for this indication; US-licensed Humira has unexpired orphan drug exclusivity for this indication.

## Introduction

On November 16, 2018, Pfizer submitted a biologics license application (BLA) under section 351(k) of the Public Health Service (PHS) Act for PF-06410293, a proposed biosimilar to US-licensed Humira (adalimumab). US-licensed Humira received marketing approval in the US on December 31, 2002.

In support of the current BLA, the Applicant provided clinical study data collected from healthy subjects and patients with rheumatoid arthritis (RA). The Applicant submitted two PK similarity studies (B5381001 and B5381007) assessing 3-way PK similarity between PF-06410293, EU-approved Humira, and US-licensed Humira (based on pairwise comparisons of PF-06410293 to US-licensed Humira, PF-06410293 to EU-approved Humira, and EU-approved Humira to US-licensed Humira) in healthy subjects. In addition, the Applicant submitted the results of one comparative clinical study (B5381002) using PF-06410293 and EU-approved Humira in patients with moderate to severe rheumatoid arthritis (RA). Supportive PK, safety, and immunogenicity data were provided from Study B5381005 (a single dose comparability study comparing PF-06410293 administered by a pre-filled pen vs. a pre-filled syringe). See

**Table 42** below.

The inflammatory bowel disease (IBD) indications were not directly studied in the PF-06410293 clinical program. For additional information on the clinical studies in RA, please refer to the multidisciplinary review from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP).

**Table 42. Overview of PF-06410293 Clinical Program**

| Study ID                                      | Design               | Objective                            | Subjects                                                                                                     | Dose         | Treatments                                                                                                                                                                                                                                                                |
|-----------------------------------------------|----------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pivotal Clinical Pharmacology Studies</b>  |                      |                                      |                                                                                                              |              |                                                                                                                                                                                                                                                                           |
| B5381001                                      | R, DB, SD, 3-arm, PG | PK, immunogenicity, safety           | Healthy male and female subjects (n=210)                                                                     | 40 mg SC     | <ul style="list-style-type: none"> <li>PF-06410293 (n=69)</li> <li>EU Humira (n=70)</li> <li>US Humira (n=71)</li> </ul>                                                                                                                                                  |
| B5381007                                      | R, DB, SD, 3-arm, PG | PK, immunogenicity, safety           | Healthy male and female subjects (n=362)                                                                     | 40 mg SC     | <ul style="list-style-type: none"> <li>PF-06410293 (n=121)</li> <li>EU Humira (n=119)</li> <li>US Humira (n=119)</li> </ul>                                                                                                                                               |
| <b>Comparative Clinical Study</b>             |                      |                                      |                                                                                                              |              |                                                                                                                                                                                                                                                                           |
| B5381002                                      | R, DB, MC, PG        | Efficacy, safety, immunogenicity, PK | RA patients <ul style="list-style-type: none"> <li>TP1 (n=597)</li> <li>TP2 re-randomized (n=552)</li> </ul> | 40 mg SC EOW | TP1: <ul style="list-style-type: none"> <li>PF-06410293 (n=297)</li> <li>EU Humira (n=300)</li> </ul> TP2: <ul style="list-style-type: none"> <li>PF-06410293/PF-06410293 (n=283)</li> <li>EU Humira/EU Humira (n=135)</li> <li>EU Humira/ PF-06410293 (n=133)</li> </ul> |
| <b>Supportive Clinical Pharmacology Study</b> |                      |                                      |                                                                                                              |              |                                                                                                                                                                                                                                                                           |
| B5381005                                      | R, OL, SD, 2-arm, PG | PK, immunogenicity, safety           | Healthy male and female subjects (n=164)                                                                     | 40 mg SC     | <ul style="list-style-type: none"> <li>PF-06410293 PFS (n=81)</li> <li>PF-06410293 PFP (n=83)</li> </ul>                                                                                                                                                                  |

R: randomized; SB: single blind; DB: double blind; EOW: every other week; OL: open label; PG: parallel group; TP: treatment period; SD: single dose; MC: multicenter; SC: subcutaneous; PFP: pre-filled pen; PFS: pre-filled syringe; TP1: Treatment Period 1 (0-26 weeks); TP2: Treatment Period 2 (26-52 weeks). Source: BLA 761118, Module 2.5

### Extrapolation of Existing Data to Support Biosimilarity to IBD Indications

The Applicant conducted a comparative clinical study with their product in patients with RA, and seeks licensure for the RA, JIA (in patients 4 years of age and older), PsA, AS, adult CD, and UC indications, all for which US-licensed Humira has been previously approved.

The collective evidence from the comparative clinical study in patients with RA supports a demonstration of no clinically meaningful differences between PF-06410293 and US-licensed Humira, as the applicant established an appropriate scientific bridge comprised of comparative PK and analytical data for PF-06410293, US-licensed Humira, and EU-approved Humira. However, the Applicant needs to provide sufficient justification for extrapolating data and information submitted in the application to support licensure of PF-06410293 as a biosimilar for each condition of use for which licensure is sought and for which US-licensed Humira has been previously approved.

The scientific justification for extrapolation should consider the following issues that are described in the FDA Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance:<sup>14</sup>

- 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; and
- 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.

All of these factors were adequately addressed by the Applicant, as summarized below, for the IBD indications. The totality of the evidence provides support for licensure of PF-06410293 for the IBD indications (ulcerative colitis and adult Crohn's disease) under section 351(k) of the PHS Act. It should be noted that the Applicant did not provide a scientific justification for extrapolation for pediatric Crohn's disease and is not requesting licensure for this indication; US-licensed Humira has unexpired orphan drug exclusivity for this indication.

### **Mechanism of Action**

The mechanisms of action of adalimumab that are relevant for RA (the comparative clinical study population) are also relevant to IBD. The Applicant provided data to support that PF-06410293 has the same known and potential mechanisms of action as US-licensed Humira, which support extrapolation to these other indications.

The primary mechanism of action of adalimumab is direct binding of TNF- $\alpha$ , resulting in blockade of TNF- $\alpha$  receptor-mediated activities. Adalimumab blocks both TNFR1 and TNFR2 receptors by binding both soluble(s) and transmembrane(tm) TNF- $\alpha$ . In addition, adalimumab has mechanisms of action involving the Fc region of the antibody which are thought to be plausible mechanisms involved in the efficacy of adalimumab for the treatment of IBD. See a list of known and potential mechanisms of US-licensed Humira related to its efficacy in the treatment of IBD (**Table 43**, below). Similar to the directly studied indication (RA), TNF- $\alpha$  plays a central role in the pathology experienced by patients with IBD. TNF- $\alpha$  inhibition plays an important role in treating these diseases as evidenced by the efficacy of the TNF- $\alpha$  inhibitor class of medications in treating IBD.

---

<sup>14</sup> FDA Guidance for Industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", April 2015, available at: <https://www.fda.gov/media/82647/download>

**Table 43. Known and Potential Mechanisms of Action of US-Humira**

| MOA of US-Humira                                                                                                                                                                                                                                                                                                  | RA    | AS    | PsA   | PsO   | CD        | UC        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|-------|-------|-----------|-----------|
| <b>Mechanisms involving the Fab (antigen binding) region:</b>                                                                                                                                                                                                                                                     |       |       |       |       |           |           |
| 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    |
| <b>Mechanisms involving the Fc (constant) region:</b>                                                                                                                                                                                                                                                             |       |       |       |       |           |           |
| Induction of CDC on tmTNF-expressing target cells (via C1q binding)                                                                                                                                                                                                                                               | -     | -     | -     | -     | Plausible | Plausible |
| Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)                                                                                                                                                                                                             | -     | -     | -     | -     | Plausible | Plausible |
| Induction of regulatory macrophages in mucosal healing                                                                                                                                                                                                                                                            | -     | -     | -     | -     | Plausible | Plausible |
| ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF |       |       |       |       |           |           |

Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors<sup>15,16,17</sup>

The Product Quality reviewers have concluded that the Applicant has adequately addressed each of the known mechanisms of action of US-licensed Humira, and has also addressed potential mechanisms of action. Specifically, the Applicant provided data to demonstrate that s/tm TNF- $\alpha$  binding, blocking of TNFR1 and TNFR2 activity, and the potential Fc region-mediated mechanisms of action are similar between PF-06410293 and US-licensed Humira. These data support the conclusion that PF-06410293 and US-licensed Humira utilize the same mechanism or mechanisms of action, to the extent such mechanism or mechanisms of action are known, for US-licensed Humira.

### Pharmacokinetics (PK)

Studies B5381001 and B5381007 were single-dose, comparative PK, and safety studies of PF-06410293, US-licensed Humira, and EU-approved Humira conducted in healthy subjects planned to evaluate 3-way PK similarity of the commercial formulation of PF-06410293, US-licensed and EU-approved Humira. It should be noted that establishment of a scientific bridge to US-licensed Humira was necessary to justify the relevance of data generated using EU-approved Humira in the PF-06410293 developmental program which were used to support an assessment of biosimilarity to US-licensed Humira.

In addition, the single comparative clinical study, Study B5381002, collected PK information, including an immunogenicity assessment.

The clinical pharmacology reviewers concluded that the applicant provided data that established 3-way PK similarity between PF-06410293, US-licensed Humira, and EU-approved

<sup>15</sup> Oikonomopoulos A et al., *Current Drug Targets*, 2013, 14, 1421-1432.

<sup>16</sup> Tracey D et al., *Pharmacology & Therapeutics* 117 (2008) 244-279.

<sup>17</sup> Olesen, C.M, et.al., *Pharmacology & Therapeutics* 159 (2016), 110-119.

Humira in healthy subjects. The publicly available data submitted by the Applicant on US-licensed Humira do not indicate any major differences in PK based on disease state for the indications for which the Applicant is seeking licensure. Therefore, it is reasonable to conclude that a similar PK profile for PF-06410293 is expected between RA patients (the studied population) and IBD patients. In addition, it should be noted that the PK of adalimumab products is also influenced by immunogenicity, which is discussed further below.

### **Immunogenicity**

Immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (RA and healthy subjects). Immunogenicity was found to be similar when comparing PF-06410293, EU-approved Humira, and US-licensed Humira in the PK similarity studies conducted in healthy subjects and between PF-06410293 and EU-approved Humira in the comparative clinical study conducted in patients with RA. Specifically, the frequency of anti-drug antibody (ADA) positive subjects, the time course of ADA development, and median ADA titer values were found to be similar. These results support a demonstration of no clinically meaningful differences between PF-06410293 and US-licensed Humira. Therefore, it is reasonable to conclude that immunogenicity in IBD patients receiving PF-06410293 would be similar to that observed in IBD patients receiving US-licensed Humira.

### **Toxicity**

The primary assessment of adverse events was done using data from the comparative PK and safety studies of single dose PF-06410293 in healthy subjects and the comparative clinical study conducted in patients with RA. In controlled clinical studies of US-licensed Humira, as described in the approved labeling, the types of adverse events and their rates were similar across indications. Given the similar product quality attributes, PK, and immunogenicity, there is no reason to expect that the safety profile in the IBD population would be different from that observed in the RA population.

### **Conclusion**

Consistent with the principles of the FDA Guidance<sup>14</sup> outlined above, the applicant provided sufficient scientific justification (based on the mechanism of action, PK, immunogenicity and toxicity profile), and sufficient data and information, including clinical data from the studied population, to support licensure of PF-06410293 for the inflammatory bowel disease indications (ulcerative colitis and adult Crohn's disease).

Wen-Yi Gao, MD, PhD  
DGIEP Clinical Reviewer

Anil Rajpal, MD, MPH  
DGIEP Clinical Team Leader

Jessica Lee, MD, MMSc  
DGIEP Associate Director

## 7.6.2. Division of Dermatology and Dental Products

### Proposed Indications:

1. **Rheumatoid Arthritis (RA):** Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
2. **Juvenile Idiopathic Arthritis (JIA):** Reducing signs and symptoms of moderately to severe active polyarticular juvenile idiopathic arthritis (JIA) in patients from 4 to 17 years of age.
3. **Ankylosing Spondylitis (AS):** Reducing signs and symptoms in adult patients with active AS.
4. **Adult Crohn's Disease (CD):** Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab products.
5. **Ulcerative Colitis (UC):** Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers.
6. **Psoriatic Arthritis (PsA):** Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
7. **Plaque Psoriasis (PsO):** The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

### Executive Summary:

The Division of Dermatology and Dental Products has concluded that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (rheumatoid arthritis), to support licensure of ABRILADA as a biosimilar, under section 351(k) of the PHS Act, for plaque psoriasis.

Although the applicant did not conduct a clinical study in plaque psoriasis patients, the Applicant has provided adequate scientific justification to support extrapolation of the data and information submitted, to support licensure under section 351(k) of the PHS Act of ABRILADA as a biosimilar for plaque psoriasis.

US-licensed Humira has been widely used in clinical practice for about 18 years. Originally licensed for use in moderately to severely active RA, additional therapeutic indications were approved subsequently for U.S.-licensed Humira, including: treatment of patients with polyarticular JIA in patients aged 2 years or older, PsA, AS, PsO. The Applicant is seeking licensure for the following indications for ABRILADA (which have been previously approved for U.S.-licensed Humira):

- rheumatoid arthritis,
- juvenile idiopathic arthritis (in patients 4 years and older),
- ankylosing spondylitis,
- adult Crohn's disease,
- ulcerative colitis,
- plaque psoriasis,
- psoriatic arthritis.

The proposed presentations of 40 mg/0.8mL are a single-dose prefilled pen (ABRILADA Pen), a single-dose prefilled glass syringe, and a single-dose glass vial for institutional use only. The proposed presentation of 20 mg/0.4 mL and 10 mg/0.2 mL is a single-dose prefilled glass syringe. The proposed adult dosing and the recommended posology of ABRILADA are the same as those approved for U.S.-licensed Humira.

US-licensed Humira is not approved for chronic moderate to severe plaque psoriasis in the pediatric population.

For additional information on the clinical data submitted to support the indications evaluated in this application, please refer to the multidisciplinary review from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for details of the submitted application.

It is the Division's conclusion that sufficient scientific justification is presented for use of ABRILADA for "the treatment of adult patients with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy."

### **Introduction:**

On December 31, 2002, the reference product US-licensed Humira was licensed in the United States initially for adults for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Subsequently, US-licensed Humira was approved for adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy on January 18, 2008. Pfizer Inc. is developing ABRILADA as a proposed biosimilar to US-licensed Humira (adalimumab).

US-licensed Humira (adalimumab) is a recombinant human IgG1 monoclonal antibody which binds to and inhibits human tumor necrosis factor-alpha (TNF $\alpha$ ). TNF- $\alpha$  is a naturally occurring cytokine that involved in normal inflammatory and immune responses considered to play an important role in pathologic inflammation. Adalimumab blocks the biological function of TNF- $\alpha$  by interacting with cell surface TNF- $\alpha$  receptors, and modulates biological responses induced or regulated by TNF- $\alpha$ .

As part of the totality of the evidence to support a demonstration of biosimilarity, the clinical development program for ABRILADA was designed to evaluate whether no clinically meaningful differences exist between ABRILADA and US-licensed Humira. This evaluation considers pharmacokinetics, efficacy, safety, and immunogenicity.

The following clinical studies provided the primary evidence, along with other data and information to establish the scientific bridge to support the relevance of clinical data generated using EU-approved Humira as the comparator, to support the determination of no clinically meaningful differences between ABRILADA and US-licensed Humira:

- Clinical PK Similarity Studies (B5381001 and B5381007). These 2 single-dose PK similarity studies in healthy subjects compared the PK, immunogenicity and safety of ABRILADA, US-licensed Humira, and EU-approved Humira. In addition, 1 single-dose PK comparability study (B5381005) using the ABRILADA PFS or ABRILADA PFP in healthy subjects, and 1 multi-dose comparative clinical study (B5381002) in subjects with moderately to severely active RA, which included an optional device sub study using the PF-06410293 PFP. Two (2) population PK analyses were also conducted using the data from these clinical studies. Specifically, 1 analysis incorporated pooled data from healthy subjects from Study B5381001 and Study B5381007, and a second analysis examined the population PK of subjects with RA from Study B5381002.
- Comparative Clinical Study (B5381002). This study compared the efficacy, safety, immunogenicity and PK of ABRILADA and EU-approved Humira administered in RA patients. This clinical study had a total of 597 subjects that were randomized to receive study treatment, stratified by geographic region of the world. Of the 596 randomized and dosed subjects, 297 received ABRILADA and 299 received EU-approved Humira. Of the 552 subjects re-randomized in Treatment Period 2, 283 subjects continued PF-06410293, 135 subjects continued EU-Humira and 134 subjects previously in the EU-Humira group were re-randomized to receive ABRILADA (i.e., underwent a single transition).

Safety considerations for US-licensed Humira include a boxed warning and multiple Warnings and Precautions. Malignancy including lymphoproliferative disorders, serious and opportunistic infections, invasive fungal infections including tuberculosis, and neurologic, hematologic and hypersensitivity reactions are among the serious or lethal adverse events which have been reported.

Safety was reviewed for the following groups:

- All subjects exposed to ABRILADA
- All subjects exposed to EU-approved Humira
- All subjects exposed to US-licensed Humira
- All subjects exposed to EU-approved Humira who underwent a single transition to ABRILADA
- All healthy subjects exposed to single-dose or multiple-dose ABRILADA

Overall, the safety profiles of ABRILADA, US-licensed Humira and EU-approved Humira were comparable between the various treatment groups; additionally, the safety profiles of ABRILADA and EU-approved Humira were comparable after a single blind transition from EU-approved Humira to ABRILADA, and consistent with the established safety profile of US-licensed Humira.

No meaningful differences in the safety profiles were observed between ABRILADA, US-licensed Humira and EU-approved Humira, including events of special interest (i.e., serious infections, hypersensitivity reactions, and malignancies). No new safety signals were identified.

#### **Extrapolation for the Plaque Psoriasis indication:**

Pfizer conducted a comparative clinical study with ABRILADA in patients with RA. Pfizer is also seeking licensure for other indications for which US-licensed Humira has been previously licensed, including plaque psoriasis.

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 has been previously licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating data and information to support a determination of biosimilarity for each non-studied condition of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the studied 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

Consistent with the principles above and as outlined in FDA guidance<sup>18</sup>, the Applicant has provided sufficient scientific justification to support licensure of ABRILADA as biosimilar to U.S.-licensed Humira for the non-studied plaque psoriasis indication through the use of extrapolation.

- The primary mechanism of action (MOA) of US-licensed Humira is direct binding and blocking of TNF receptor-mediated biological activities. US-licensed Humira 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 well as in PsO. The data provided by the Applicant showed similar TNF binding and potency to neutralize TNF $\alpha$ , supporting that U.S.-licensed Humira and ABRILADA have the same MOA.
- The publicly available data submitted by the Applicant on US-licensed Humira do not indicate any major differences in PK between the RA and plaque psoriasis disease states. Because similar PK was demonstrated between ABRILADA and US-licensed Humira, a similar PK profile would be expected for ABRILADA in patients with chronic moderate to severe plaque psoriasis.
- No differences in expected toxicities that are relevant to the plaque psoriasis population were noted between the ABRILADA product and the EU-approved Humira arms in the clinical studies. Because the Applicant established an adequate scientific bridge to US-licensed Humira, no differences in toxicities are expected between ABRILADA and US-licensed Humira.
- The immunogenicity analysis of ABRILADA were similar to ADA results for US-licensed Humira (healthy subjects) and EU-approved Humira (healthy subjects and patients with RA).<sup>19</sup> The Applicant established an adequate scientific bridge to justify the relevance of the data generated with EU-approved Humira. Therefore, it is reasonable to conclude that immunogenicity in plaque psoriasis patients receiving ABRILADA would be similar to that observed in plaque psoriasis patients receiving US-licensed Humira.

### Overall Conclusion:

DDDP has determined that the Applicant has provided sufficient scientific justification to support extrapolation of data and information submitted by the applicant to support licensure under section 351(k) of ABRILADA as a biosimilar to US-licensed Humira for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic or phototherapy for which US-licensed Humira has been previously approved.

### Authors:

Gary T Chiang MD, MPH  
DDDP Clinical Reviewer

David Kettl, MD  
DDDP Clinical Team Lead

---

<sup>18</sup> FDA Guidance for Industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", April 2015, available at: <https://www.fda.gov/media/82647/download>

<sup>19</sup> See BLA 761118 Multidisciplinary Review.

## 8. Labeling Recommendations

---

### 8.1. Nonproprietary Name

The Applicant's nonproprietary name, adalimumab-afzb, was found to be conditionally accepted by the Agency.

### 8.2. Proprietary Name

The Applicant's proposed proprietary name for PF-06410293, Abrilada, has been conditionally approved. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded that the name is acceptable (DMEPA review dated Jan 4, 2019).

### 8.3. Other Labeling Recommendations

PF-06410293 is a proposed biosimilar to US-Humira. The Applicant is proposing the following dosage forms and strength:

- Injection: 40 mg/0.8 mL in a single-dose prefilled pen
- Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe
- Injection: 20 mg/0.4 mL in a single-dose prefilled glass syringe
- Injection: 10 mg/0.2 mL in a single-dose prefilled glass syringe
- Injection: 40 mg/0.8 mL in a single-dose glass vial for institutional use only

The proposed PF-06410293 prescribing information incorporated relevant data and information from the US-Humira prescribing information, with appropriate modifications. The Applicant is seeking licensure for the following indications, for which US-Humira has been previously approved: rheumatoid arthritis, juvenile idiopathic arthritis in patients 4 years of age and older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis.

The Applicant is not seeking licensure for the following indications for which US-Humira has been previously approved: juvenile idiopathic arthritis in patients 2 to less than 4 years of age, pediatric Crohn's disease, hidradenitis suppurativa, and uveitis. The Applicant's proposed labeling does not include these indications and certain information relating to them.

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), and is consistent with labeling guidance recommendations and CDER/OND best labeling practices and policies, is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The Applicant proposed to omit certain injection training information based on the results of the Human factor (HF) study conducted in untrained participants. However, the Division of Medication Error Prevention and Analysis (DMEPA) determined that while the data supports that the product could be used without training within the participants in the study, the sample of participants in the study may not represent all potential users of the product and there may be some users that would need training. Therefore, the Division did not agree with the removal of the need for injection training. Pfizer agreed to include information on the need for injection training in the labeling. In addition, Pfizer agreed to the changes requested by the Division to improve the readability, clarity, and accuracy of the prescribing information.

**Authors:**

---

Jin Chen, MD, PhD  
Clinical Reviewer

---

Rachel Glaser, MD  
Clinical Team Leader

## 9. Advisory Committee Meeting and Other External Consultations

---

No advisory committee meeting was held, as it was determined that there were no issues where the Agency needed input from the committee.

**Authors:**

---

Jin Chen, MD, PhD  
Clinical Reviewer

---

Rachel Glaser, MD  
Clinical Team Leader

## 10. Pediatrics

---

The applicant's iPSP was discussed at the PeRC meeting on August 28, 2019. The PeRC agreed with the requested deferrals for JIA (2 to less than 4 years of age), CD (6-17 years of age), and UC (5-17 years of age). See Section 11.2.

The Agency has determined at this time that, with respect to the following indications, no pediatric studies will be required under the Pediatric Research Equity Act (PREA) for the Applicant's BLA:

- JIA in 0 to less than 2 years of age;
- PsA;
- AS;
- CD in 0 to less than 6 years of age;
- UC in 0 to less than 5 years of age; and
- PsO.

Refer to memo dated November 12, 2019.

**Authors:**

---

Jin Chen, MD, PhD  
Clinical Reviewer

---

Rachel Glaser, MD  
Clinical Team Leader

## **11. Risk Evaluation and Mitigation Strategies (REMS) and Postmarketing Requirements and Commitments**

---

### **11.1. Recommendations for Risk Evaluation and Mitigation Strategies**

None

### **11.2. Recommendations for Postmarket Requirements and Commitments**

The Applicant is required to submit a pediatric assessment under PREA for the following:

- patients with JIA 2 to <4 years of age
- patients with CD 6 to 17 years of age
- patients with UC 5 to 17 years of age.

The following three PREA PMRs were agreed upon by the Applicant on September 20, 2019::

PMR-1: Assessment of Abrilada (adalimumab-afzb) for the treatment of polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 to less than 4 years of age.  
Final Report Submission Date: September 2021

PMR-2: Assessment of Abrilada (adalimumab-afzb) for the treatment of pediatric Crohn's disease (CD) in pediatric patients 6 years to 17 years of age.  
Final Report Submission Date: September 2021

The Applicant may fulfill these PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate justification under the BPCI Act for extrapolating the pediatric information from US-Humira to PF-06410293.

PMR-3: Assessment of Abrilada (adalimumab-afzb) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age.  
Final Report Submission Date: December 2020

US-Humira is not licensed for the treatment of pediatric ulcerative colitis in patients 5 to 17 years of age. The Applicant may fulfill this PREA requirement by seeking to update its labeling, supported by

biosimilar extrapolation or appropriate data, that includes relevant pediatric information after the labeling of US-Humira is updated with that information.

In addition, the following postmarketing commitments (PMCs) were agreed upon by the Applicant on September 20, 2019:

PMC#1 Develop and implement a control strategy for the FC-domain-mediated effector functions of Abrilada, including antibody-dependent cell mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Final report submission date: September 30, 2020

PMC#2 Include [REDACTED] (b) (4) syringes and vials as positive controls for routine container closure integrity testing.

Final report submission date: May 31, 2020

PMC#3 Submit data supporting capping and crimping parameters (minimal, nominal, and maximum pressures) using a dye ingress container closure integrity test that includes [REDACTED] (b) (4) positive control vials.

Final report submission date: May 31, 2020

PMC#4 Provide the polysorbate 80 (PS80) test method (drug product release method) and method transfer report to commercial laboratory.

Final report submission date: September 30, 2020

**Authors:**

---

Jin Chen, MD, PhD  
Clinical Reviewer

---

Rachel Glaser, MD  
Clinical Team Leader

## **12.Division Director/Designated Signatory Comments**

---

I concur with the review and conclusions by the review team. The regulatory action is approval.

**Author:**

Nikolay Nikolov, M.D.

DPARP Designated Signatory

## 13. Appendices

---

### 13.1. References

1. Keystone, E.C., et al., *Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial*. *Arthritis Rheum*, 2004. **50**(5): p. 1400-11.
2. Weinblatt, M.E., et al., *Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial*. *Arthritis Rheum*, 2003. **48**(1): p. 35-45.
3. Kim, H-Y., et al., *A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate*. *APLAR Journal of Rheumatology*, 2007. **10**(1): p. 9-16.
4. Chen, D.Y., et al., *Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis*. *J Formos Med Assoc*, 2009. **108**(4): p. 310-9.
5. Chan, I. S. F. and Zhang, Z. *Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions*. *Biometrics*, 1999. **55**: p. 1202–1209.
6. Santner, T. J. and Snell, M. K, *Small-Sample Confidence Intervals for  $p_1 - p_2$  and  $p_1/p_2$  in  $2 \times 2$  Contingency Tables*. *Journal of the American Statistical Association*, 1980. **75**: p. 386–394.
7. Food and Drug Administration. *Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry*. 2016.
8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *E9: Statistical principles for clinical trials*, 1998.

### 13.2. Financial Disclosure

The Applicant provided financial disclosure information on all investigators that participated in the four clinical studies listed in **Table 3**. The Applicant also submitted Financial Certification and Disclosure – Bias Statement for each of four clinical studies with details about “Steps Taken to Minimize the Potential for Bias”.

Among a total of 934 clinical investigators who participated in the four clinical studies, there were:

- N=7 clinical investigators who were employees (full-time or part-time) of the sponsor of the covered study. All participated in Study B5381001 (the first comparative PK study).

- N=2 clinical investigators with certification of due diligence. Each investigator was from a different site located in South Korea, sites #2261 and #2262, in Study B5381002 (comparative clinical study). The Applicant was unable to obtain completed Financial Disclosure Forms for the investigators, despite acting with due diligence to obtain the required financial information. One subject was enrolled from each of the two sites and both were assigned to the PF-06410293 group.
- N=13 clinical investigators with financial disclosures (Form FDA 3455). All 13 investigators participated in Study B5381002. as listed in **Table 44**. All received significant payments of other sorts (>\$25,000) mostly for purposes of speaker honoraria based on the Applicant's submitted the list of investigators and study sites, FDA Forms 3455 and 3454. Two investigators also received a research grant from the Applicant (\$60,000 and \$424,000 each), which was, as per the Applicant, directly paid to the institution rather than to the individual clinical investigator.
  - Enrollment from the 13 sites was (b) (6) subjects ((b) (6) % of total enrolled (b) (6))
  - Overall enrollment from the 13 sites were balanced between the two groups (b) (6)
  - One of 13 sites, Site (b) (6) (b) (6) however, no issues were noted on OSI inspection of this site (see Section 4.5 OSI inspection for details).

Study B5381001, was a double-blind, randomized study with a primary endpoint of PK, and therefore, the disclosed interests are unlikely to influence the outcome of the study. In Study B5381002, the number of patients enrolled at the individual investigator sites were small compared to the total number of patients enrolled in the overall study, and overall balanced by treatment group. Furthermore, the multi-center and blinded nature of Study B5381002 make it unlikely that the financial interest(s) could have influenced or biased the results of the study. Accordingly, any outstanding concerns regarding the impact of the disclosed financial interests have been adequately addressed.

**Covered Clinical Studies: B5381001, B5381002, B5381005 and B5381007**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         |                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| 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: <u>934</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                         |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>7</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>13</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                         |                                                                  |
| <p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>13</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <u>0</u></p> |                                         |                                                                  |
| 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>2</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

**Table 44.** Enrollment in the 13 investigators/sites with financial disclosures in Study B5381002

| Site#                          | (b) (6) |     |    |    |    |    |    |    |    |    |    |    | Total   |
|--------------------------------|---------|-----|----|----|----|----|----|----|----|----|----|----|---------|
| Investigator <sup>†</sup>      | (b) (6) |     |    |    |    |    |    |    |    |    |    |    | (b) (6) |
| Enrollment <sup>‡</sup>        | (b) (6) |     |    |    |    |    |    |    |    |    |    |    | (b) (6) |
| EU-Humira                      | (b) (6) |     |    |    |    |    |    |    |    |    |    |    | (b) (6) |
| PF-06410293                    | (b) (6) |     |    |    |    |    |    |    |    |    |    |    | (b) (6) |
| Amount \$ <sup>*</sup> (x1000) | 425     | 385 | 60 | 58 | 47 | 46 | 45 | 43 | 42 | 38 | 34 | 32 |         |

<sup>†</sup> Number of investigators participated in the related sites was extracted from the Applicant’s Form FDA 3455 (*Summary Table of Significant Payment of Other Sorts*)

<sup>‡</sup> From the Applicant’s BIMO dataset *clinsite* through running the Site Selection Tool;

\* All were received by the principal investigators at the related sites

**Authors:**

Jin Chen, MD, PhD  
 Clinical Reviewer

Rachel Glaser, MD  
 Clinical Team Leader

**13.3. Office of Clinical Pharmacology Appendices**

**13.3.1. Summary of Bioanalytical Method Validation and Performance**

**13.3.2. Pharmacokinetics**

For the PK similarity study (B5381007), serum EU-Humira, US-Humira and PF-06410293 concentrations measured using a validated ELISA method (B5389001) were suitable for assessment of PK similarity. Both the method validation entitled “B5389001” and sample analysis for the study were performed (b) (4). In this method, recombinant human TNFa (Life Technology PHC3013) coated in 96-well plate was used to capture the “test product” in serum. The bound “test product” was detected with an enzyme-antibody conjugate, monkey-adsorbed goat anti-human IgG horseradish peroxidase (HRP), incubated at room temperature for 1 hour with shaking. Tetramethylbenzidine (TMB-3,3',5,5') was utilized as a substrate for signal generation and colorimetric readout. **Table 45** shows the summary of ELISA method performance in quantification of serum EU-Humira, US-Humira and PF-06410293 during the method validation.

**Table 45 Summary of the bioanalytical method validation and in-study performance for measurement of EU-Humira, US-Humira, and PF-06410293**

|                                                                                                                                                                                                                         |                                                                                                                                                                                                                            |                                              |                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|----------------------|
| Bioanalytical method review summary                                                                                                                                                                                     | B5389001                                                                                                                                                                                                                   |                                              |                      |
| Materials used for calibration curve & concentration                                                                                                                                                                    | <ul style="list-style-type: none"> <li>EU-Humira</li> <li>250, 450, 800, 1500, 2500, 4800, 7600, and 10000 ng/mL</li> </ul>                                                                                                |                                              |                      |
| Validated assay range                                                                                                                                                                                                   | 250-10000 ng/mL                                                                                                                                                                                                            |                                              |                      |
| Material used for QCs & concentration                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>EU-Humira, US-Humira, PF-06410293</li> <li>250.0 (LLOQ), 750 (Low), 2000 (Medium), 7500 (High), 10000 (ULOQ) ng/mL and 2,500,000 ng/mL (validation dilution sample, DQC)</li> </ul> |                                              |                      |
| Minimum required dilutions (MRDs)                                                                                                                                                                                       | 1:100                                                                                                                                                                                                                      |                                              |                      |
| Source & lot of reagents (LBA)                                                                                                                                                                                          | EU-Humira, Lot #: 21327XH10<br>US-Humira, Lot#: 240482E<br>PF-06410293, Lot #: 008A13                                                                                                                                      |                                              |                      |
| Regression model & weighting                                                                                                                                                                                            | 5-parameter logistic, weighting factor = 1/Y                                                                                                                                                                               |                                              |                      |
| <b>Validation Parameters</b>                                                                                                                                                                                            | <b>Method Validation Summary</b>                                                                                                                                                                                           |                                              | <b>Acceptability</b> |
| Calibration curve performance during accuracy & precision<br><br>Per BMV,<br>At least 75% and minimum of 6 non-zero calibrators without anchor points and<br>LBA: $\pm 20\%$ bias ( $\pm 25\%$ at LLOQ), $\leq 20\%$ CV | No of standard calibrators from LLOQ to ULOQ                                                                                                                                                                               | 8                                            | Yes                  |
|                                                                                                                                                                                                                         | Cumulative accuracy (%bias) from LLOQ to ULOQ<br><br>EU-Humira                                                                                                                                                             | -4.0 to 6.0%                                 | Yes                  |
|                                                                                                                                                                                                                         | Cumulative precision (%CV) from LLOQ to ULOQ<br><br>EU-Humira                                                                                                                                                              | 4.6 to 14.7%                                 | Yes                  |
| QCs performance during accuracy & precision<br>Per BMV,<br>LBA QCs: $\pm 20\%$ bias ( $\pm 25\%$ at LLOQ), $\leq 20\%$ CV and $\leq 30\%$                                                                               | Cumulative accuracy (%bias) in 5 QCs<br><br>EU-Humira<br>US-Humira<br>PF-06410293                                                                                                                                          | -4.0 to 6.4%<br>-1.3 to 1.0%<br>2.8 to 11.0% | Yes                  |
|                                                                                                                                                                                                                         | Inter-batch %CV<br><br>EU-Humira<br>US-Humira<br>PF-06410293                                                                                                                                                               | 6.2 to 10.0%<br>4.5 to 14.2%<br>4.4 to 11.6% | Yes                  |

|                                                                                                                                      |                                                                                                                                                                                                                                         |                                               |     |
|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----|
| total error ( $\leq 40\%$ at LLOQ)                                                                                                   | Percent total error (TE)<br>EU-Humira<br>US-Humira<br>PF-06410293                                                                                                                                                                       | 8.2 to 16.4%<br>5.9 to 15.0%<br>12.9 to 16.3% | Yes |
| Selectivity & matrix effect<br>(10 lots of Normal, 10 lots of Rheumatoid Arthritis, 10 lots of Crohn's disease)                      | EU-Humira: 30 out of 30 Lots Passed<br>US-Humira: 27 out of 30 Lots Passed<br>PF-06410293: 29 out of 30 Lots Passed                                                                                                                     |                                               | Yes |
| Interference & specificity<br>(Interference of ADA tested using PC, an affinity purified rabbit anti-Adalimumab polyclonal antibody) | Interference to LLOQ and ULOQ VS and 100 and 400 $\mu\text{g/mL}$ VS was not observed in<br>EU-Humira: up to 1.0 $\mu\text{g/mL}$ of PC<br>US-Humira: up to 1.0 $\mu\text{g/mL}$ of PC<br>PF-06410293: up to 1.0 $\mu\text{g/mL}$ of PC |                                               | Yes |
| Hemolysis effect                                                                                                                     | EU-Humira: 6 out of 6 Lots Passed at ULOQ<br>PF-06410293: 6 out of 6 Lots Passed at ULOQ                                                                                                                                                |                                               | Yes |
| Lipemic effect                                                                                                                       | EU-Humira: 6 out of 6 Lots Passed at ULOQ<br>PF-06410293: 6 out of 6 Lots Passed at ULOQ                                                                                                                                                |                                               | Yes |
| Dilution linearity & hook effect                                                                                                     | Up to 2,500,000 ng/mL, highest dilution factor 5000                                                                                                                                                                                     |                                               | Yes |
| Bench-top/process stability                                                                                                          | EU-Humira, US-Humira and PF-06410293: 25 Hours at Room Temperature                                                                                                                                                                      |                                               | Yes |
| Freeze-Thaw stability                                                                                                                | EU-Humira, US-Humira and PF-06410293:<br>At least 6 Cycles at $-20^{\circ}\text{C}$<br>At least 6 Cycles at $-70^{\circ}\text{C}$                                                                                                       |                                               | Yes |
| Long-term storage                                                                                                                    | PF-06410293: 735 days $-70^{\circ}\text{C}/-20^{\circ}\text{C}$<br>EU-Humira: 730 days $-70^{\circ}\text{C}/-20^{\circ}\text{C}$<br>US-Humira: 1811 days $-70^{\circ}\text{C}$                                                          |                                               | Yes |
| Parallelism                                                                                                                          | Done with incurred samples                                                                                                                                                                                                              |                                               | Yes |
| <b>Method Performance in Study B5381007</b>                                                                                          |                                                                                                                                                                                                                                         |                                               |     |
| Assay passing rate                                                                                                                   | <ul style="list-style-type: none"> <li>No. of Acceptable Runs /No. of Failed or Aborted Runs:<br/>246 /2</li> </ul>                                                                                                                     |                                               | Yes |

|                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Standard curve performance                   | <ul style="list-style-type: none"> <li>Precision (%CV) 1.4% to 7.2%</li> <li>Accuracy (%RE) -1.7% to 4.5%</li> </ul>                                                                                                                                                                                                                                                                                                                                      | Yes |
| QC performance (low, medium, high and QCDIL) | <ul style="list-style-type: none"> <li>Precision (%CV) 5.5% to 6.1%</li> <li>Accuracy (%RE) -0.1% to 4.4%</li> </ul>                                                                                                                                                                                                                                                                                                                                      | Yes |
| Method reproducibility                       | <ul style="list-style-type: none"> <li>The incurred sample reanalysis was performed on 383 study samples, from 120 subjects. Incurred sample repeats were considered acceptable if the original and reassay values from two-thirds of the repeated samples had a relative percent difference of within <math>\pm 30.0\%</math> for ligand binding assays.</li> <li>The results of the incurred sample repeats met the ISR acceptance criteria.</li> </ul> | Yes |
| Study sample analysis/ stability             | 365 Days at -20°C and 362 Days at -70°C                                                                                                                                                                                                                                                                                                                                                                                                                   |     |

**13.3.3. What bioanalytical methods were used to assess the pharmacodynamic (PD) biomarker(s) and/or the PD effect(s) of the biologic?**

Not applicable.

**13.4. Nonclinical Pharmacology and Toxicology Appendices**

**13.4.1. Safety Assessment of Extractables and Leachables for the Container Closure System**

Relevant DMFs:

DMF (b) (4)  
 DMF (b) (4)  
 DMF (b) (4)  
 DMF (b) (4)  
 DMF (b) (4)  
 DMF (b) (4)  
 DMF (b) (4)

The PF-06410293 drug substance is filled (b) (4). The drug product is packaged either in glass vial (40 mg) or in PFS (10/20/40 mg) that can be further enclosed in PFP for 40 mg/0.8 ml strength. The primary container closure system for glass vial package includes 2 mL (b) (4) clear glass vial with (b) (4) stopper and crimp seal with flip-off cap. The primary container closure systems for PFS and PFP are the same and includes 1 mL

(b) (4) glass syringe with a (staked) needle, a (b) (4) elastomer needle shield with a (b) (4) rigid cover, and a (b) (4) elastomeric plunger stopper.

For the safety evaluation for (b) (4) components that have direct/potential contact with drug substance is (b) (4). This component was subject to an extractable study and to ongoing leachable studies with drug substance batch 16L137L001 in (b) (4) stored at relevant storage conditions (b) (4) (data >24-month time points not available).

For the safety evaluation for glass vial and PFS, components that have direct/potential contact with drug substance include (b) (4) stopper/plunger stopper, tip cap, syringe barrel, syringe needle, and syringe needle (b) (4). These components were subject to extractable studies and to ongoing leachable studies with drug product batch# 031M16 (10mg/0.2mL, PFS), 025M16 (40mg/0.8mL, PFS), 067B16 (40mg/0.8mL, vial) stored at accelerated conditions (30°C) for 1-months and long-term storage conditions (2-8°C) for up to 36 months (data >12-month time points not available).

The extractables studies were performed under presumably the worst-case scenario. In general, any organic (nonmetal) compound with expected patient exposure below the Qualification Threshold (QT) of (b) (4) µg/day for compounds lacking genotoxic potential and irritant potential or Safety Concern Threshold (SCT) of (b) (4) µg/day for compounds with genotoxic potential as recommended by Product Quality Research Institute (PQRI) was considered qualified for safety. For compounds with expected patient exposure > (b) (4) µg/day, available toxicological data was reviewed to assess human risk. For metals, the Guideline for Elemental Impurities (ICH Q3D, 2014) was followed for safety assessment. Extractables found from (b) (4) (b) (4) glass vial and PFS/PFP components requiring monitoring in leachables study include (b) (4)

## Extractable Study

### Methods:

The sponsor conducted extractables studies (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

### Results:

Total Daily Intake (TDI) was calculated for each extractable using the maximum daily dosage of 160 mg for PF-06410293 10 mg syringe (total 16 injections as worst case scenario), 40 mg vial, and (b) (4) (the worst scenario compared to (b) (4)

(b) (4) An Analytical Uncertainty Factor (AUF) (b) (4) was used for extractable compound calculations to account for potential response factor differences when an authentic standard was not used to determine the extractable compound concentration.

### Final list of potential Leachable Compounds

The studies utilized guidance from the PQRI titled “Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products” (PQRI, 2006). To select potential leachables based on extractables identified, an initial SCT of (b) (4) µg/day TDI was placed. For compound with structural alert, SCT maybe adjusted based on further assessment. For compound without structural alert, SCT will be set as (b) (4) µg/day TDI. Extractables from critical components from (b) (4) glass vial, PFS/PFP drug products were identified as target leachable compounds for monitoring in leachables study if they were detected above their corresponding SCTs.

*Glass vial and PFS/PFP drug products (Study# INX100361346):* the following compounds were identified as target leachable compounds (**Table 46**, excerpted from the sponsor’s submission). For elements, the analytical method’s quantitation limit (QL) was used as SCT for each element. (b) (4) were included in the list since both of these are used in the manufacture of the syringe.

**Table 46. Selected Potential Leachable Compounds from glass vial, PFS, and PFP and Initial Safety Concern Threshold**

| Potential Leachable | Source | Safety Concern Threshold |
|---------------------|--------|--------------------------|
| (b) (4)             |        |                          |

(b) (4)

**Table 47. Selected Potential Leachable Compounds (b) (4) and Initial Safety Concern Threshold**

| Potential Leachable | Safety Concern Threshold |
|---------------------|--------------------------|
| (b) (4)             |                          |

**Leachable Studies**

The leachable studies evaluated extractables above SCT from critical components that has leaching potential from the container closure system into the drug product/patient. The extractable studies described above guided the leachable evaluation. Safety assessment was conducted for potential leachables based on worst case observed levels in on-going leachable studies. Extractables with an SCT, QL or observed TDI > (b) (4) µg/day but < the PQRI derived

qualification threshold of (b) (4) µg/day were confirmed not mutagenic, and no further evaluation was performed. For extractables > (b) (4) µg/day, available toxicological data was reviewed to assess human risk. For metals, the Guideline for Elemental Impurities (ICH Q3D, 2014) was followed.

### Methods

For Glass vial and PFS/PFP drug products, a leachables assessment was conducted on DP Lot 067B16 (40 mg / 0.8 mL vial), Lot 025M16 (40 mg / 0.8 mL prefilled syringe), and Lot 031M16 (10 mg / 0.2 mL prefilled syringe) to accurately determine the levels of leachables potentially exposed to the patient. Containers are stored at (b) (4)

(b) (4) The study is ongoing and samples in the 1-month study at 1 month and samples in the 36-month study at initial, 6 and 12 months were tested and data provided in the BLA submission.

For (b) (4) a leachables assessment was conducted on PF-06410293 drug substance batch 16L137L001 to accurately determine the levels of leachables potentially exposed to the patient. PF-06410293 drug substance was stored at - (b) (4) °C for up to (b) (4) months. The study is ongoing and samples at initial, 6 and 12 months were tested and data provided in the BLA submission.

### Results

All leachables detected with highest TDI/DL/QL were listed in Table 48 based on reports for Study# INX100361346 and INX100361362.

**Table 48. Leachables detected with highest TDIs or QLs in (b) (4) glass vial, and PFS/PFP drug products**

| Compound Name | CAS # | Highest Calculated TDI/DL/QL ( $\mu\text{g}/\text{day}$ ) | SCT ( $\mu\text{g}/\text{day}$ ) |
|---------------|-------|-----------------------------------------------------------|----------------------------------|
| (b) (4)       |       |                                                           |                                  |

DL: detection limit; QL: quantitation limit; N/A: not available

(b) (4)

(b) (4)

The highest TDI/DL/QLs of these leachables were below SCT of (b) (4)  $\mu\text{g}/\text{day}$ . In addition, all these compounds were negative in Ames test based on REACH Registration, National toxicology program, or Vitic\_Lhasa Database 2.6.1 (version 2017.1.0). (b) (4) is also an ICH Q3C Class 2 solvent with a permissible daily exposures (PDE) of (b) (4)  $\text{mg}/\text{day}$  (ICH Q3C [R7], 2018). Therefore, the potential exposures of these compounds as leachables in (b) (4) Glass vial and PFS/PFP drug products are not considered to have a safety concern.

(b) (4) The TDI/QLs (b) (4) were (b) (4) -fold below the typical

amounts found in multimineral/multivitamin supplements for daily use (Centrum Adults LBL-00000541, version 3.0). The QLs (b) (4) were (b) (4) (b) (4) -fold below PDE for parenterals (ICH Q3D, 2014). The QLs (b) (4) was (b) (4) µg/day. The accepted level of PDE (b) (4) is not addressed in ICH Q3D (2014). Since (b) (4) was negative in Ames test<sup>20</sup> and the QL was below the PQRI SCT (b) (4) µg/day, the potential exposures (b) (4) as well as other 8 metals above as leachables in (b) (4) Glass vial and PFS/PFP drug products are not considered to have a safety concern.

(b) (4) These 3 leachables are ICH Q3C Class 3 solvent with a PDE of (b) (4) mg/day (ICH Q3C [R7], 2018). The highest TDI/DL/QLs of these leachables were (b) (4) fold below the PDEs. Therefore, the potential exposures of these compounds as leachables in Glass vial and PFS/PFP drug products are not considered to have a safety concern.

(b) (4) The highest TDI (b) (4) was (b) (4) µg/day. The PDE for (b) (4) was not established. In acute parenteral toxicity studies in rats and rabbits, (b) (4) up to 5000 mg/kg given subcutaneous (s.c.), intraperitoneal (i.p.), and intramuscular (i.m.) was not found lethal<sup>21</sup>. In a 90-day inhalation toxicity studies in rats, pulmonary (b) (4) ((b) (4) centistokes, cSt) dose up to 54 mg/kg did not induce systemic toxicity<sup>22</sup>.

In Embryo-Fetal Developmental (EFD) rat and rabbit studies, (b) (4) ((b) (4) cSt) s.c. up to 1000 mg/kg/day did not produce fetal abnormalities<sup>23</sup>. In Fertility and Early Developmental (FEED) study in rats, (b) (4) ((b) (4) cSt) s.c. up to 200 mg/kg/day in male (3 times/week for 10 weeks prior to mating) and female (7 times/week for 2 weeks prior to mating) did not affect reproductive performance<sup>4</sup>. In a peri- and post-natal development (PPND) study in female rats, (b) (4) ((b) (4) cSt) s.c. up to 1000 mg/kg/day (from day 15 of gestation through lactation) did not affect gestation, viability and lactation indices<sup>4</sup>.

In carcinogenicity studies, (b) (4) oral (in-feed) up to 5800 mg/kg/day in mouse<sup>24</sup> or 1000 mg/kg/day in rat<sup>25</sup> did not produce adverse systemic toxicity effects or treatment-

---

20 (b) (4)

21 (b) (4)

22 (b) (4)

23 (b) (4)

24 (b) (4)

25 (b) (4)

related neoplastic findings. Similarly, in a chronic oral (in-feed) carcinogenicity study conducted in rats with (b) (4) (b) (4) cSt) at doses up to 1000 mg/kg/day, there was no indication of systemic toxicity or treatment-related neoplastic findings observed (European Centre for Ecotoxicology and Toxicology of Chemicals, 2011).

(b) (4) (b) (4) cSt) was negative in Ames test<sup>6</sup>. In addition, (b) (4) was not found skin irritating (b) (4) cSt) in rats or sensitizing (b) (4) cSt) in guinea pigs<sup>6</sup>.

Based on a NOAEL of 1000 mg/kg/day in the rat carcinogenicity study, the PDE was calculated by applying a general safety factor of 5 (F1) for cross-species extrapolation from rat to human, a factor of 10 (F2) for variability between individuals, a factor of 1 (F3) for a 2-year study in rodents, a factor of 1 (F4) since no systemic toxicity was noted, a factor of 1 (F5) since a NOAEL was used, and a factor of 100 (F6) since oral bioavailability for (b) (4) was not clear and assumed to be <1%, the worst case scenario. The PDE was (b) (4) mg/day for a 60kg adult. This is ~250-fold higher than the maximum exposure (b) (4) µg/day) determined for this product. Overall, the potential exposure (b) (4) as a leachable from syringe barrel is not considered to have a safety concern.

In conclusion, there appears to be no nonclinical safety concerns (b) (4) for drug substance storage and the primary container closure systems for the Glass vial and PFS/PFP drug products. Also, all leachables and their sources were identified in extractable studies. While the leachables stability study is still ongoing, based on the data up to date the levels of leachables are not expected to exceed SCT, PDE or level typical for daily use.

### 13.4.2. Nonclinical Pharmacology

#### Primary Pharmacology

Tumor necrosis factor (TNF)-α plays an important pathogenic role in multiple inflammatory diseases such as Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (Ps). US-Humira is a recombinant fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that specifically binds, via Fab domain, to soluble TNF-α (sTNF) and transmembrane TNF-α (mTNF), therefore blocks its interaction with cell surface TNF receptors and neutralizes the effect of TNF in inflammatory conditions<sup>26</sup>.

PF-06410293, the proposed biosimilar, is a recombinant fully human IgG1 kappa mAb that has the same primary amino acid sequence, dosage form, route of administration and dosing

---

(<http://www.ecetoc.org/wp-content/uploads/2014/08/JACC-055-Linear-Polydimethylsiloxanes-CAS-No.-63148-62-9-Second-Edition.pdf>)

<sup>26</sup> Wajant H, Pfizenmaier K, Scheurich P. Tumor necrosis factor signaling. *Cell Death Differ.* 2003; 10: 45–65

regimen as US- Humira. Three-way in vitro tiered similarity assessments among PF-06410293, US-Humira and EU-Humira were conducted with respect to Fab and Fc-based biological activity in a number of functional and binding assays.

The Applicant's pharmacology studies were evaluated as part of the product quality assessment. Refer to the Office of Biotechnology Products (OBP) Integrated Quality Assessment for detailed discussion of these studies.

### **Safety pharmacology**

The potential effects of PF-06410293 compared to EU-Humira on central nervous system (CNS), cardiovascular (CV) system and respiratory system and were assessed in an 1-month repeat-dose toxicity study in male and female cynomolgus monkeys, comparing 5 subcutaneous (SC) dose (157 mg/kg QW) of PF-06410293 and EU-Humira (Study 12GR307). No drug-related effect on CNS (clinical signs), CV (ECG parameters, heart rate and ECG waveform morphology) or respiratory system (respiration rate) was noted.

### **13.4.3. Nonclinical Pharmacokinetics and Pharmacodynamics**

TK and ADA evaluations were included in the 1-month repeat-dose toxicity study for PF-06410293 and EU-Humira in cynomolgus monkeys (Study 12GR307). The study was conducted using the SC route because this is the intended clinical route of administration for PF-06410293 and the comparator product (EU-Humira) is only available as a prefilled syringe for SC injection. The TK profiles of PF-06410293 and EU-Humira were considered to be similar on both Day 1 and Day 22. No incidence of ADA induction to PF-06410293 was noted. See Section 16.4.4 below for details.

High mannose N-linked glycans were identified as a minor species present in 2% PF-06410293, 8% US-Humira and 8% EU-Humira, which could impact clearance through binding to mannose receptor. To evaluate the potential functional effects of differences in high mannose N-glycan content between PF-06410293 and US-Humira, the cellular uptake of AF647 (fluorophore) - labelled PF-06410293 and US-Humira into NR8383 cells (rat macrophage cell line) was investigated in the absence and presence of mannan, a competitor for macrophage mannose receptor (MMR) -mediated cellular uptake (Study# PF-06410293\_21Apr16\_091413). The majority of cellular uptake of PF-06410293 (98.1%) and US-Humira (92.7%) was not found to be MMR -dependent, suggesting the minor difference in high mannose N-linked glycans would not have potential impact on similarity of PK/TK profiles between PF-06410293 and US-Humira as described in Section 16.4.4 below. This conclusion is also supported by PK similarity demonstrated among PF-06410293 and US-Humira in the comparative PK study in humans (Section 6).

### **13.4.4 General Toxicology**

A 1-month repeat-dose general toxicity study in cynomolgus monkeys (3/sex/group) was conducted comparing 5 SC doses (157 mg/kg QW) of PF-06410293 and of EU-Humira. The study

included histopathological examinations of a complete panel of organs and tissues. Observed drug-related spleen findings (i.e., decreased organ weights and lymphoid cellularity) in the two test article groups were considered to be pharmacodynamic (PD) effects. The toxicity and TK profiles of PF-06410293 and EU-Humira were considered to be similar. No incidence of ADA induction to PF-06410293 was noted.

### Single-Dose Toxicity/Toxicokinetics

No single-dose toxicity studies were submitted with the BLA.

### Repeat-Dose Toxicity/Toxicokinetics

#### Study title: 1-MONTH SUBCUTANEOUS TOXICITY STUDY OF PF-06410293 IN CYNOMOLGUS MONKEYS

|                                     |                                                                                                                             |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Study no.:                          | 12GR307                                                                                                                     |
| Study report location:              | SDN# 1                                                                                                                      |
| Conducting laboratory and location: | Pfizer Worldwide Research & Development<br>Drug Safety Research & Development<br>Eastern Point Road<br>Groton, CT 06340 USA |
| Date of study initiation:           | November 20, 2012                                                                                                           |
| GLP compliance:                     | Yes                                                                                                                         |
| QA statement:                       | Yes                                                                                                                         |
| Drug, lot #, and % purity:          | PF-06410293 (Lot# 12L137L002, 99.6%) and EU-Humira (Lot# 13251XH10 and 13257XD14, 100%)                                     |

### Key Study Findings

- In a 1-month study, sexually mature monkeys (3/sex/group) received subcutaneous doses of PF-06410293 vehicle, PF-06410293 (157 mg/kg), EU-Humira vehicle, and EU-Humira (157 mg/kg) once weekly for a total of 5 doses.
- Histopathological findings were seen in the spleen with minimal decreased cellularity in lymphoid follicles and germinal centers in 2/3 PF-06410293 -treated females, 1/3 EU-Humira -treated males and 2/3 EU-Humira -treated females. Immunohistochemistry (IHC) assessment revealed minimal to mild decreases in cellularity and density of CD21-positive, IgG-positive, and IgM-positive cells in the spleen of all PF-06410293 and EU-Humira -treated animals. The spleen findings were associated with decreased spleen weights and were considered PD effects. Overall, there were no toxicologically significant differences in the histopathological findings between PF-06410293 and EU-Humira groups and no new histopathological findings for PF-06410293 group.
- For toxicokinetics, the mean AUC<sub>168</sub> values were slightly higher for PF-06410293 compared to EU-Humira (105% and 120% on Days 1 and 22, respectively), but were considered similar. Similarly, the mean C<sub>max</sub> values were slightly higher for PF-06410293 compared to EU-

Humira (105% and 124% on Days 1 and 22, respectively), but were considered similar. Both drug products also showed similar accumulation ratios between Day 1 and Day 22 with R value of 2.90 and 2.54 for PF-06410293 and EU-Humira, respectively.  $T_{max}$  was longer for PF-06410293 compared to EU-Humira on Day 1 (96 hr vs 64 hr), but similar on Day 22 (56 hr vs 55 hr). No incidence of ADA was detected in PF-06410293 -treated animals. The serum concentration-time profiles of PF-06410293 and EU-Humira in monkeys on both Days 1 and 22 were similar.

- In conclusion, the toxicity and TK profiles of PF-06410293 and EU-Humira were considered to be similar.

## Methods

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Doses:                         | 157 mg/kg for PF-06410293 and EU-Humira                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Frequency of dosing:           | Once weekly (on Study Days 1, 8, 15, 22 and 29)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Route of administration:       | Subcutaneous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Dose volume:                   | 3.14 mL/kg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Formulation/Vehicle:           | <u>Vehicle Control Article/Diluent 1 for PF-06410293:</u><br>0.756 mg/mL L-histidine, 3.132 mg/mL L-histidine hydrochloride monohydrate, 85 mg/mL sucrose, 0.2 mg/mL polysorbate 80, 0.05 mg/mL EDTA, and 0.2 mg/mL L-methionine, pH 5.5.<br><u>Vehicle Control Article/Diluent 2 for EU-Humira:</u> 0.76 mg/mL monobasic sodium phosphate monohydrate, 2.30 mg/mL sodium phosphate dibasic heptahydrate, 0.3 mg/mL sodium citrate dihydrate, 1.3 mg/mL citric acid monohydrate, 6.16 mg/mL sodium chloride, 12 mg/mL mannitol, 1.0 mg/mL polysorbate 80, and sodium hydroxide for pH adjustment (final target pH 5.2) |
| Species/Strain:                | Cynomolgus monkeys                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Number/Sex/Group:              | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Age:                           | 4 years 8 months to 6 years 9 months. Animals were sexually mature based on histopathology and/or documentation of ovulation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Weight:                        | 4.5-6.6 kg for males and 2.9-4.3 kg for females                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Satellite groups:              | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Unique study design:           | Immunogenicity assay to detect anti-drug antibodies (ADA)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Deviation from study protocol: | None that would be expected to impact the quality, integrity or interpretations of the data or the conclusions of the study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

Biosimilar Multi-disciplinary Evaluation and Review (BMER)

BLA 761118

PF-06410293 a proposed biosimilar to Humira

APPEARS THIS WAY ON ORIGINAL

**Table 49. Study Design for The 28-day Monkey Toxicology Study**

| Group Number | Test or Control Article or Vehicle | Dose (mg/kg/week) <sup>a</sup> | Concentration (mg/mL) | Dose Volume (mL/kg/week) <sup>b</sup> | Animal Numbers |         |
|--------------|------------------------------------|--------------------------------|-----------------------|---------------------------------------|----------------|---------|
|              |                                    |                                |                       |                                       | Males          | Females |
| 1            | Vehicle Control Article/Diluent 1  | 0                              | 0                     | 3.14                                  | 1-3            | 13-15   |
| 2            | Adalimumab-Pfizer                  | 157                            | 50                    | 3.14                                  | 4-6            | 16-18   |
| 3            | Vehicle Control Article/Diluent 2  | 0                              | 0                     | 3.14                                  | 7-9            | 19-21   |
| 4            | Adalimumab-EU                      | 157                            | 50                    | 3.14                                  | 10-12          | 22-24   |

<sup>a</sup> All dose levels are expressed as mg of active drug per kg of body weight per week.

<sup>b</sup> The dose volume was based on the most recent individual body weight.

(Excerpted from Sponsor submission)

### Observations and Results

There were no treatment-related effects associated with either PF-06410293 or EU-Humira for the following parameters: mortality, clinical signs, body weight (BW) change, food consumption, ophthalmology, respiration, electrocardiographic (ECG parameters, heart rate and ECG waveform morphology), hematology, coagulation, clinical chemistry, urinalysis, gross pathology and injection sites.

### Organ Weights

Decreases in spleen weight (absolute weight, % of BW, and % brain weight [BRW]) relative to corresponding vehicle controls were noted for both PF-06410293 and EU-Humira -treated animals (**Table 50**). These changes correlated with the histopathological spleen findings noted below and were considered PD effects. The decreases in spleen weights were similar between PF-06410293 and EU-Humira -treated male groups while the decreases in PF-06410293 -treated female group were higher than EU-Humira -treated female group. This modest difference may be attributable to the small group size and/or imbalance in spleen weights among the two female vehicle groups.

**Table 50. Mean Spleen Weight Changes Relative to Vehicle Controls for Monkeys Treated with PF-06410293 and EU-Humira**

| Sex               | Male      |             |           |           | Female    |             |           |           |
|-------------------|-----------|-------------|-----------|-----------|-----------|-------------|-----------|-----------|
| Group             | Vehicle 1 | PF-06410293 | Vehicle 2 | EU-Humira | Vehicle 1 | PF-06410293 | Vehicle 2 | EU-Humira |
| BW (kg)           | 6.27      | -6%         | 5.80      | -18%      | 3.77      | +5%         | 3.83      | -3%       |
| BRW (g)           | 69.5      | 2%          | 74.9      | -5%       | 62.8      | +10%        | 65.2      | -2%       |
| Spleen weight (g) | 11.9      | -17%        | 12.3      | -23%      | 9.50      | -32%        | 8.14      | -10%      |
| % BW              | 0.189     | -11%        | 0.216     | -7%       | 0.247     | -34%*       | 0.212     | -8%       |
| % BRW             | 17.4      | -20%        | 16.3      | -19%      | 15.1      | -38%        | 12.5      | -9%       |

\*: p ≤ 0.05

### Histopathology

**Adequate Battery:** Yes. An adequate panel of organs and tissues from each monkey in the study was collected and subjected to histopathological examination. IHC assessment was conducted for transverse section (~3 mm thick) of spleen, thymus, and mesenteric lymph node from each animal.

**Peer Review:** Yes

### Histological Findings

Drug-related findings were noted in the spleen of PF-06410293 and EU-Humira -treated animals, including minimal decreased cellularity in lymphoid follicles and germinal centers in 2/3 of PF-06410293 -treated females, 1/3 of EU-Humira -treated males and 2/3 of EU-Humira -treated females (**Table 51**). Minimal to mild decreases in cellularity and density of CD21-positive, IgG-positive, and IgM-positive cells in the spleen of all PF-06410293 and EU-Humira -treated animals. These findings were considered PD effects. There were no other PF-06410293 and EU-Humira -related changes in CD2, CD4, CD8, CD68, or CD20 in the spleen. Also, there were no PF-06410293 and EU-Humira -related changes in IgG, IgM, CD21, CD2, CD4, CD8, CD68, or CD20 in the thymus or mesenteric lymph node.

**Table 51. Group Incidence and Severity of Test and Control Article-Related Microscopic and Immunohistochemistry Findings**

| Test article                              | Adalimumab-Pfizer                 |   |     |   | Adalimumab-EU                     |   |     |   |
|-------------------------------------------|-----------------------------------|---|-----|---|-----------------------------------|---|-----|---|
|                                           | 1                                 |   | 2   |   | 3                                 |   | 4   |   |
| Group                                     | Vehicle Control Article/Diluent 1 |   | 157 |   | Vehicle Control Article/Diluent 2 |   | 157 |   |
| Dose (mg/kg/week)                         |                                   |   |     |   |                                   |   |     |   |
| Sex                                       | M                                 | F | M   | F | M                                 | F | M   | F |
| No. of animals                            | 3                                 | 3 | 3   | 3 | 3                                 | 3 | 3   | 3 |
| Organ/Finding/Severity                    |                                   |   |     |   |                                   |   |     |   |
| Spleen                                    |                                   |   |     |   |                                   |   |     |   |
| Decreased cellularity: lymphoid follicles | 0                                 | 0 | 0   | 2 | 0                                 | 0 | 1   | 2 |
| Minimal                                   | 0                                 | 0 | 0   | 2 | 0                                 | 0 | 1   | 2 |
| Decreased cellularity: germinal center    | 0                                 | 0 | 0   | 2 | 0                                 | 0 | 1   | 2 |
| Minimal                                   | 0                                 | 0 | 0   | 2 | 0                                 | 0 | 1   | 2 |
| Decreased CD21 cells                      | 0                                 | 0 | 3   | 3 | 0                                 | 0 | 3   | 3 |
| Minimal                                   | 0                                 | 0 | 2   | 1 | 0                                 | 0 | 1   | 1 |
| Mild                                      | 0                                 | 0 | 1   | 2 | 0                                 | 0 | 2   | 2 |
| Decreased IgG cells                       | 0                                 | 0 | 3   | 3 | 0                                 | 0 | 3   | 3 |
| Minimal                                   | 0                                 | 0 | 3   | 3 | 0                                 | 0 | 3   | 3 |
| Decreased IgM cells                       | 0                                 | 0 | 3   | 3 | 0                                 | 0 | 3   | 3 |
| Minimal                                   | 0                                 | 0 | 1   | 0 | 0                                 | 0 | 2   | 0 |
| Mild                                      | 0                                 | 0 | 2   | 3 | 0                                 | 0 | 1   | 3 |

Excerpted from the sponsor's submission. Adalimumab-Pfizer: PF-06410293. EU-Humira: EU-Humira.

Additional histopathological findings were noted in 1-2 individual animals and were considered incidental with the exception of eosinophilic infiltrate in the thymus of 5/6 animals receiving EU-Humira without a corresponding finding in animals receiving PF-06410293. While the thymus (decreased cellularity by IHC and involution) was a target organ of toxicity in 39-week monkey studies with the innovator product, the relationship to the findings in the present study is uncertain.

Overall, there were no toxicologically significant differences in the histopathological findings between PF-06410293 and EU-Humira groups and no new histopathological findings for PF-06410293 group.

### Toxicokinetics

No incidence of ADA induction to PF-06410293 was noted in vehicle control 1 or PF-06410293 - treated animals. However, ADA induction to EU-Humira was noted in 2/6 vehicle control 2 (Animal# 0007M and 0009M) and 1/6 EU-Humira -treated animals (Animal# 0011M) with the log<sub>10</sub> titers (2.5 and 1.82, respectively) slightly above the negative cutoff (1.40) for the assay and were noted at only 1-2 timepoints. The induction of ADA in the one EU-Humira -treated animal

did not impact the overall TK interpretation in this study since the mean  $C_{max}$  and  $AUC_{168}$  values for EU-Humira -treated group were similar with or without the data from the positive EU-Humira dosed animal. It was noted that levels of PF-06410293 or EU-Humira present in samples may be high enough to interfere with the detection of ADA.

There were no apparent sex related differences in exposures for PF-06410293 and EU-Humira. The mean  $AUC_{168}$  values were slightly higher for PF-06410293 compared to EU-Humira (105% and 120% on Days 1 and 22, respectively, **Table 52**). Similarly, the mean  $C_{max}$  values were slightly higher for PF-06410293 compared to EU-Humira (105% and 124% on Days 1 and 22, respectively). The systemic exposures for PF-06410293 and EU-Humira were considered similar since they remained within the 80-125% range. Both drug products also showed similar accumulation ratios between Day 1 and Day 22 with R value ( $AUC_{168-Day\ 22} / AUC_{168-Day\ 1}$ ) of 2.90 (= 589,000 / 203,000) and 2.54 (= 492,000 / 194,000) for PF-06410293 and EU-Humira, respectively.  $T_{max}$  was longer for PF-06410293 compared to EU-Humira on Day 1 (96 hr vs 64 hr), but similar on Day 22 (56 hr vs 55 hr).

**Table 52. Mean Toxicokinetic Parameters for PF-06410293 and EU-Humira in Cynomolgus Monkeys after Once Weekly Administration of PF-06410293 or EU-Humira -All Animals**

| Dose (mg/kg/week)     | Study Day | Sex     | $C_{max}$ ( $\mu\text{g/mL}$ ) |      |   | $C_{max}$ Ratio <sup>a</sup> | $T_{max}$ (Hours) |     |    | $AUC_{168}$ ( $\mu\text{g}\cdot\text{Hours/mL}$ ) |        |       | $AUC_{168}$ Ratio <sup>a</sup> |   |     |
|-----------------------|-----------|---------|--------------------------------|------|---|------------------------------|-------------------|-----|----|---------------------------------------------------|--------|-------|--------------------------------|---|-----|
|                       |           |         | Mean                           | SD   | n |                              | Mean              | SD  | n  | Mean                                              | SD     | n     |                                |   |     |
| 157-Adalimumab-Pfizer | 1         | Male    | 1470                           | 183  | 3 | 1.1                          | 97                | 65  | 3  | 209000                                            | 26300  | 3     | 1.0                            |   |     |
|                       |           | Female  | 1390                           | 80.2 | 3 |                              | 96                | 24  | 3  | 196000                                            | 10400  | 3     |                                |   |     |
|                       |           | Overall | 1430                           | 135  | 6 |                              | 96                | 44  | 6  | 203000                                            | 19300  | 6     |                                |   |     |
| 157-Adalimumab-EU     | 1         | Male    | 1370                           | 252  | 3 |                              | 81                | 78  | 3  | 194000                                            | 25500  | 3     |                                |   |     |
|                       |           | Female  | 1340                           | 195  | 3 |                              | 48                | 0.0 | 3  | 194000                                            | 25500  | 3     |                                |   |     |
|                       |           | Overall | 1360                           | 202  | 6 |                              | 64                | 53  | 6  | 194000                                            | 22800  | 6     |                                |   |     |
| 157-Adalimumab-Pfizer | 22        | Male    | 4400                           | 100  | 3 |                              | 1.2               | 56  | 37 | 3                                                 | 646000 | 34400 |                                | 3 | 1.2 |
|                       |           | Female  | 3650                           | 295  | 3 |                              |                   | 56  | 28 | 3                                                 | 531000 | 43700 |                                | 3 |     |
|                       |           | Overall | 4030                           | 457  | 6 |                              |                   | 56  | 29 | 6                                                 | 589000 | 72000 |                                | 6 |     |
| 157-Adalimumab-EU     | 22        | Male    | 3070                           | 613  | 3 | 63                           |                   | 67  | 3  | 455000                                            | 77500  | 3     |                                |   |     |
|                       |           | Female  | 3430                           | 406  | 3 | 48                           |                   | 24  | 3  | 529000                                            | 69300  | 3     |                                |   |     |
|                       |           | Overall | 3250                           | 505  | 6 | 55                           |                   | 46  | 6  | 492000                                            | 77200  | 6     |                                |   |     |

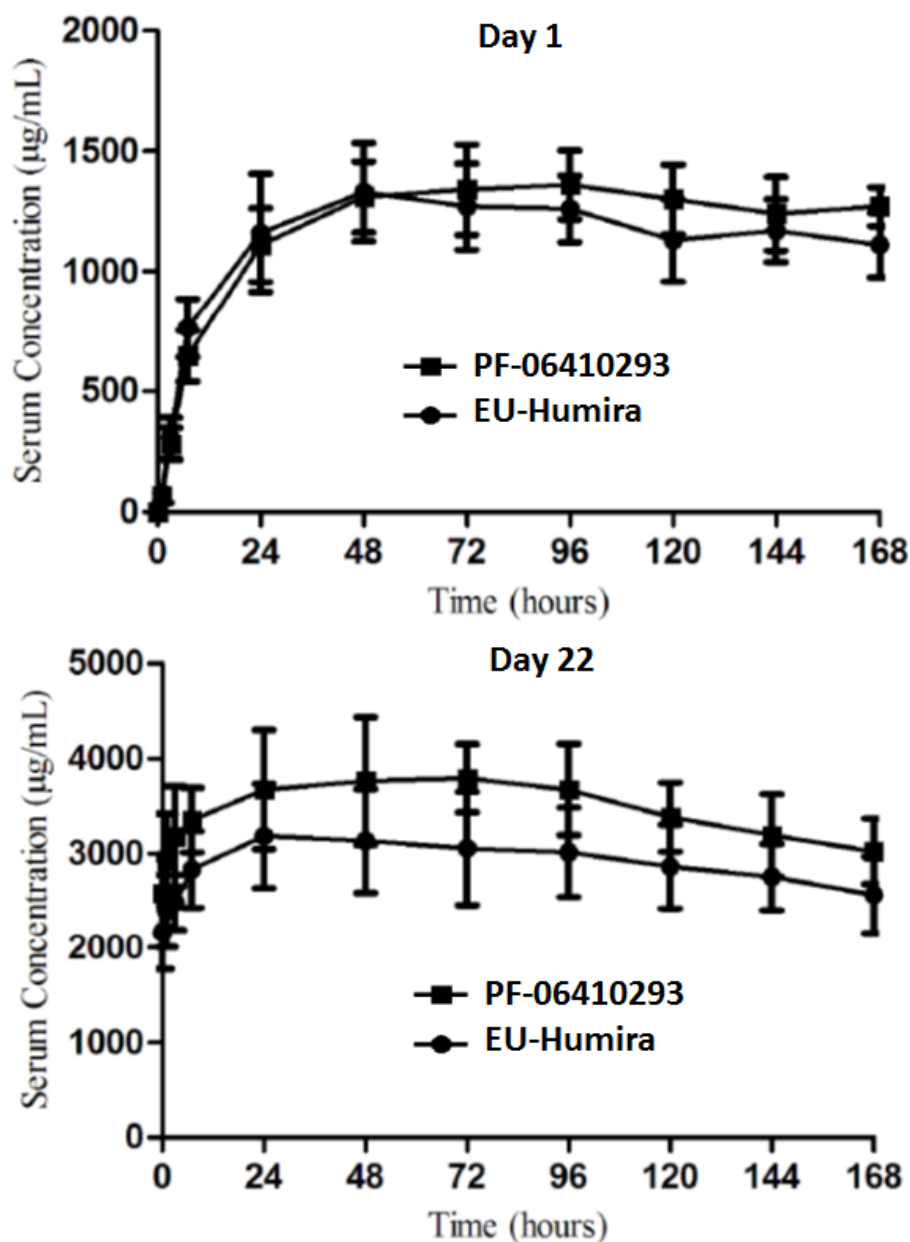
$AUC_{168}$  = Area under the serum drug concentration-time curve for 0-168 hours;  $C_{max}$  = Highest drug concentration observed in serum; n = Number; Overall = Male and female combined; SD = Standard deviation;  $T_{max}$  = Time to reach  $C_{max}$ .

a. Adalimumab-Pfizer:adalimumab-EU ratio.

Excerpted from the sponsor's submission. Adalimumab-Pfizer: PF-06410293. EU-Humira: EU-Humira.

The serum concentration-time profiles of PF-06410293 and EU-Humira in monkeys on both Days 1 and 22 were similar as shown in **Figure 16**.

**Figure 16. Mean +/- SD Concentration versus Time for PF-06410293 and EU-Humira on Days 1 and 22**



Excerpted from the sponsor's submission with legends modified

### Dosing Solution Analysis

PF-06410293: The stock solution (106.7 mg/mL) was provided by Pfizer BioTx PharmSci, and was stored at -80°C or below until thawed and then stored 2-8°C. The stock solution was diluted to 50 mg/mL using Vehicle Control Article/Diluent 1 prior to dosing. Samples from every dosing solution on Days 1 and 22 were analyzed for concentration. PF-06410293 was not detected

from vehicle control samples. All PF-06410293 formulations samples were within acceptable range ( $\pm 10\%$  of the nominal) (**Table 53**). Homogeneity test was not conducted since the formulations were solutions. Solutions of diluted PF-06410293 formulation samples in Vehicle/Diluent prepared in dissolving solvent were stable for up to 2 days when stored refrigerated, unprotected from light.

**Table 53. Analytical Results – PF-06410293**

| Formulation Preparation Date       | Sample Identification | Intended Conc. (mg/ml) | Actual Conc. (mg/ml) | Percent of Intent | Homogeneity % RSD |
|------------------------------------|-----------------------|------------------------|----------------------|-------------------|-------------------|
| 05Dec2012<br>(Sample Set ID 11160) | Spl 1 0 mg/ml         | 0                      | ND                   | NA                | NA                |
|                                    | Spl 2 50 mg/ml        | 50.0                   | 50.4                 | 101               | NA                |
| 19Dec2012<br>(Sample Set ID 14190) | Spl 1 0 mg/ml         | 0                      | ND                   | NA                | NA                |
|                                    | Spl 2 50 mg/ml        | 50.0                   | 49.5                 | 99                | NA                |

Conc. = Concentration; NA = Not applicable; ND = None detected; Spl = Sample; RSD = Relative standard deviation

EU-Humira: EU-Humira was supplied as a PFS containing 40 mg in a 0.8 mL syringe (50 mg/mL) for dosing. EU-Humira was provided by Pfizer BioTx PharmSci, and was stored refrigerated and protected from light per instruction. Concentration analyses of the commercially available preparation EU-Humira were not conducted.

**Other Toxicity Studies:**

No genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or additional toxicity studies were conducted per ICH S6(R1) Guidance (June, 2011) and FDA guidance for industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April, 2015).

## 13.5. Clinical and Statistics Appendices

### 13.5.1. Study B5381002 Additional Tables and Figures

**Table 54. Probability of ACR20 Response at Other Study Visit Weeks, B5381002**

|                        | EU-Humira<br>(N=326) |             | PF-06410293<br>(N=324) |             | Difference in<br>Response<br>(%) | 90% CI<br>Lower<br>(%) | 90% CI<br>Upper<br>(%) |
|------------------------|----------------------|-------------|------------------------|-------------|----------------------------------|------------------------|------------------------|
|                        | N                    | Count (%)   | N                      | Count (%)   |                                  |                        |                        |
| <b>ACR20 @ week 2</b>  |                      |             |                        |             |                                  |                        |                        |
| ITT: NRI               | 300                  | 96 (32.0%)  | 297                    | 93 (31.3%)  | -0.69                            | -7.07                  | 5.70                   |
| ITT: Observed          | 295                  | 96 (32.5%)  | 294                    | 93 (31.6%)  | -0.91                            | -7.34                  | 5.47                   |
| PP: NRI                | 254                  | 85 (33.5%)  | 267                    | 85 (31.8%)  | -1.89                            | -8.79                  | 5.03                   |
| <b>ACR20 @ week 4</b>  |                      |             |                        |             |                                  |                        |                        |
| ITT: NRI               | 300                  | 157 (52.3%) | 297                    | 152 (51.2%) | -1.15                            | -7.96                  | 5.69                   |
| ITT: Observed          | 294                  | 157 (53.4%) | 294                    | 154 (52.4%) | -1.02                            | -7.89                  | 5.86                   |
| PP: NRI                | 254                  | 137 (53.9%) | 267                    | 140 (52.4%) | -1.11                            | -8.36                  | 6.19                   |
| <b>ACR20 @ week 6</b>  |                      |             |                        |             |                                  |                        |                        |
| ITT: NRI               | 300                  | 178 (59.3%) | 297                    | 181 (60.9%) | 1.61                             | -5.17                  | 8.27                   |
| ITT: Observed          | 294                  | 179 (60.9%) | 295                    | 182 (61.7%) | 0.81                             | -5.85                  | 7.45                   |
| PP: NRI                | 254                  | 154 (60.6%) | 267                    | 167 (62.5%) | 1.44                             | -5.67                  | 8.55                   |
| <b>ACR20 @ week 8</b>  |                      |             |                        |             |                                  |                        |                        |
| ITT: NRI               | 300                  | 204 (68.0%) | 297                    | 205 (69.0%) | 1.02                             | -5.33                  | 7.41                   |
| ITT: Observed          | 293                  | 204 (69.6%) | 292                    | 206 (70.5%) | 0.92                             | -5.43                  | 7.20                   |
| PP: NRI                | 254                  | 178 (70.1%) | 267                    | 191 (71.5%) | 1.46                             | -5.20                  | 8.08                   |
| <b>ACR20 @ week 18</b> |                      |             |                        |             |                                  |                        |                        |
| ITT: NRI               | 300                  | 218 (72.7%) | 297                    | 229 (77.1%) | 4.44                             | -1.59                  | 10.41                  |
| ITT: Observed          | 287                  | 221 (77.0%) | 293                    | 232 (79.2%) | 2.18                             | -3.62                  | 7.93                   |
| PP: NRI                | 254                  | 195 (76.8%) | 267                    | 214 (80.1%) | 2.46                             | -3.50                  | 8.52                   |
| <b>ACR20 @ week 26</b> |                      |             |                        |             |                                  |                        |                        |
| ITT: NRI               | 300                  | 231 (77.0%) | 297                    | 245 (82.5%) | 5.49                             | -0.12                  | 11.00                  |
| ITT: Observed          | 278                  | 234 (84.2%) | 289                    | 248 (85.8%) | 1.64                             | -3.36                  | 6.71                   |
| PP: NRI                | 254                  | 211 (83.1%) | 267                    | 231 (86.5%) | 1.05                             | -4.00                  | 6.13                   |

Results and 90% CI were based on exact binomial score test conducted at each visit week.

PP analysis for weeks 18 and 30 were not included since the per-protocol population was defined up to week 12.

Abbreviations: ACR=American College of Rheumatology; CI=confidence intervals; ITT=intent to treat; NRI=non-responder imputation; PP=per protocol; @=at

[Source: Reviewer]

**Table 55. Change from Baseline for the Individual Components of ACR at Scheduled Visit Weeks Based on all Data Collected Regardless of Study Treatment Discontinuation by Treatment Arm**

| Visit week | Treatment group | Descriptive statistics | SJC (Out of 66) | TJC (Out of 68)  | Patient (0 – 100mm) | Physician (0 – 100mm) | Patient pain (0 – 100mm) | HAQ-DI (0 – 3) | CRP (mg/L)       |
|------------|-----------------|------------------------|-----------------|------------------|---------------------|-----------------------|--------------------------|----------------|------------------|
| 2          | EU-Humira       | Mean (SD); n           | 10.9 (9.3); 295 | 19.4 (13.9); 295 | 52.1 (23.1); 296    | 46.2 (20.5); 296      | 52.2 (22.9); 296         | 1.4 (0.7); 296 | 9.5 (13.1); 291  |
|            |                 | Med (Min, Max)         | 8 (0, 54)       | 16 (0, 68)       | 54 (0, 100)         | 47 (0, 90)            | 55 (1, 100)              | 1.4 (0.0, 2.9) | 5.1 (0.2, 103.0) |
|            | PF-06410293     | Mean (SD); n           | 9.6 (7.7); 294  | 16.8 (11.9); 294 | 50.6 (22.2); 294    | 44.4 (19.3); 294      | 50.8 (22.0); 294         | 1.3 (0.6); 294 | 9.9 (16.3); 289  |
|            |                 | Med (Min, Max)         | 8 (0, 56)       | 14 (0, 68)       | 52.5 (1, 97)        | 44.5 (2, 89)          | 52 (2, 98)               | 1.2 (0.0, 3.0) | 3.9 (0.2, 127.0) |
| 4          | EU-Humira       | Mean (SD); n           | 8.7 (9.6); 294  | 15.9 (13.7); 294 | 47.2 (22.7); 294    | 38.0 (19.5); 294      | 48.7 (23.0); 294         | 1.3 (0.7); 294 | 9.9 (15.1); 292  |
|            |                 | Med (Min, Max)         | 6.5 (0, 66)     | 11 (0, 68)       | 49.3 (0, 95)        | 36 (0, 85)            | 50 (0, 97)               | 1.2 (0.0, 2.9) | 4.4 (0.2, 112.0) |
|            | PF-06410293     | Mean (SD); n           | 7.6 (6.9); 294  | 14.0 (11.4); 294 | 44.6 (22.1); 294    | 36.2 (19.5); 294      | 45.1 (22.8); 294         | 1.2 (0.6); 294 | 9.9 (16.5); 292  |
|            |                 | Med (Min, Max)         | 6 (0, 45)       | 12 (0, 68)       | 45 (2, 97)          | 35 (1, 84)            | 45 (2, 98)               | 1.2 (0.0, 3.0) | 4.2 (0.2, 114.0) |
| 6          | EU-Humira       | Mean (SD); n           | 7.3 (9.0); 294  | 13.5 (13.0); 294 | 44.8 (23.8); 294    | 33.6 (19.3); 294      | 44.1 (24.1); 294         | 1.2 (0.7); 294 | 10.3 (15.5); 293 |
|            |                 | Med (Min, Max)         | 5 (0, 66)       | 9.0 (0, 68)      | 46 (0, 95)          | 32 (0, 84)            | 44 (0, 96)               | 1.2 (0.0, 2.9) | 4.5 (0.2, 101.0) |
|            | PF-06410293     | Mean (SD); n           | 6.3 (7.2); 295  | 11.4 (10.8); 295 | 42.3 (22.6); 295    | 32.5 (19.4); 295      | 41.8 (22.2); 295         | 1.1 (0.6); 295 | 10.0 (17.2); 295 |
|            |                 | Med (Min, Max)         | 4 (0, 42)       | 8 (0, 68)        | 44 (1, 98)          | 32 (0, 87)            | 42 (0, 98)               | 1.1 (0.0, 2.6) | 3.6 (0.2, 136.0) |
| 8          | EU-Humira       | Mean (SD); n           | 5.9 (7.7); 293  | 11.2 (11.6); 293 | 39.8 (23.7); 293    | 29.7 (18.2); 293      | 40.3 (24.1); 293         | 1.1 (0.7); 293 | 10.9 (18.0); 292 |
|            |                 | Med (Min, Max)         | 4 (0, 47)       | 7 (0, 68)        | 40 (0, 92)          | 26 (0, 84)            | 40 (0, 91)               | 1.1 (0.0, 3.0) | 4.8 (0.2, 157.0) |
|            | PF-06410293     | Mean (SD); n           | 5.4 (6.3); 292  | 9.8 (9.6); 292   | 38.8 (22.6); 293    | 29.2 (18.3); 292      | 39.0 (23.1); 293         | 1.0 (0.6); 293 | 12.4 (21.8); 292 |
|            |                 | Med (Min, Max)         | 3 (0, 33)       | 7 (0, 53)        | 39 (0, 98)          | 28 (0, 89)            | 40 (0, 100)              | 1.0 (0.0, 2.6) | 4.7 (0.2, 147.0) |
| 12         | EU-Humira       | Mean (SD); n           | 5.1 (7.3); 293  | 10.4 (11.3); 293 | 36.8 (23.5); 293    | 26.2 (17.7); 293      | 37.3 (23.6); 293         | 1.1 (0.7); 293 | 10.6 (15.3); 293 |
|            |                 | Med (Min, Max)         | 2 (0, 52)       | 6 (0, 68)        | 36 (0, 97)          | 22 (0, 80)            | 36 (0, 97)               | 1.1 (0.0, 2.9) | 5.0 (0.2, 130.0) |
|            | PF-06410293     | Mean (SD); n           | 4.8 (6.0); 291  | 8.6 (8.7); 291   | 35.4 (22.2); 292    | 24.9 (16.1); 292      | 35.2 (22.4); 292         | 1.0 (0.6); 292 | 12.0 (21.0); 291 |
|            |                 | Med (Min, Max)         | 2 (0, 34)       | 6 (0, 47)        | 31 (0, 93)          | 24 (0, 78)            | 32 (0, 95)               | 1.0 (0.0, 2.8) | 4.9 (0.2, 179.0) |

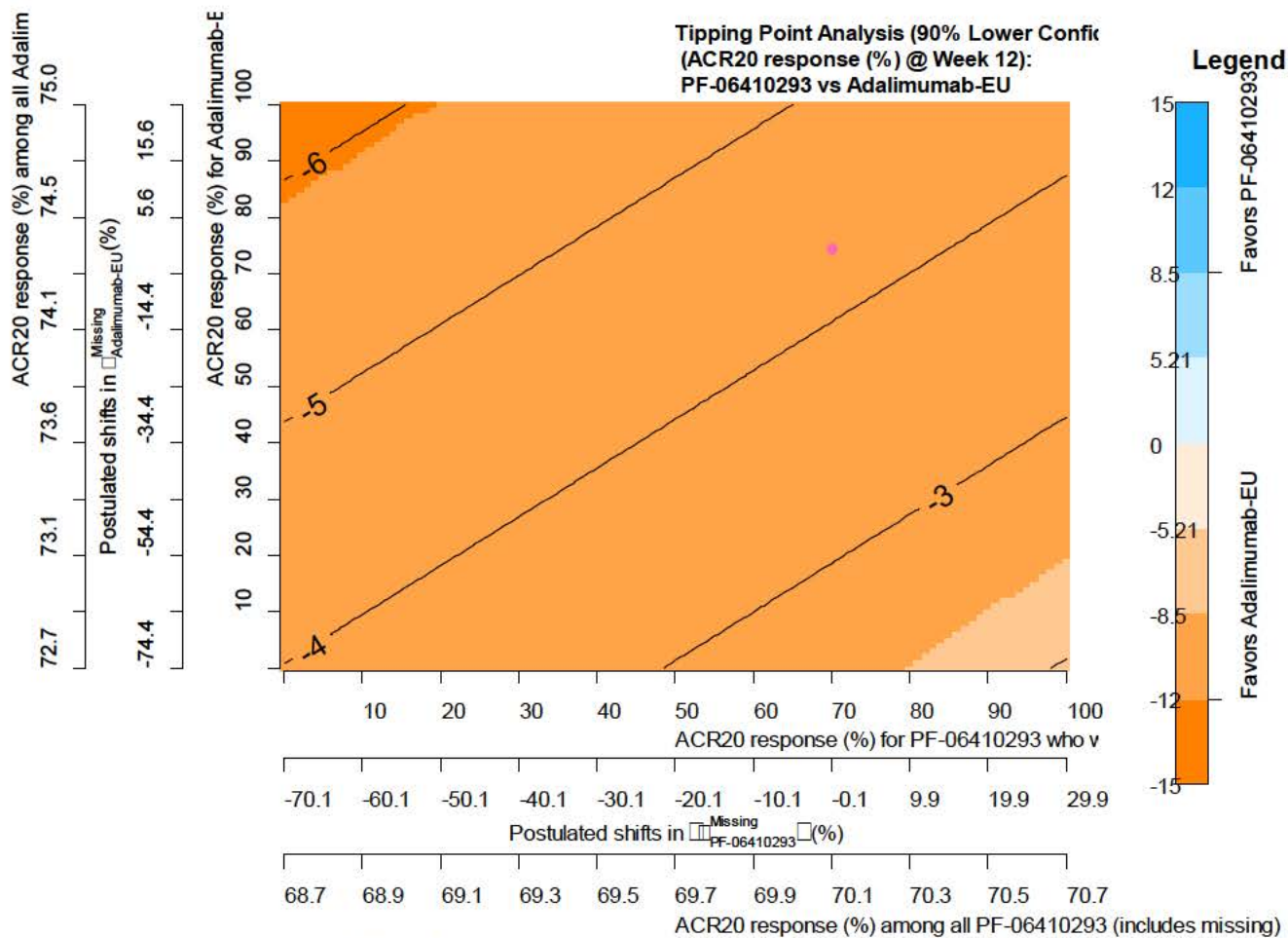
Abbreviations: ACR=American College of Rheumatology; CRP=C-reactive protein; Max=maximum; Med=median; Min=minimum; SD=standard deviation; SJC=swollen joint counts; TJC=tender joint counts; IR=information request  
 [Source: Reviewer]

**Table 56. Change from Baseline for the Individual Components of ACR at Scheduled Visit Weeks Based on all Data Collected Regardless of Study Treatment Discontinuation by Treatment Arm (continued from Table 55)**

| Visit week | Treatment group | Descriptive statistics | SJC (Out of 66) | TJC (Out of 68) | Patient (0 – 100mm) | Physician (0 – 100mm) | Patient pain (0 – 100mm) | HAQ-DI (0 – 3) | CRP (mg/L)       |
|------------|-----------------|------------------------|-----------------|-----------------|---------------------|-----------------------|--------------------------|----------------|------------------|
| 18         | EU-Humira       | Mean (SD); n           | 3.8 (6.3); 287  | 8.8 (11.0); 287 | 34.1 (23.5); 287    | 22.8 (17.1); 287      | 34.4 (23.0); 287         | 1.0 (0.7); 287 | 10.5 (16.7); 286 |
|            |                 | Med (Min, Max)         | 2 (0, 50)       | 5 (0, 68)       | 31 (0, 96)          | 19 (0, 83)            | 31 (0, 93)               | 1.0 (0.0, 3.0) | 4.2 (0.2, 145.0) |
|            | PF-06410293     | Mean (SD); n           | 4.0 (5.7); 293  | 7.2 (7.8); 293  | 32.4 (21.2); 293    | 20.8 (14.8); 293      | 32.3 (21.4); 293         | 0.9 (0.6); 293 | 10.0 (16.1); 292 |
|            |                 | Med (Min, Max)         | 2 (0, 47)       | 4 (0, 40)       | 30 (0, 97)          | 19 (0, 83)            | 29 (0, 98)               | 1.0 (0.0, 2.5) | 4.3 (0.2, 120.0) |
| 26         | EU-Humira       | Mean (SD); n           | 3.3 (4.9); 278  | 6.8 (9.3); 278  | 31.8 (23.1); 278    | 20.4 (16.2); 278      | 31.9 (23.4); 278         | 1.0 (0.7); 278 | 9.0 (13.8); 276  |
|            |                 | Med (Min, Max)         | 1 (0, 28)       | 3.5 (0, 63)     | 28 (0, 96)          | 16 (0, 83)            | 28.0 (0, 90)             | 1.0 (0.0, 2.9) | 3.8 (0.2, 118.0) |
|            | PF-06410293     | Mean (SD); n           | 3.0 (4.0); 289  | 5.5 (6.0); 289  | 28.3 (20.2); 289    | 17.8 (13.6); 288      | 28.6 (20.8); 289         | 0.9 (0.6); 289 | 10.2 (17.1); 288 |
|            |                 | Med (Min, Max)         | 1 (0, 20)       | 4 (0, 37)       | 24 (0, 93)          | 15 (0, 89)            | 24.0 (0, 94)             | 0.9 (0.0, 2.6) | 4.1 (0.2, 120.0) |

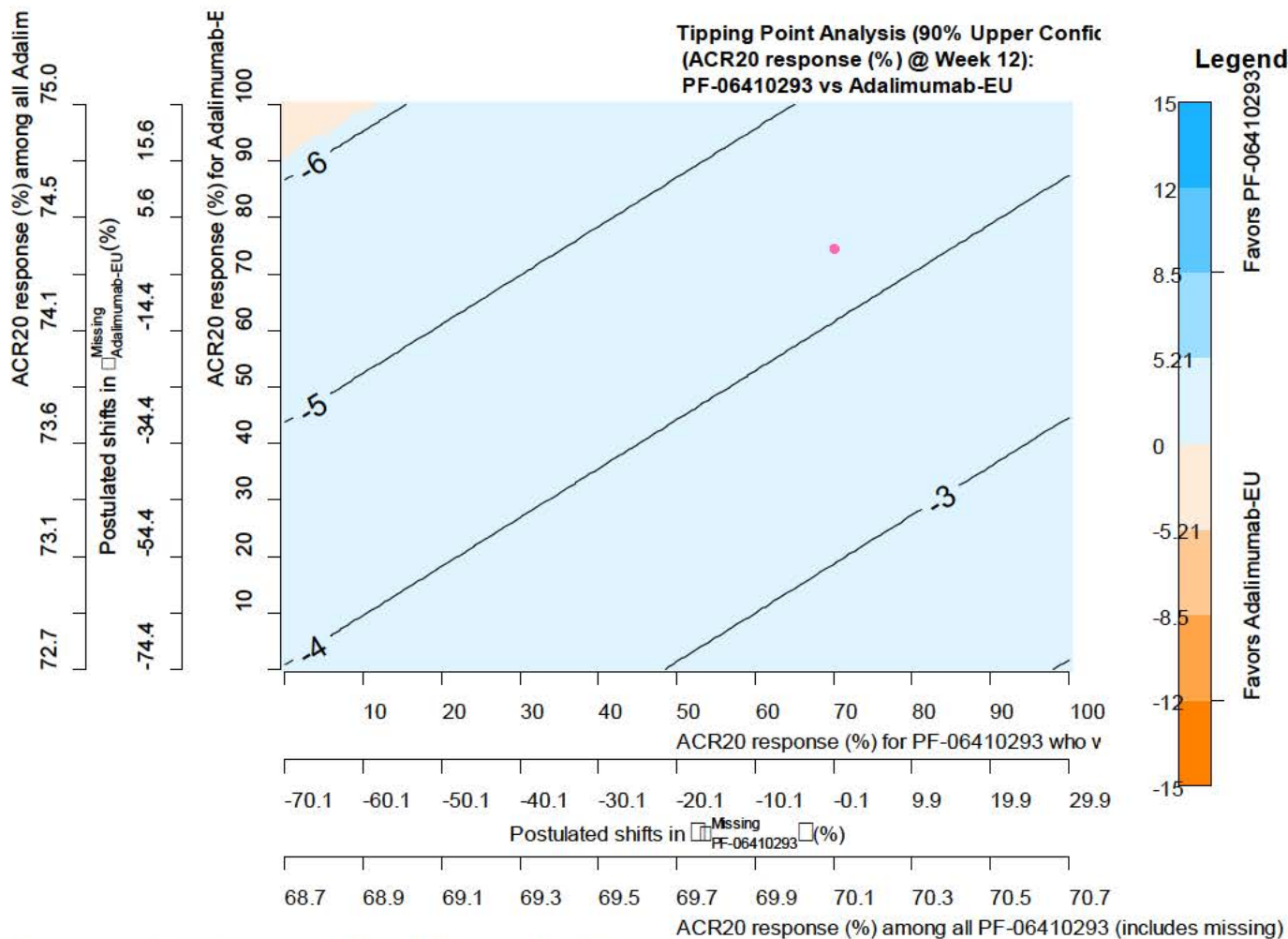
Abbreviations: ACR=American College of Rheumatology; CRP=C-reactive protein; Max=maximum; Med=median; Min=minimum; SD=standard deviation; SJC=swollen joint counts; TJC=tender joint counts  
 [Source: Reviewer]

**Figure 17. Tipping Point Analyses Results for 90% Lower CL (Heatmap) and Point Estimates (Contour Lines): Inference on the Difference Between PF06410293 and EU-Humira in the Probability of Week 12 ACR20 Responses under Varying Assumptions**



Abbreviations: ACR=American College of Rheumatology; CL=confidence limits; Adalimumab-EU=EU-Humira  
 [Source: Statistical Reviewer]

**Figure 18. Tipping Point Analyses Results for 90% Upper CL (Heatmap) and Point Estimates (Contour Lines): Inference on the Difference Between PF06410293 and EU-Humira in the Probability of Week 14 ACR20 Responses under Varying Assumptions**



Abbreviations: ACR=American College of Rheumatology; CL=confidence limits; Adalimumab-EU=EU-Humira  
 [Source: Statistical Reviewer]

### 13.5.2. Study B5381002 Tipping Point Analysis Methodology<sup>27</sup>

The goal is to evaluate the potential effect of violations in assumptions about missing data on the reliability of conclusions. Suppose that outcomes  $Y$  are independently distributed on the control and test drug arms. The parameter of interest is the difference in means  $\theta$ . Consider the following parameterization and notation to describe the probabilities of completing the study (non-missingness), the true means in completers and dropouts, and the numbers of completers and total patients on the two treatment arms:

**Table 57. Parameters and Notation for Tipping Point Analysis in Presence of Missing Data**

| Arm     | Probability of non-missing | Mean among completers | Mean among dropouts | Number of completers | Sample size per arm |
|---------|----------------------------|-----------------------|---------------------|----------------------|---------------------|
| Placebo | $\pi_c$                    | $\mu_c$               | $\mu_c + \delta_c$  | $N_c$                | $n_c$               |
| Treated | $\pi_t$                    | $\mu_t$               | $\mu_t + \delta_t$  | $N_t$                | $n_t$               |

Given this parameterization, the target of inference is  $\theta = [\pi_t\mu_t + (1 - \pi_t)(\mu_t + \delta_t)] - [\pi_c\mu_c + (1 - \pi_c)(\mu_c + \delta_c)] \equiv \mu_t + (1 - \pi_t)\delta_t - [\mu_c + (1 - \pi_c)\delta_c]$ . An analysis based on completers will provide reliable inference on  $\theta$  if the missing-at-random assumption, i.e., the assumption that  $\delta_c = \delta_t = 0$ , is valid. We will perform sensitivity analyses that allow for the possibility that outcomes among dropouts are not missing-at-random by performing inference under different assumed values of the parameters  $\delta_c$  and  $\delta_t$ .

Denote  $M_{ij}$  to be an indicator that patient  $j$  on treatment  $i$  is a completer, i.e., his or her outcome is observed where  $i = c, t$ , and  $j = 1, \dots, n_i$ . By assuming fixed values of sensitivity parameters  $\delta_c$  and  $\delta_t$ , an estimator of  $\theta$  can be represented by

$$\hat{\theta} = \hat{\mu}_t + (1 - \hat{\pi}_t)\delta_t - [\hat{\mu}_c + (1 - \hat{\pi}_c)\delta_c]$$

where  $\hat{\mu}_i = \frac{1}{N_i} \sum_{k=1}^{n_i} Y_{ik} | M_{ik} = 1$  is the sample mean in the completers and  $\hat{\pi}_i = \frac{N_i}{n_i} \equiv \frac{\sum_{k=1}^{n_i} M_{ik}}{n_i}$  is the sample proportion of completers on the treatment arm  $i$ , with  $i$  taking values  $c$  or  $t$ .

The test statistic can be constructed as follows:

$$\frac{\hat{\theta} - \theta}{\sqrt{\frac{s_t^2}{N_t} + \frac{s_c^2}{N_c} + \frac{\delta_t^2 \hat{\pi}_t (1 - \hat{\pi}_t)}{n_t} + \frac{\delta_c^2 \hat{\pi}_c (1 - \hat{\pi}_c)}{n_c}}}$$

where  $s_i^2$  is the sample variance of the outcome. Under suitable conditions, the sampling test statistic is asymptotically normal with mean 0 and standard deviation 1.

<sup>27</sup> Source: Gregory Levin

The Wald-based 100 (1- $\alpha$ ) % confidence interval of the form  $\hat{\theta} \pm$

$z_{1-\alpha/2} \sqrt{\frac{s_t^2}{N_t} + \frac{s_c^2}{N_c} + \frac{\delta_t^2 \hat{\pi}_t(1-\hat{\pi}_t)}{n_t} + \frac{\delta_c^2 \hat{\pi}_c(1-\hat{\pi}_c)}{n_c}}$  can be constructed where  $z_q$  is the q quantile of the standard normal distribution.

### 13.5.3 Study B5381002 TP3 Safety Summary Tables

**Table 58. Extent of exposure during TP3 in RA Study**

|                                         | Previous Assignment in TP2 |                    |                                      | Total<br>N=505 |
|-----------------------------------------|----------------------------|--------------------|--------------------------------------|----------------|
|                                         | PF-06410293<br>N=258       | EU-Humira<br>N=120 | EU-Humira to<br>PF-06410293<br>N=127 |                |
| Duration of Treatment                   |                            |                    |                                      |                |
| Median (range) (weeks)                  | 24.1 (0-27)                | 24.1 (0-26)        | 24.1 (0-26)                          | 24.1 (0-27)    |
| Median (range) (days)                   | 169.0 (1-190)              | 169.0 (1-184)      | 169.0 (1-183)                        | 169.0 (1-190)  |
| Total Number of Doses                   |                            |                    |                                      |                |
| Median (range)                          | 13 (1-14)                  | 13 (1-14)          | 13 (1-14)                            | 13 (1-14)      |
| Mean (SD)                               | 12 (2.1)                   | 12 (2.2)           | 12 (2.5)                             | 12 (2.2)       |
| Subjects with any missed dose,<br>n (%) | 47 (18.2)                  | 30 (25.0)          | 13 (10.2)                            | 90 (17.8)      |

Source: Applicant's **Tables 55 and 56** in CSR of Study B5381002 (Week 92).

**Table 59. Overall AE profile during the open-label extension (TP3) in Safety Population**

|                             | Previous Assignment in TP2    |                             |                                                |
|-----------------------------|-------------------------------|-----------------------------|------------------------------------------------|
|                             | PF-06410293<br>N=258<br>n (%) | EU-Humira<br>N=120<br>n (%) | EU-Humira to PF-<br>06410293<br>N=127<br>n (%) |
| Number of AEs               | 206                           | 146                         | 94                                             |
| Subjects with AEs           | 110 (42.6)                    | 61 (50.8)                   | 47 (37.0)                                      |
| Subjects with SAEs          | 9 (3.5)                       | 9 (7.5)                     | 3 (2.4)                                        |
| Subjects with Grade 3 AEs   | 14 (5.4)                      | 7 (5.8)                     | 3 (2.4)                                        |
| Subjects with Grade 4 AEs   | 0                             | 3 (2.5)                     | 0                                              |
| Subjects with Grade 5 AEs   | 0                             | 1 (0.8)                     | 0                                              |
| Death                       | 0                             | 1 (0.8)                     | 0                                              |
| AE-related Discontinuation  |                               |                             |                                                |
| Temporary discontinuation   | 14 (5.4)                      | 9 (7.5)                     | 2 (1.6)                                        |
| Discontinued from treatment | 6 (2.3)                       | 3 (2.5)                     | 2 (1.6)                                        |
| Discontinued from study     | 4 (1.6)                       | 3 (2.5)                     | 1 (0.8)                                        |

Source: Applicant's **Table 14.3.1.2.1.1.3** in CSR of Study B5381002 (Week 92)

**Table 60. All-causality non-SAEs (by ≥2% Subjects) during TP3 (open-label extension)**

| SOC and PT<br>n (%)                     | Treatment arms assigned previously in TP2 |                    |                                | Total<br>N=505    |
|-----------------------------------------|-------------------------------------------|--------------------|--------------------------------|-------------------|
|                                         | PF-06410293<br>N=258                      | EU-Humira<br>N=120 | EU-Humira/PF-06410293<br>N=127 |                   |
| <b>Any AEs</b>                          | <b>110 (42.6)</b>                         | <b>61 (50.8)</b>   | <b>47 (37.0)</b>               | <b>218 (43.2)</b> |
| <b>Blood and Lymphatic System</b>       | <b>7 (2.7)</b>                            | <b>6 (5.0)</b>     | <b>5 (3.9)</b>                 | <b>18 (3.6)</b>   |
| Anaemia                                 | 5 (1.9)                                   | 4 (3.3)            | 1 (0.8)                        | 10 (2.0)          |
| Neutropenia                             | 1 (0.4)                                   | 1 (0.8)            | 3 (2.4)                        | 5 (1.0)           |
| <b>Gastrointestinal Disorders</b>       | <b>10 (3.9)</b>                           | <b>11 (9.2)</b>    | <b>8 (6.3)</b>                 | <b>29 (5.7)</b>   |
| Diarrhoea                               | 3 (1.2)                                   | 3 (2.5)            | 2 (1.6)                        | 8 (1.6)           |
| Nausea                                  | 2 (0.8)                                   | 2 (1.7)            | 1 (0.8)                        | 5 (1.0)           |
| Abdominal pain upper                    | 0                                         | 0                  | 2 (1.6)                        | 2 (0.4)           |
| <b>Infections and Infestations</b>      | <b>52 (20.2)</b>                          | <b>23 (19.2)</b>   | <b>26 (20.5)</b>               | <b>101 (20.0)</b> |
| Bronchitis                              | 5 (1.9)                                   | 3 (2.5)            | 1 (0.8)                        | 9 (1.8)           |
| Nasopharyngitis                         | 13 (5.0)                                  | 3 (2.5)            | 10 (7.9)                       | 26 (5.1)          |
| Sinusitis                               | 4 (1.6)                                   | 2 (1.7)            | 1 (0.8)                        | 7 (1.4)           |
| Tonsillitis                             | 5 (1.9)                                   | 1 (0.8)            | 1 (0.8)                        | 7 (1.4)           |
| Influenza                               | 4 (1.6)                                   | 3 (2.5)            | 1 (0.8)                        | 8 (1.6)           |
| Upper respiratory tract infection       | 2 (0.8)                                   | 2 (1.7)            | 6 (4.7)                        | 10 (2.0)          |
| Urinary tract infection                 | 2 (0.8)                                   | 2 (1.7)            | 3 (2.4)                        | 7 (1.4)           |
| <b>Injury, Poisoning and Procedural</b> | <b>13 (5.0)</b>                           | <b>6 (5.0)</b>     | <b>1 (0.8)</b>                 | <b>20 (4.0)</b>   |
| Fall                                    | 3 (1.2)                                   | 2 (1.7)            | 0                              | 5 (1.0)           |
| <b>Investigations</b>                   | <b>13 (5.0)</b>                           | <b>11 (9.2)</b>    | <b>7 (5.5)</b>                 | <b>31 (6.1)</b>   |
| ALT increased                           | 3 (1.2)                                   | 3 (2.5)            | 3 (2.4)                        | 9 (1.8)           |
| AST increased                           | 3 (1.2)                                   | 3 (2.5)            | 1 (0.8)                        | 7 (1.4)           |
| Blood alkaline phosphatase              | 0                                         | 0                  | 2 (1.6)                        | 2 (0.4)           |
| Blood urea increased                    | 0                                         | 2 (1.7)            | 0                              | 2 (0.4)           |
| Weight decreased                        | 0                                         | 2 (1.7)            | 0                              | 2 (0.4)           |
| <b>Musculoskeletal and Connective</b>   | <b>28 (10.9)</b>                          | <b>21 (17.5)</b>   | <b>13 (10.2)</b>               | <b>62 (12.3)</b>  |
| Arthralgia                              | 4 (1.6)                                   | 2 (1.7)            | 0                              | 6 (1.2)           |
| Back pain                               | 2 (0.8)                                   | 3 (2.5)            | 2 (1.6)                        | 7 (1.4)           |
| Rheumatoid arthritis                    | 13 (5.0)                                  | 11 (9.2)           | 5 (3.9)                        | 29 (5.7)          |
| Spinal pain                             | 3 (1.2)                                   | 1 (0.8)            | 0                              | 4 (0.8)           |
| <b>Nervous System Disorders</b>         | <b>8 (3.1)</b>                            | <b>5 (4.2)</b>     | <b>2 (1.6)</b>                 | <b>15 (3.0)</b>   |
| Headache                                | 6 (2.3)                                   | 3 (2.5)            | 0                              | 9 (1.8)           |
| <b>Respiratory, Thoracic and</b>        | <b>7 (2.7)</b>                            | <b>7 (5.8)</b>     | <b>1 (0.8)</b>                 | <b>15 (3.0)</b>   |
| Cough                                   |                                           |                    |                                |                   |
| Oropharyngeal pain                      | 0                                         | 2 (1.7)            | 0                              | 2 (0.4)           |
| <b>Skin and Subcutaneous Tissue</b>     | <b>6 (2.3)</b>                            | <b>3 (2.5)</b>     | <b>2 (1.6)</b>                 | <b>11 (2.2)</b>   |
| Urticaria                               | 0                                         | 0                  | 2 (1.6)                        | 2 (0.4)           |
| <b>Vascular Disorders</b>               | <b>4 (1.6)</b>                            | <b>5 (4.2)</b>     | <b>5 (3.9)</b>                 | <b>14 (2.8)</b>   |
| Hypertension                            | 4 (1.6)                                   | 2 (1.7)            | 5 (3.9)                        | 11 (2.2)          |

Source: Applicant's Table 30 in CSR of Study B5381002 (Week 92)

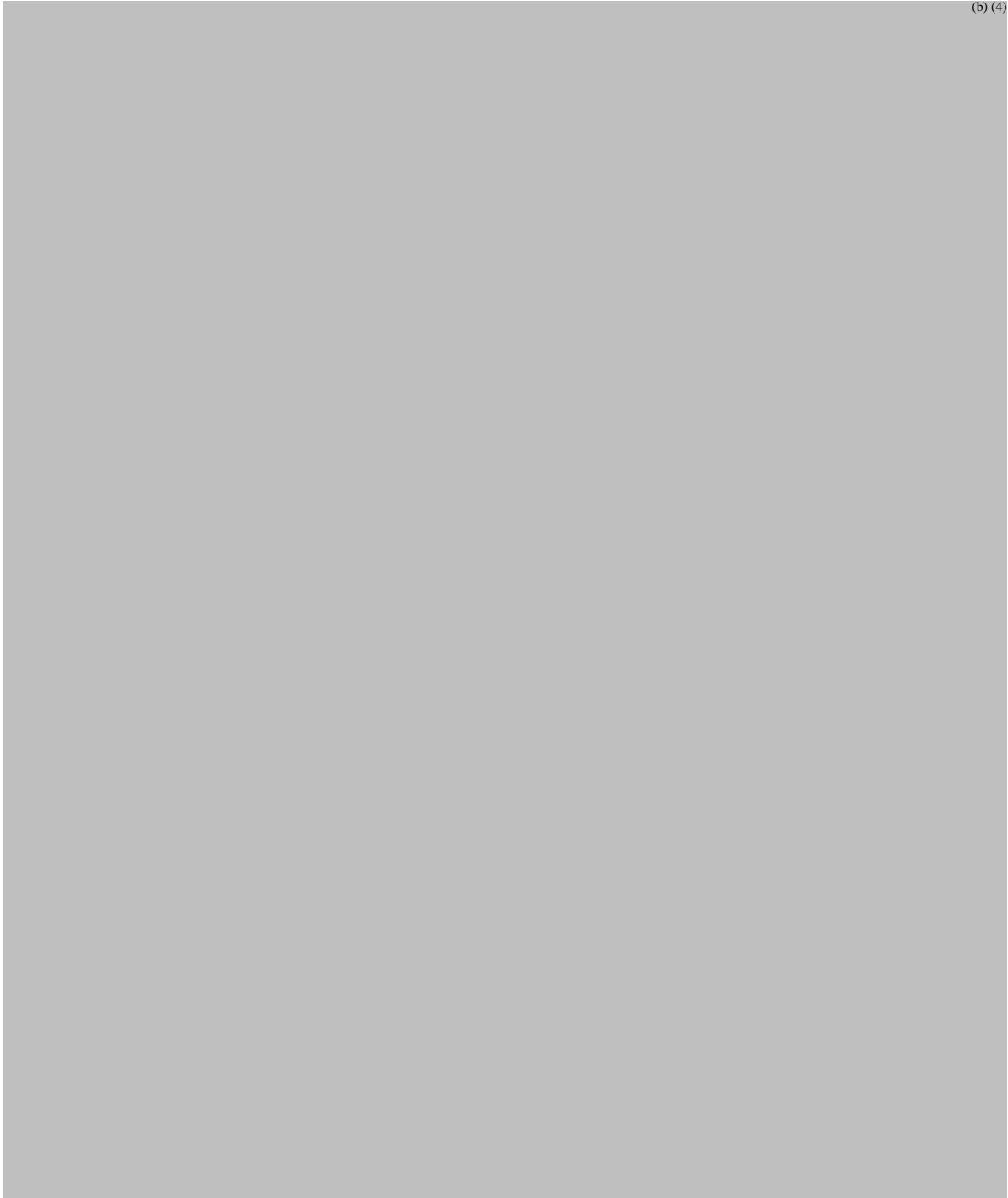
**Table 61. Adverse Events of Special Interest (AESI) during TP3**

| AESI (PT)                                              | PF-06410293<br>N=258<br>n (%) | EU-Humira<br>N=120<br>n (%) | EU-Humira/ PF-<br>06410293<br>N=127<br>n (%) |
|--------------------------------------------------------|-------------------------------|-----------------------------|----------------------------------------------|
| ISR                                                    | 2 (0.8)                       | 0                           | 0                                            |
| ISR                                                    | 2 (0.8)                       | 0                           | 0                                            |
| <b>Opportunistic infections</b>                        | <b>1 (0.4)</b>                | <b>0</b>                    | <b>0</b>                                     |
| Latent tuberculosis                                    | 1 (0.4)                       | 0                           | 0                                            |
| <b>Urticaria/angioedema/<br/>anaphylactic reaction</b> | <b>0</b>                      | <b>1 (0.8)</b>              | <b>2 (1.6)</b>                               |
| Shock                                                  | 0                             | 1 (0.8)                     | 0                                            |
| Urticaria                                              | 0                             | 0                           | 2 (1.6)                                      |
| <b>Total</b>                                           | <b>3 (1.2)</b>                | <b>1 (0.8)</b>              | <b>2 (1.6)</b>                               |

Source: Applicant's **Table 32** in CSR of Study B5381005 (Week 92); RD1: risk difference between PF-06410293 and EU-Humira; RD2: risk difference between EU-Humira/ PF-06410293 and EU-Humira

#### 13.5.4 Substudy B5381002 Figures

**Figure 19. Observer Assessment Tool (OAT) for Actual PFP Use Evaluation**



3 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

NIKOLAY P NIKOLOV

11/15/2019 05:21:00 PM

Signed under the authority delegated by Dr. Sally Seymour, Division Director, DPARP.