Saudi Public Assessment Report

Abrilada®

Active Pharmaceutical Ingredient(s): Adalimumab

ATC code/CAS no.: L04AB04

Pharmaceutical/Dosage Form: Solution for injection in PreFilled pen,
Solution for Injection in PreFilled Syringe

Dosage Strength:

a. Prefilled Pen
   - Injection: 40 mg/0.8 mL in a single-dose pen.

b. Prefilled Syringe
   - Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe.

Marketing Authorization Holder: Pfizer Saudi Limited

Shelf life: 36 months

Storage conditions: Store in a refrigerator (2°C – 8°C), do not freeze.

Registration No.: 2305210746 - 2305210745

Decision and Decision Date: Approved on 26/03/2021

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1. Terms, Definitions, Abbreviations

Terms	Definitions
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 antibody
AE	Adverse Event
ANOVA	Analysis of variance
AUC	Area Under the Curve
AUC0-2wk	Area under the serum concentration-time profile from time 0 to the nominal 2-week time point
AUC168	Area under the concentration-time curve from time 0 to 168 hours postdose
AUCinf	Area under the serum concentration-time profile from time 0 extrapolated to infinity
AUCt and AUClast	Area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration
BCG	Bacillus Calmette-Guérin
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CIs	Confidence Interval
CL/F	Apparent clearance
Cmax,	Maximum observed serum concentration
CTD	Common Technical Document
CV	Coefficient of Variation
DAS	DISEASE ACTIVITY SCORE
DAS28-4(CRP)	DISEASE ACTIVITY SCORE-28; 4 COMPONENTS BASED ON HS-CRP
DS	Drug Substance
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
EMA	European Medicines Agency
EU	European Union
EULAR	The European League Against Rheumatism
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HAQ-DI	Health Assessment Questionnaire-Disability Index
HC	Heavy chains

hs-CRP	High sensitivity C-reactive protein
huTNF-α	Human Tumor Necrosis Factor Alpha
ICH	International Conference on Harmonisation
IgG1	Immunoglobulin G1
IM	Intramuscular
INN	International Nonproprietary Names
ISR	Injection site reaction
ITT	Intention-to-treat
LC	Light chains
mAb	Monoclonal antibody
MS	Multiple sclerosis
MTX	Methotrexate
N	Total number of subjects randomized
NA	Not Available
NAb	Neutralizing antibodies
NRI	Non-responder imputation
ON	Optic Neuritis
PAAP	Patient's assessment of arthritis pain
PD	Pharmacodynamics
PF-06410293	Pfizer biosimilar to Humira® (adalimumab)
PFP	Prefilled pen
PFS	Prefilled syringe
PGA	Patient's global assessment of arthritis
PGAA	Physician's global assessment of arthritis
PIL	Patient information leaflet
PIMS	Phase 1 Management System
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive multifocal leukoencephalopathy
PP	Per Protocol
QTPP	Quality Target Product Profile
RA	Rheumatoid Arthritis
REML	Restricted maximum likelihood
RPLS	Reversible posterior Leukoencephalopathy syndrome
SAE	Serious Adverse Events
SC	Subcutaneous
SD	Standard Deviation
SFDA	Saudi Food and Drug Authority
SOC	System Organ Class
T ½	Terminal elimination half-life/Apparent terminal elimination half-life/terminal half-life
Tmax	Time of maximum observed serum concentration/Time to reach Cmax
TB	Tuberculosis
TNF	Tumor necrosis factor
TP	Treatment period
TP1	Treatment Period 1

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UC	Ulcerative colitis
U.S FDA	U.S Food and Drug Administration
US	United state
USAN	United States Adopted Names
Vz/F	Apparent volume of distribution
WW	Worldwide

2. Background

2.1. Submission Details

Type of submission: New Biosimilar Drug.

Pharmacological class: Tumor necrosis factor alpha (TNF-α) inhibitors (adalimumab)

Submitted Indication:

- **Rheumatoid Arthritis (RA):** ABRILADA is indicated for 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. ABRILADA can be used alone or in combination with methotrexate (MTX) or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).
- **Juvenile Idiopathic Arthritis**: ABRILADA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older. ABRILADA can be used alone or in combination with (MTX).
- **Psoriatic Arthritis**: ABRILADA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. ABRILADA can be used alone or in combination with non-biologic DMARDs.
- **Ankylosing Spondylitis**: ABRILADA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.
- **Adult Crohn's Disease**: ABRILADA is indicated for 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. ABRILADA is indicated for 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:** ABRILADA is indicated for 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 tumor necrosis factor (TNF) blockers.
- **Plaque Psoriasis**: ABRILADA is indicated for 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.

ABRILADA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

Submitted Dosage: Solution for injection, 20 mg/0.4 mL and 40 mg/0.8 mL.

2.2 Regulatory Background

This product is considered a New Biosimilar Drug for Saudi regulatory purposes. Furthermore, this product is qualified to follow the regulatory pathway of regular submission.

Regulatory status in other countries:

Abrilada® is currently authorized as a biosimilar subcutaneous (SC) injection in a pre-filled syringe and pre-filled pen to the reference product Humira by the US FDA since the 15th of November 2019. The US FDA approval was granted for seven indications for which the reference Humira was approved: RA, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis. In European Medicines Agency (EMA), Abrilada was approved on the 13th of February 2020 under the name Amsparity for the same indications as the reference product Humira.

Country	Product name	Dosage form/Strength	Approval Authority	Date of Approval
United States	Abrilada	Injection/40 MG	USDA	11/15/2019
		Injection/20 MG		
		Injection/10 MG		
European Union	Amsparity	Injection/40 MG	EMA	13/02/2020
		Injection/20MG		

List of other biosimilars approved by SFDA and/or clinical studies

Product name	Strength /unit	Dosage form	MAH
Hyrimoz	40 mg	Injection	Sandoz GmbH
Amgivita	40mg	Injection	AMGEN

The registered reference product in SFDA

Trade name	Active ingredient	Registration number
HUMIRA®	Adalimumab	1-921-15

2.3 Product Information

The officially approved Summary of Product Characteristics (SPC) can be accessed via Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

3. Scientific discussion about the product:

3.1 Quality Aspects

Abrilada ® has been developed as a proposed biosimilar to Humira®, in which both have adalimumab as the active substance. Adalimumab targets and blocks TNF, available as a sterile preservative free solution for injection supplied in a 1 mL long Type I glass prefilled syringe (PFS) with a 29-gauge thin walled ½ -inch staked needle. Pfizer -Adalimumab (PF-0641029) is an Immunoglobulin G1 (IgG1) kappa monoclonal antibody (mAb) produced by intracellular processing by Chinese Hamster Ovary (CHO) proteases.

3.1.1 Drug Substance

- **General Information**:

  (Adalimumab-mAb) with two identical heavy chains (HC) and two identical light chains (LC), covalently linked with four inter-chain disulfide bonds. The detailed descriptions of structural and functional studies conducted to characterize the PF-06410293 are presented in relevant sections (Section 3.2.S.3.1 Elucidation of Structure and Other Characteristics) and (section 3.2.R.3.2.2 Biological Activity - Biological Activity and Mechanisms of Action).

- **Manufacture, characterization, and process control**:
  The manufacturing process begins with the thawing of a vial of the working cell bank, which is a CHO cell line transfected with an expression vector. After that, the culture is serially expanded in cell mass and volume for inoculation into the production bioreactor. The cell culture fluid is subsequently purified with a series of steps, including chromatography, viral inactivation and viral filtration. Lastly, the excipients are added to the product to achieve the final formulation of drug substance (DS), followed by final filtration and freezing. Prior to drug product (DP) manufacture, DS is thawed and transported to the DP manufacturing site. Detailed process descriptions of each cell culture and harvest step and each purification step are provided in the relevant sections with the required process controls and process inputs are presented in figures and tables within the detailed unit operation process descriptions.
  The characterization of PF-06410293 includes determination of the structures (primary, secondary, and higher-order), glycosylation, charge variants, purity/impurities, cellular potency and binding activity provided, the results and conclusions of these studies are discussed in common technical document (CTD) section 3.2.R, Biosimilarity, as the characterization studies are also part of the biosimilarity assessment.
- **Control of the drug substance**:
  Specifications were set for quantity, identity, biological activity, purity and impurities, and safety, taking the principles of the ICH Q6B guideline into account. Other general tests (appearance, pH, osmolality) are also included in the specification.
  Overall, the test parameters proposed to be included in the DS specification are considered appropriate and in line with relevant guidance. The analytical methods used for DS and DP release testing have been described in detail and validated according to ICH Q2. Validation summaries, and detailed validation reports have been submitted for those methods that are not conducted according to compendial methods. In addition, the suitability of the compendial method addressing safety aspects (endotoxin and microbial enumeration) has been verified. The provided validation results indicate that the analytical methods for active substance release control are suitable for their intended use.
- **Reference materials**:
  Reference standards are established to demonstrate consistency in the manufacturing process of each development stage through an extensive set of analytical tests, including biological and physicochemical assays. Also, reference standards are used for method development and validation, and assessment of continuity of reference standards. In particular, reference standards are used to evaluate the system suitability of analytical methods.

- **Stability**:
  There are no issues pertaining to DS stability. The shelf life claim is supported by primary stability programs, which include three DS batches in addition to four supportive batches stored at the proposed long-term conditions in the proposed container closure system. The analytical procedures used in the stability programs were developed to monitor the biological activity, protein concentration, purity, identity, appearance, and general quality.

3.1.2 Drug Product

- **Description of the product and Pharmaceutical Development:**
  Pfizer has developed a single-dose delivery device designed to accommodate a 1 mL long Prefilled type 1 glass Syringe with a staked needle to deliver a SC fixed dose of DP between 0.5 and 1.0 mL. This base platform device has been further developed for use as the PF-06410293 Prefilled Pen (PFP), which accommodates the PFS containing 0.8 mL of PF-06410293 Solution for Injection. The composition of each PF-06410293 presentation is provided, along with the function and quality standard applicable to each component. PF-06410293 is provided at pH 5.5 in a concentration of 50 mg/mL.

- **Manufacture of the product**:
  The manufactured process of the DP starts when the DS is supplied refrigerated and stored at 2-8 ºC prior to formulation. The DS is pooled into a stainless steel vessel for formulation. Dilution buffer is prepared, and the DS is diluted with the buffer to the target protein concentration of 50 mg/mL and is then filtered using a bioburden reduction filter. The bulk DP is then sterile filtered in-line through two redundant sterilizing grade filters and aseptically filled into syringes. Each filled syringe is sealed with a plunger stopper. Following this plunger stopper placement, the syringes are inspected and packaged. The prefilled syringes may be stored at 2-8 °C prior to inspection. The PF-06410293 (PFS) without a backstop and a plunger rod (unassembled PFS) can be further manufactured into the final finished commercial PF-06410293 PFS assembled with a backstop and a plunger rod. In addition, the unassembled 0.8 mL PFS can be further manufactured into the final finished PF-06410293 (PFP). Controls for critical process steps are employed during the manufacture of PF-06410293 DP to ensure that product quality and integrity are maintained. The Quality Target Product Profile (QTPP) describes the PFP in terms of quality characteristics and is the driver for the design and development of the product. As a guide to development, the QTPP lists the intended product quality and performance characteristics to be achieved for the PFP. Comparable information for the PFS contained within the PFP is provided. The shipping qualification studies considered both thermal and mechanical aspects of shipping and included operations

qualification and performance qualification testing. These studies demonstrated the ability of the shipping containers to maintain the payload within specified temperature ranges and without physical damage to the product under the actual conditions to which the shipper will be exposed in the shipping lane.

- **Product contro**l:

  The specification for PF-06410293 DP was established to ensure the quality, purity, potency/biological activity, and safety of the commercial DP at release and during storage. The determination of quality attributes to be monitored and the analytical procedures to be used to monitor these quality attributes within the DP specification was made during the demonstration of PF-06410293 manufacturing process consistency and during the demonstration of similarity to the licensed adalimumab product (Humira). All analytical procedures are validated. The proposed specifications for the PFP are acceptable. There are no objections to the registration of Abrilada (adalimumab) from sterility, endotoxin, container safety and viral safety related aspects. The specifications for the PF-06410293 PFP are established to ensure the performance, safety and quality of the commercial PFP at final assembly release and during shelf life. The choice of tests to be included in the release and stability specifications for the PF-06410293 PFP was established through the user requirements and design input requirements that form the basis for the design output and the design verification testing of the PFP. The results of these design activities together with risk management activities confirmed that the mechanical and functional tolerances in the design of the PFP would support the user-related acceptance criteria for the PFP functional tests. Relevant literature and institutional experience with other PFP products were also considered during the setting of the acceptance criteria.

- **Reference materials**:
  The reference standard used for DP analysis is the same as that used for DS.

- **Stability of the product**:
  Stability information for PF-06410293 40 mg, PFS and 40 mg PFP (DP) stored under the recommended long-term condition of 5 ± 3 °C, the accelerated condition of 30 ±2 °C, as well as thermal stress, thermal cycling, and photostability conditions are provided, all the provided information supported the proposed shelf life of 36 months when stored at the recommended temperature of 2 - 8°C.

3.1.3 Comparability exercises

The sponsor performed a comprehensive similarity program, physicochemical/biological comparability has been conducted utilizing sufficient batches, comparability criteria and method qualification. Analytical comparability studies included primary, secondary and

higher order structures, post-translational modifications (charge variants and glycan profiles), purity and impurities, quantity, biological activity in fragment antigen-binding related functions, and comparative stability studies. High similarity was demonstrated. Minor differences between Abrilada (adalimumab) and EU-sourced Humira (adalimumab) were observed for some quality attributes.

3.2 Clinical Aspects

3.2.1 Clinical Pharmacology

The suggested mechanism of action and drugs in the same pharmacological class:

Adalimumab (also referred to as PF-06410293 in this report) is a recombinant fully human (IgG1) kappa (mAb) specific for (TNFα). TNF is a naturally occurring cytokine involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in both the pathologic inflammation and the joint destruction in multiple inflammatory diseases. Inhibition of the TNF receptor-ligand interaction by TNF antagonist therapy results in down regulation of mediators of the inflammatory cascade and is associated with clinical improvement of inflammatory diseases such as RA, psoriasis, and inflammatory bowel disease, among others. PF-06410293 specifically binds to TNF alpha (α) and blocks its interaction with the p55 and p75 cell surface TNF receptors, thereby neutralizing the effect of TNF in inflammatory conditions.

In addition to the reference product Humira, a biosimilar, Amgevita, is already registered by SFDA. Another biosimilar, Hyrimoz, is also approved by the clinical trials studies unit and is in the process of marketing approval. Abrilada's approval by SFDA will introduce the fourth option of Adalimumab to the Saudi market.

3.2.1.1 Pharmacokinetic studies

List of pharmacokinetic studies

Study/ Clinical trials identifier	Study Design	Primary Objective	Population
B5381001 **NCT Number:** 01870986	Phase 1, double blind, randomized (1:1:1), parallel-group, single dose, 3-arm, comparative pharmacokinetic study of PF-06410293 and adalimumab sourced from US and EU Administered to healthy volunteers.	-To compare the PK of PF-06410293 tadalimumab-EU, and PF-06410293 to adalimumab- US. - To compare the PK of adalimumab-EU to adalimumab-US.	Healthy subjects between 18 to 55 years of age.

		-To evaluate the single-dose safety and tolerability.	
B5381007 **NCT Number:** 01870986	Phase 1, double blind, randomized (1:1:1), parallel-group, 3-arm, single-dose, comparative pharmacokinetic study of PF-06410293 and adalimumab sourced from US and EU administered to healthy male and female subjects.	To compare the PK of PF-06410293 to adalimumab-EU, and of PF-06410293 to adalimumab-US.	Healthy subjects between 18 to 45 years of age.
B5381005 **NCT Number:** 02572245	Phase 1, open-label, randomized (1:1), single dose, parallel group, 2-arm comparability study to assess the PK of PF-06410293 following SC administration using a PFS or a PFP in healthy adult subjects.	To compare the single-dose PK of PF-06410293 Administered SC with a PFP device containing the PF-06410293 PFS, as compared to that of the PFS, in healthy adult subjects.	Healthy subjects between 20 to 55 years of age.

Study 1

Title: Phase 1, Double Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-06410293 and Adalimumab Sourced from US and EU Administered to Healthy Subjects.	
Study identifier	B5381001, NCT Number: 01870986
Design	A double-blind (Sponsor-open), randomized (1:1:1), parallel-group, 3-arm, single 40 mg dose, PK similarity study of PF-06410293 and adalimumab sourced from the US and EU administered SC in the lower abdomen by a PFS to healthy adult subjects.
Hypothesis	Equivalence
Total study duration including	Single dose From 28 May 2013 to 03 February 2014
Treatment arms	PF-06410293 or adalimumab-US or adalimumab-EU Route: Single use, PFS for SC injection Dose Regimen: 40mg [0.8 mL of a 50 mg/mL solution] on Study Day 1
Randomization	Subjects were given a unique identification number on phase 1 management system (PIMS). Then, prior to dosing, a randomization number was allocated. This number was retained throughout the study and corresponded to a treatment schedule determined by a sponsor-generated randomization code. The number also appeared on the study medication containers. Randomization was stratified by study site.
Blinding	This study was subject and investigator-blinded
Primary Endpoint	C_{max}, AUC_t and AUC_{inf}
Secondary endpoints	CL/F, Vz/F and T 1⁄2, AUC_{0-2wk}, T_{max}

Blood samples point	Blood samples for PK analysis were collected prior to the first dose on Study Day 1 and post dose through Day 43.
Statistical analysis	**Determination of Sample Size** Based on limited available information for the reference product (Humira), powering assumptions for this analysis included a test-to- reference geometric mean ratio (GMR) of 1.05, a maximal Coefficient of Variation (CV) for AUC of 30%, a maximal CV for C_{max} of 35%, and a 5% non-evaluable rate. **Analysis:** - A one-way analysis of variance (ANOVA) with treatment as a factor was conducted for each natural log-transformed PK parameter (C_{max}, AUC_{0-2wk}, AUC_t, and AUC_{inf}). - PK similarity for a given test-to-reference comparison was considered to have been demonstrated if the 90% CIs for the test to reference ratios of C_{max}, AUC_t, and AUC_{inf} fell within the 80.00% to 125.00% equivalence window.
Study Results	– A total of 199 subjects were included in the PK data analysis. Two subjects discontinued from the study due to withdrawal by subject, of whom 1 subject was still evaluable in the PK population. Eleven (11) subjects were excluded from the primary PK analysis due to pre-dose concentrations >5% of C_{max} or inadequate samples in the terminal phase of the concentration-time profile. – Consistent with the median concentration-time profiles, the mean C_{max}, AUC_{0-2wk}, AUC_t and AUC_{inf} estimates were numerically slightly higher for PF-06410293, and the PK parameters associated with terminal elimination (AUC_t and AUC_{inf}) were lowest for adalimumab-US (Table 1). **Table 1:** Mean (SD)Pharmacokinetics parameter estimates For PF-06410293, Adalimumab- US, and Adalimumab- EU (Day1-43, Per Protocol (PP) population) (Study B5381001)

Parameters (units)	PF-06410293 (N=66)	Adalimumab-US (N=67)	Adalimumab-EU (N=66)
C_{max} (µg/mL)	3.63 ± 1.13	3.41 ± 1.07	3.37 ± 1.02
AUC_{0-2wk} (µg•hr/mL)	988.5 ± 318.40	927.5 ± 286.06	903.7 ± 286.92
AUC_t (µg•hr/mL)	2200 ± 723.80	1869 ± 598.48	1958 ± 579.48
AUC_{inf} (µg•hr/mL)	2969 ± 1284.7	2357 ± 918.4	2587 ± 1039.7
CL/F (mL/hr)	16.39 ± 7.77	20.04 ± 8.88	18.32 ± 8.74
V_z/F (mL)	8575 ± 3135.9	9088 ± 3532.7	9080 ± 2891.9
$t_{½}$ (hr)	427.5 ± 200.65	367.3 ± 187.64	403.4 ± 199.64
T_{max}[a] (hr)	168	168	168

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– The inter-subject variability for each of the PK parameters, though considerable, was similar across the 3 study drugs, with percent coefficient of variation (%CV) values of 30% to 31% for C_{max}, 31% to 32% for AUC_{0-2wk}, 30% to 33% for AUC_t, and 39% to 43% for AUC_{inf}.

– Similarity criteria were met for C_{max} and AUC_{0-2wk} for the comparisons of PF-06410293 to adalimumab-EU and PF-06410293 to adalimumab-US, and for AUC_t for the comparison of PF-06410293 to adalimumab-EU. However, the upper limits of the 90%CIs exceeded 125.00% for the AUC_t comparison of PF-06410293 to adalimumab-US (ratio: 117.39, 90% CI: 106.41-129.50), and for the AUC_{inf} comparisons of PF-06410293 to adalimumab-EU and PF-06410293 to adalimumab-US (ratio: 124.04, 113.10, 90% CI 109.81-140.11, 100.08-127.82 , respectively) , thus, similarity criteria were not met for these parameters.

- The pre-specified acceptance criteria were met for the test to reference ratios for all PK parameters for the comparison of adalimumab-EU to adalimumab-US (Table 2).

Table 2: Summary of Statistical Comparison of PK Exposure Parameters (C_{max}, AUC_{0-2wk}, AUC_{inf}) between test and reference products (Day 1-43,PP Analysis Set) (Study B5381001)

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means	90% CI for Ratio[a]
	Test	Reference		
PF-06410293 (Test) Versus Adalimumab-EU (Reference)				
C_{max} (µg/mL)	3.44	3.20	107.58	97.73, 118.42
AUC_{0-2wk} (µg•hr/mL)	932.7	851.9	109.48	98.77, 121.35
AUC_t (µg•hr/mL)	2075	1866	111.21	100.77, 122.72
AUC_{inf} (µg•hr/mL)	2700	2388	113.10	100.08, 127.82
PF-06410293 (Test) Versus Adalimumab-US (Reference)				
C_{max} (µg/mL)	3.44	3.25	106.07	96.39, 116.72
AUC_{0-2wk} (µg•hr/mL)	932.7	880.0	105.99	95.65, 117.44
AUC_t (µg•hr/mL)	2075	1768	117.39	106.41, 129.50
AUC_{inf} (µg•hr/mL)	2700	2177	124.04	109.81, 140.11
Adalimumab-EU (Test) Versus Adalimumab-US (Reference)				
C_{max} (µg/mL)	3.20	3.25	98.59	89.60, 108.49
AUC_{0-2wk} (µg•hr/mL)	851.9	880.0	96.81	87.37, 107.27
AUC_t (µg•hr/mL)	1866	1768	105.56	95.69, 116.45
AUC_{inf} (µg•hr/mL)	2388	2177	109.67	97.09, 123.88

Study 2

Title: Phase 1, Double Blind, Randomized, Parallel-Group, 3-Arm, Single-Dose, Comparative Pharmacokinetic Study of PF-06410293 and Adalimumab Sourced from US and EU Administered to Healthy Male and Female Subjects.	
Study identifier	B5381007, NCT Number: 01870986
Design	A double-blind (Sponsor-open), randomised (1:1:1), parallel-group, 3-arm, single 40 mg dose PK similarity study of PF-06410293 and adalimumab sourced from the US and EU, administered to healthy adult subjects as a SC injection by PFS in the lower abdomen.
Hypothesis	Equivalence
Total study duration including	Single dose From 22 Sep 2014 to 17 Mar 2015
Treatment arms	PF-06410293 or adalimumab-US or adalimumab-EU Route: Single use, PFS for SC injection Dose Regimen: 40mg [0.8 mL of a 50 mg/mL solution] on Study Day 1
Randomization	Randomization was performed manually at each site based on a randomly generated schedule provided by Sponsor to the site. Randomization was stratified by 3 weight groups based on Day -1 weight: <75 kg, 75 kg to <90 kg, and ≥90 kg, and each study site received a randomization schedule generated for each weight group. In accordance with the assigned randomization number, the subject received the study treatment regimen indicated by the associated randomization code. Subjects who were enrolled and randomized into the study but did not receive a full 40 mg dose of study drug could have been replaced.
Blinding	The study was blinded to both subjects and Investigators
Primary Endpoint	C_{max}, AUC_{0-2wk}, AUC_t, AUC_{inf}
Secondary endpoints	T_{max}, CL/F, Vz/F, and t½
Blood samples point	Blood samples for PK analysis were collected prior to the first dose on Study Day 1 and post dose through Day 50.
Statistical analysis	The planned sample size for this study was approximately 360 subjects (120 subjects per treatment arm). **Determination of Sample Size** Powering assumptions included a GMR of 1.05, a maximal CV for any individual PK parameter of 45%, and a 10% non-evaluable rate. This study was designed based on observed data from Study B5381001. Specifically, the highest CV was 43% for AUC_{inf} in Study B5381001; therefore, Study B5381007 was powered with

	the assumption that the CV for AUC_{inf} could be as high as 45%. As a result, the sample size in Study B5381007 was substantially larger than in Study B5381001. **Analysis:** - An ANOVA with treatment as a factor was conducted for each natural log transformed PK parameter (C_{max}, AUC_{0-2wk}, AUC_t, AUC_{inf}) for each pair-wise comparison. - PK similarity for a given test to reference comparison was claimed if the 90% CIs of the test-to-reference ratios in C_{max}, AUC_{0-2wk}, AUC_t, and AUC_{inf} fell within the 80.00%- 125.00% range.
Study Results	– A total of 311 subjects were included in the PK data analysis, among them, 106, 101, and 104 subjects received PF-06410293, adalimumab-US, and adalimumab-EU, respectively. The 3 study drugs exhibited a comparable PK profile, which was characterized by an increase of serum drug concentration following SC dosing, with the maximum serum concentration achieved after approximately 5-6 days, followed by a multi-phasic decline in drug concentrations. – Consistent with the mean concentration-time profiles, the mean C_{max}, AUC_{0-2wk}, AUC_t, and AUC_{inf} estimates were similar among the 3 study drugs, with estimates of these parameters for PF-06410293 being slightly higher. The inter-subject variability for each of the PK parameters, though considerable, was similar across the 3 study drugs, with percent coefficient of variation values of 28-29%, 26-29%, 29-33%, and 33-40% for C_{max}, AUC_{0-2wk}, AUC_t, and AUC_{inf} respectively (Table 3). **Table 3:** Summary of Statistical Comparison of PK Exposure Parameters (C_{max}, AUC_{0-2wk}, AUC_{inf}) between test and Comparator products

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Comparator) of Adjusted Means[a]	90% CI for Ratio[a]
	Test	Comparator		
PF-06410293 (Test) versus Adalimumab-EU (Comparator)				
C_{max} (µg/mL)	4.344	3.901	111.36	103.97 – 119.27
AUC_{0-2wk} (µg•hr/mL)	1199	1072	111.88	104.19 – 120.15
AUC_t (µg•hr/mL)	2430	2275	106.80	98.76 – 115.49
AUC_{inf} (µg•hr/mL)	2866	2718	105.44	96.43 – 115.29
PF-06410293 (Test) versus Adalimumab-US (Comparator)				
C_{max} (µg/mL)	4.344	3.891	111.64	104.18 – 119.64
AUC_{0-2wk} (µg•hr/mL)	1199	1064	112.73	104.92 – 121.12
AUC_t (µg•hr/mL)	2430	2172	111.87	103.39 – 121.05
AUC_{inf} (µg•hr/mL)	2866	2556	112.12	102.47 – 122.68
Adalimumab-EU (Test) versus Adalimumab-US (Comparator)				
C_{max} (µg/mL)	3.901	3.891	100.25	93.52 – 107.47
AUC_{0-2wk} (µg•hr/mL)	1072	1064	100.76	93.74 – 108.30
AUC_t (µg•hr/mL)	2275	2172	104.75	96.77 – 113.38
AUC_{inf} (µg•hr/mL)	2718	2556	106.34	97.17 – 116.37

3.2.1.2 Pharmacodynamic studies

No well-established pharmacodynamic markers are available for TNF inhibitors; therefore, no pharmacodynamic data is required. However, Serum high sensitivity C-reactive protein (hs-CRP) was assessed as a PD biomarker in study B5381002.

Assessors' comment on clinical pharmacology

In study B5381001, the investigators faced the higher than expected observed inter-subject variability in PK parameters. The study was not considered to be adequately powered to assess certain differences sensitively. In addition, the sampling time point was too short to assess the equivalence in PK parameters between arms. To minimize these differences, the investigators conducted another study (study B5381007) by using the results from the previous study to increase the study power and the sample size. Furthermore, they modified the randomization method to be stratified by body weights to reduce heterogeneity between groups. This was influenced by the results of an exploratory analysis in study B5381001, in which the weight was used as a covariate.

This analysis resulted in 90% CIs of C_{max}, $AUC_{0\text{-}2wk}$, AUC_t, and AUC_{inf} within 80%-125% in comparison with Humira-EU. Stratification by bodyweight was also practiced in other biosimilars of Humira. In addition, they extended the sampling time points to cover almost 4 half-lives. Therefore, Study B5381007 was considered to be more appropriately powered due to these differences observed in Study B5381001.

Overall study design in B5381007 was acceptable. The parallel groups design and duration of study were suitable due to the long half-life of adalimumab (11 to 18 days), which has a potential effect on the PK parameters and the immunogenicity response. Hence, a crossover design is not feasible.

The blood samples for PK assessment were collected at pre-dose and on days 1 (3 and 12 hours), 2, 3, 4, 5, 6, 7, 8, 9, 12, 15, 22, 29, 36, 43, and day 49 (1176 hour) post-dose is considered semi-adequate to compare the PK profiles, evaluate the safety and immunogenicity of the product. The investigators should have extended the blood samples until 70 days to cover five half-lives.

The PK parameters C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were used to establish the bioequivalence assessment between PF-06410293 (Abrilada) and the reference product (Humira). These PK parameters were justified and consistent with the EMA guideline requirements (EMA/CHMP/ BMWP/ 403543/2010). The bioanalytical method that they used was appropriate and validated.

According to the study results, the 90% CIs for the GMR of C_{max}, AUC_t and AUC_{inf} were within the pre-defined criteria of 80% –125%. Although, the drug concentrations for the test group were still higher than the reference group. The investigators' explanation for the higher concentrations was that it is most likely due to small differences in bioavailability for the PF-06410293 treatment compared to either adalimumab-EU or adalimumab-US.

In conclusion, the bioequivalence was demonstrated for both pairs of comparisons, between PF-06410293 /EU- Humira, and US-Humira/EU-Humira.

3.2.2 Clinical Efficacy

3.2.2.1 List of submitted clinical efficacy studies

Study ID*	No. of study centres / locations	Design	Objective	Subjs by arm entered/ compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
B5381002 **NCT#:** 02480153	173 Centers	Multi-national, 2-armed, randomized (1:1), double-blind, parallel-group study designed to evaluate the safety, efficacy, population PK, and immunogenicity of PF-06410293 versus adalimumab-EU in combination with MTX to treat subjects with moderately to severely active RA who had an inadequate response to MTX therapy.	To compare the treatment efficacy between PF-06410293 and adalimumab-EU in subjects with moderately to severely active RA who were treated with adalimumab in combination with MTX.	N: 597 **TP1:** **Randomized:** PF-06410293=297 adalimumab-EU=300 **Treated:** PF-06410293=297 adalimumab-EU=299 **Completed TP1 :** PF-06410293=286 adalimumab-EU=273 **TP2:** **Re-randomized:** PF-06410293/PF 06410293=283 adalimumab-EU/ adalimumab-EU=135 adalimumab-EU/ PF-06410293=134 **Treated:** PF-06410293/ PF-06410293=283 adalimumab-EU/adalimumab-EU=135	Multiple dose for 18 months	Moderately to severely active RA Incl. criteria: – Male and female subjects aged 18 years or older with moderately to severely active RA who had an inadequate response to MTX therapy. – Diagnosis of RA based on 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA for at least a 4-month duration. – Patients should meet Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA.	The proportion of subjects achieving a 20% or greater improvement in ACR clinical response at Week 12.

				adalimumab-EU/ PF-06410293=133 **Completed TP2:** PF-06410293/ PF-06410293=258 adalimumab-EU/ adalimumab-EU=120 adalimumab-EU/ PF-06410293=126		– Subjects must have received oral, SC, or intramuscular (IM) (MTX) for at least 12 weeks and been on a stable dose for at least 4 weeks prior to first dose of study drug. – Female subjects of childbearing potential who are willing to use a highly effective method of contraception of and women of non-childbearing potential	

3.2.2.2 Data integrity and GCP

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.

3.2.2.3 Inter-changeability studies

Study B5381002 was designed to evaluate the clinical response, safety and immunogenicity after study drug transition (randomized blind single transition) from adalimumab-EU to PF-06410293 after 6 or 12 months of adalimumab-EU treatment.

Study 3

<table>
<tr><td colspan="3"><u>Title:</u> A Phase 3 Randomized, Double-Blind Study Assessing the Efficacy and Safety of PF-06410293 and Adalimumab in Combination with MTX in Subjects with Moderately to Severely Active RA Who Have Had an Inadequate Response to MTX.</td></tr>
<tr><td>Study identifier</td><td colspan="2">B5381002, NCT Number: 02480153</td></tr>
<tr><td rowspan="4">Design</td><td colspan="2">This was a multi-national, 2-arm, randomized, double-blind, parallel-group study designed to evaluate the safety, efficacy, population PK, and immunogenicity of PF-06410293 versus adalimumab-EU in combination with MTX to treat subjects with moderately to severely active RA who had an inadequate response to MTX therapy.</td></tr>
<tr><td>Duration of main phase:</td><td>26 weeks</td></tr>
<tr><td>Duration of Run-in phase:</td><td>21 days</td></tr>
<tr><td>Duration of Extension phase</td><td>Blinded Period 2: 26 weeks Open-label extension Period 3: 26 weeks Safety follow-up: 16 weeks after the final dose of study drug</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Equivalence</td></tr>
<tr><td rowspan="2">Treatments arms</td><td colspan="2">Test product: PF-06410293, 40mg every other week by SC injection, throughout the study treatment periods.</td></tr>
<tr><td colspan="2">Reference product: EU-Humira, 40mg every other week by SC injection, throughout the study treatment periods.</td></tr>
</table>

Randomization	**Randomization ratio:** (1:1) **Randomization method:** Subject unique identifiers were associated with their randomization and re-randomization schedules and treatment assignments and were retained centrally throughout the study.
Blinding	Double blinded study
Endpoints and definitions	**The primary efficacy endpoint** was the proportion of subjects achieving a 20% or greater improvement in ACR clinical response at Week 12.
	The secondary endpoints (TP1) were: – ACR20 at Weeks 2, 4, 6, 8, 18 and 26. – ACR50 and ACR70 at Week 12 and other time points (Weeks 2, 4, 6, 8, 18 and 26). – Individual components of the ACR criteria (including HAQ-DI) with change from baseline at Week 12 and other time points (Weeks 2, 4, 6, 8, 18 and 26). – Mean change from baseline in disease activity measured by Disease Activity Score-28; 4 components based on hs-CRP (DAS28-4 (CRP)) at Week 12 and other time points (Weeks 2, 4, 6, 8, 18 and 26). – Proportion of subjects with a no, moderate, or good response, defined according to the EULAR response criteria, at Week 12 and other time points (Weeks 2, 4, 6, 8, 18 and 26). – Proportion of subjects with DAS remission (DAS ≤2.6) at Week 12 and other time points (Weeks 2, 4, 6, 8, 18 and 26). – Proportion of subjects with ACR/EULAR remission at Week 12 and other time points (Weeks 2, 4, 6, 8, 18 and 26).
	The secondary endpoints (TP2) were: ACR20; ACR50; ACR70; DAS remission (≤2.6); EULAR response; ACR/EULAR remission; DAS28-4 (CRP) and its change from baseline; HAQ-DI and its change from baseline; Swollen joint count (66) and its change from baseline; Tender joint count (68) and its change from baseline; Patient's assessment of arthritis pain (PAAP) and its change from baseline; Patient's global assessment of arthritis (PGA) and its change from baseline; Physician's global assessment of arthritis (PGAA) and its change from baseline; and hs-CRP and its change from baseline.
Database lock	Week 52 database lock: 26 May 2017; Final database lock: 05 Jan 2018

Results and Analysis

Sample size determination

This study planned to enroll approximately 560 subjects. The sample size was determined to have approximately 85% power to demonstrate equivalence between the 2 treatment arms (PF-06410293 and adalimumab-EU) at Week 12 if the 2-sided 95%CI for the observed difference in ACR20 response rates fell within the equivalence margin of (-14%, 14%). These sample size and power calculations were performed for the ITT population.

Analysis of primary and secondary Efficacy Endpoint- Treatment Period 1:

- The primary analysis for ACR20 was performed for the ITT population with non-response imputed for subjects who discontinued treatment earlier than Week 12 or had a missing Week 12 assessment (non-responder imputation [NRI] method).
- The proportion of subjects achieving ACR20 response rate at Week 12 was analyzed by calculating a point estimate for the response difference between the 2 treatment arms [PF-06410293 (test) and adalimumab–EU (reference)].
- CIs (95% and 90%) calculated by the score statistic method were used for the inference of equivalence for the primary efficacy endpoint.

Equivalence between the 2 arms would be declared if the 2-sided 95% CI fell within the symmetric equivalence margin (-14%, 14%); this approach was endorsed by the EMA and the Pharmaceuticals and Medical Devices Agency (PMDA). The FDA endorsed the alternative approach where equivalence would be declared if the 2-sided 90% CI fell within the asymmetric equivalence margin (-12%, 15%).

Descriptive statistics were presented for all secondary efficacy endpoints on the ITT population and ACR20 response rate, and DAS28-4 (CRP) for the PP population. DAS28-4 (CRP) changes from baseline were analyzed using a restricted maximum likelihood (REML) based on a repeated measures approach. In addition, a tipping point analysis was performed.

Results:

Treatment Period 1 (TP1)

A total of 597 subjects were randomized to receive study treatment. One (1 [0.3%]) subject in the adalimumab-EU arm was randomized but not dosed. Of the 596 randomized and dosed subjects, 297 received PF-06410293 and 299 received adalimumab-EU. A total of 286 (96.3%) subjects in the PF-06410293 arm and 273 (91.0%) subjects in the adalimumab-EU arm completed TP1 (Table 4).

Table 4: Subjects Disposition, ITT Population -TPI

Number (%) of Subjects	PF-06410293	Adalimumab-EU
Screened: 1231		
Randomized to study treatment (ITT population)	297	300
Randomized but not treated	0	1 (0.3)
Completed TP1	286 (96.3)	273 (91.0)
Entered TP2	283 (95.3)	268 (89.3)
Did not re-randomize into TP2	3 (1.0)	5 (1.7)
Did not complete TP1	11 (3.7)	26 (8.7)
Withdrew from treatment and continued in study	6 (2.0)	14 (4.7)
Discontinued from both treatment and study	5 (1.7)	12 (4.0)

Baseline demographic and disease characteristics:

The majority of the subjects in the ITT population for TP1 were female (78.7%) and White (86.6%). The mean age (±SD) of all subjects was 52.5 (±13.2) years and the mean BMI was 27.8 (±6.7) kg/m2. Similar baseline demographic characteristics were observed in the PP populations.

The baseline disease characteristics were similar between the 2 treatment arms. Subjects had active RA with a mean (standard deviation; SD) of 16.2 (8.9) swollen joints, 25.5 (13.6) tender joints, hs-CRP of 22.1 (24.0) mg/L and DAS28-CRP of 6.0 (0.9) at study baseline.

Primary Efficacy Endpoint results – Treatment Period 1

In the ITT population (observed data), 204 (68.7%) subjects in the PF-06410293 arm and 218 (72.7%) subjects in the adalimumab-EU arm achieved an ACR20 response at Week 12, with a treatment difference of -3.98% in Week 12 ACR20 response rate for PF-06410293 (test) as compared to adalimumab-EU (reference). ACR20 response rates (observed data) were also similar for both treatments in the PP population, with a treatment difference of -4.41% (Table 5).

Table 5: Descriptive Summary of ACR20 response at week 12-TP1

Visit	Exact Method	PF-06410293 n (%)	Adalimumab-EU n (%)	Difference in ACR20 Response Rate (PF-06410293 – Adalimumab-EU) (%) Point Estimate	95% CI	90% CI
			ITT Population			
Week 12	N	297	300			
	Score statistic method[a]	203 (68.4)	214 (71.3)	-2.98	-10.38, 4.44	-9.25, 3.28
	Unconditional approach	203 (68.4)	214 (71.3)	-2.98	-11.02, 5.02	-9.74, 3.73
			PP Population			
Week 12	N	266	254			
	Score statistic method[a]	189 (71.1)	191 (75.2)	-4.14	-11.79, 3.61	-10.60, 2.38
	Unconditional approach	189 (71.1)	191 (75.2)	-4.14	-12.71, 4.48	-11.34, 3.10

The primary analysis for ACR20 at Week 12 was performed with non-response imputed for subjects who discontinued treatment earlier than Week 12 or had a missing Week 12 assessment (NRI method) (Table 6).

Table 6: Exact Binomial Approach for ACR20 response rate at week 12, Using Non-Responder Imputation for Missing data, ITT and PP Population- TP1 (95% and 90% CIs)

Visit	ACR20 Response	PF-06410293 n (%)	Adalimumab-EU n (%)	Difference in ACR20 Response Rate (PF-06410293 – Adalimumab-EU) (%)
			ITT Population	
Week 12	N1	297	300	
	Yes	204 (68.7)	218 (72.7)	-3.98
	No	87 (29.3)	75 (25.0)	
	Missing	6 (2.0)	7 (2.3)	
			PP Population	
Week 12	N2	267	254	
	Yes	189 (70.8)	191 (75.2)	-4.41
	No	77 (28.8)	63 (24.8)	
	Missing	1 (0.4)	0	

Treatment Period 2

Of the 552 subjects re-randomized in TP2 (TP2 ITT population), 283 subjects continued PF-06410293, 135 subjects continued adalimumab-EU and 134 subjects previously in the adalimumab-EU group were re-randomized to receive PF-06410293. One (1) subject in the adalimumab-EU/PF-06410293 group was re-randomized but not treated in TP2. Overall, 504 (91.3%) subjects completed TP2 including 258 (91.2%), 120 (88.9%) and 126 (94.0%) subjects in the PF-06410293/PF-06410293, adalimumab-EU/adalimumab-EU and adalimumab-EU/PF-06410293 groups, respectively, with the last subject completing the Week 52 visit on 01 March 2017 (Table 7).

Table 7: Subject Disposition, ITT Population –TP2

Number (%) of Subjects	PF-06410293/ PF-06410293 (N = 283)	Adalimumab-EU/ Adalimumab-EU (N = 135)	Adalimumab-EU/ PF-06410293 (N = 134)
Re-randomized in TP2	283	135	134[a]
Re-randomized but not treated in TP2	0	0	1 (0.7)[a]
Completed TP2	258 (91.2)	120 (88.9)	126 (94.0)
Did not complete TP2	25 (8.8)	15 (11.1)	7 (5.2)
Withdrew from treatment and continued in study	4 (1.4)	1 (0.7)	1 (0.7)
Discontinued from both treatment and study	21 (7.4)	14 (10.4)	6 (4.5)

Baseline demographic and disease characteristics

The majority of the re-randomized TP2 population were female (78.3%) and White (86.8%) (Table 5). The geographic distribution of the TP2 ITT population included 71.9% from the Rest of the World, 17.2% from North America and Western Europe, 6.5% from Latin America, 2.7% from Japan, and 1.6% from South Korea/Taiwan. No notable demographic differences were observed among the 3 treatment groups at baseline. The 552 subjects, who entered TP2, as compared to the 597 original study subjects who were randomized to TP1, were comparable for demographic parameters at the study baseline.

Baseline demographic and disease characteristics were similar among the 3 treatment groups, and similar for the TP2 population as compared to the study subjects overall at baseline. As subjects were required to demonstrate a minimal disease response in order to be re-randomized into TP2, RA disease activity at Week 26 for the TP2 population was substantially lower with a mean (SD) of 5.9 (7.3) tender joints, 3.0 (4.4) swollen joints, hs-CRP of 9.3 (15.1) mg/L and DAS28-CRP of 3.2 (1.2) at Week 26.

Efficacy results – Treatment Period 2

The ACR20 response rates at Week 52 were 82.7%, 79.3% and 84.3% for the PF-06410293/PF-06410293, adalimumab-EU/adalimumab-EU, and adalimumab-EU/PF-06410293 groups, respectively. Results were comparable between subjects receiving PF-06410293 or adalimumab-EU through Week 52, and between adalimumab-EU subjects that switched to PF-06410293 at Week 26 and the non-switching PF-06410293 subjects.

The ACR50 response rates at Week 52 were 62.9%, 55.6% and 72.4% for the PF-06410293/PF-06410293, adalimumab-EU/adalimumab-EU, and adalimumab-EU/PF-06410293 groups, respectively.

For each individual ACR component including tender joint count (68), swollen joint count (66), PAAP, PGA, PGAA, hs-CRP and HAQ-DI, mean values and changes from study baseline and Week 26 pre-dose were comparable in all treatment groups across TP2.

Treatment Period 3

A total of 507 subjects entered TP3: 259, 121 and 127 subjects in the PF/PF/PF, EU/EU/PF and EU/PF/PF groups, respectively, and 505 subjects received study treatment in TP3 (Table S2). Overall, 474 (93.5%) subjects completed TP3, with comparable completion rates observed in the 3 treatment groups.

Efficacy Results:

ACR Responses: ACR20 and ACR50 (Figure 1), and ACR70 (Figure 2) response rates were sustained and comparable across the 3 treatment groups in TP3

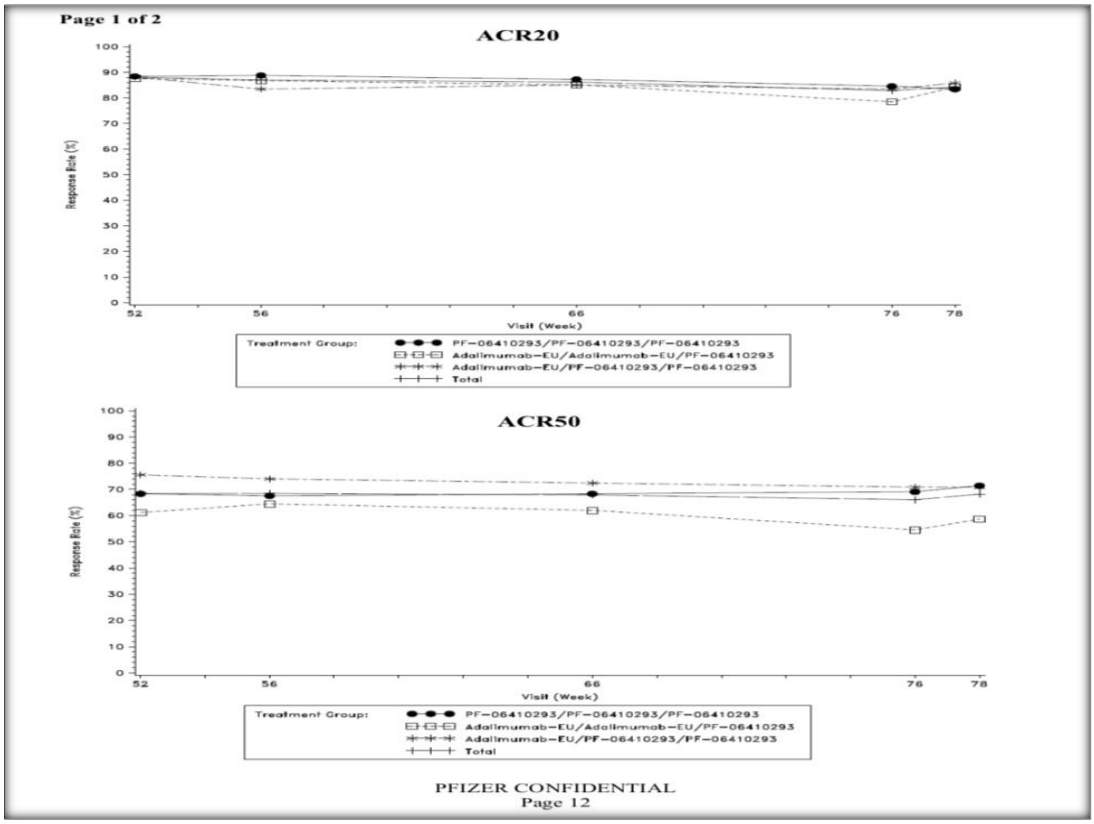


Figure 1: ACR20 and ACR50 Response Rate by visit, TP3, ITT population

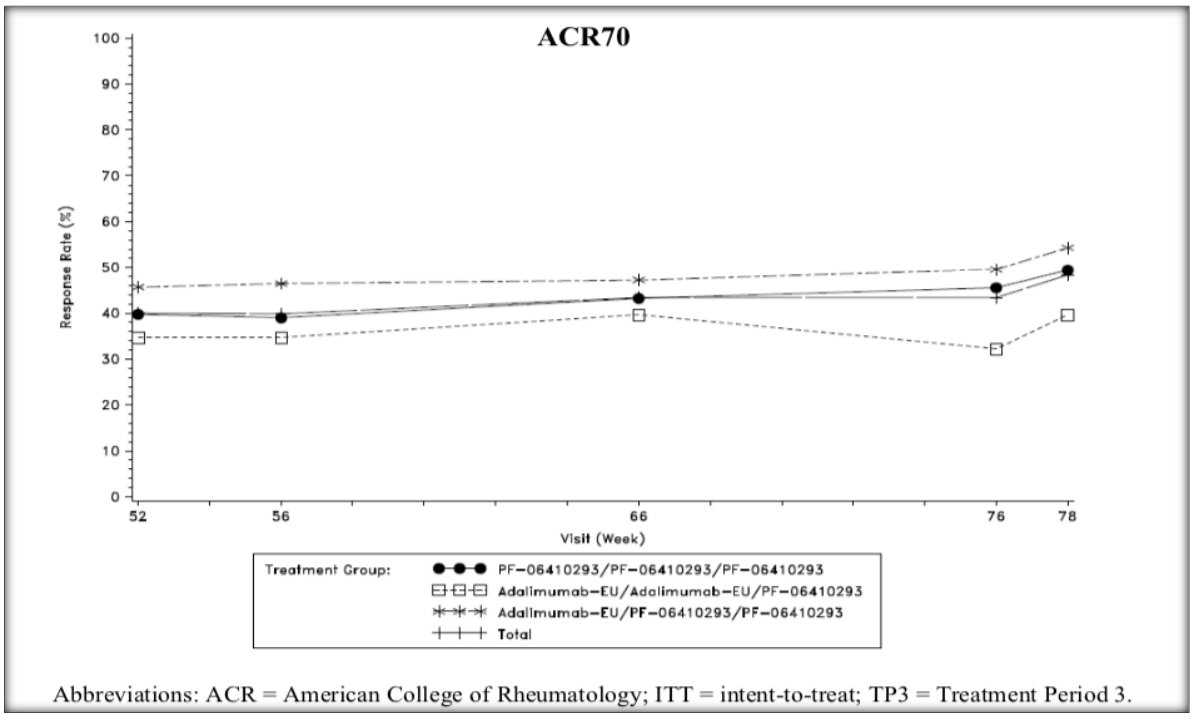


Figure 2: ACR 70 Response Rate by visit, TP3, ITT population

3.2.3 Overall conclusion of clinical 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 MTX in patients with moderately to severely active RA who have had an inadequate response to MTX. The study was a 52-week double-blind treatment followed by 26 weeks of open-label extension in which all subjects received PF-0641029.

Overall, the study design, including dose, route of administration, treatment duration, and assessment of the primary endpoint was appropriate. The choice of equivalence margin was justified as it was derived using a meta-analysis of historical published study data. RA was chosen as the most sensitive indication to confirm the biosimilarity of PF-06410293 to Humira based on the following reasons:

Subjects with RA represent a sensitive population to detect differences in efficacy among effective agents.

Subjects with RA have the largest clinical utilization, immunogenicity, and safety experience of the various licensed indications for Humira.

Consistent with other adalimumab biosimilars, RA was used in almost all of them to test the clinical efficacy comparability with Humira.

According to study results, the estimated difference of ACR20 at week 12 on the absolute scale comparing PF-06410293 relative to EU-Humira was -2.98% (95% exact (CI): -10.38%, 4.44%) (90% exact (CI): -9.25%, 3.28%). The 2–sided 95% CIs and 90% CIs of the treatment differences were entirely contained within the symmetric margin of (–14% to 14%) and the asymmetric margin of (-12% to 15%), respectively, in both the ITT and PP populations, demonstrating therapeutic equivalence between PF-06410293 and adalimumab-EU treatments.

3.2.3 Clinical Safety

The safety profile of PF-06410293 has been investigated in 4 clinical studies:

- Two single SC dose PK studies in healthy volunteers
- One single SC dose study using (PFS) or (PFP) in healthy volunteers,
- One multi-dose safety and efficacy study in subjects with moderately to severely active RA which included an optional device substudy using PFP.

In all studies, subjects received 40 mg of SC 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. The primary safety data were derived from the comparative clinical study B5381002.

3.2.3.1 Patient exposure

A total of 1,329 subjects received at least 1 dose of study medication including:

210, 359, and 164 healthy volunteers in Studies B5381001, B5381007, and B5381005, respectively.

596 subjects with active RA in B5381002.

3.2.3.2 Immunogenicity studies

Blood samples for the assessment of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were collected in all 4 clinical studies (B5381001, B5381002, B5381005, and B5381007).

Immunogenicity in healthy subjects after single dose (study B5381007, B5381001 and B5381005) (Table 8, 9 and 10).

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 8: Immunogenicity result for binding ADA and Nab in study B 5381007

	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

Table9: Immunogenicity result for binding ADA and Nab in study B 5381001

Number (%) of Subjects	PF-06410293 (N=69)	Adalimumab-US (N=71)	Adalimumab-EU (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.

Table 10: ADA and Nab for ISR/Rash AE and control Subjects by visit (Study B5381005)

Number of Tested Subjects	With ISR/Rash AE N = 15	Without ISR/Rash AE N = 15
ADA at baseline (pre-dose)	0	0
ADA post-dose		
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%)
NAb post-dose		
Overall number (%) of subjects with at least 1 positive NAb post-dose	7 (63.6%)[a]	5 (71.4%)[a]

Source: **Table 12**, CSR B5381005

Immunogenicity in RA subjects after multiple dose (Study B5381002)

The overall incidence of ADA in treatment period 1 (TP1) 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.

<u>The ADA and NAb incidences after the single transition from EU-Humira to PF-06410293</u>

At Week 26, prior to the first injection of the study drug in the treatment period2 (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 results 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.

3.2.3.2 Adverse events

Serious adverse events and deaths

SAEs

In Study B5381002, the total number of subjects who experienced an SAE was 25 (4.2%) during TP1, 13 (2.4%) during TP2 and 21 (4.2%) during TP3.

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 System Organ Class (SOC) were reported most frequently and were reported by 3 subjects in each treatment arm. The most frequently reported SAE by PT was 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).

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%). The most frequently SAEs were reported within the Infections and Infestations SOC 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.

Deaths

No deaths were reported in the healthy subjects in the PK studies, 85381001, 85381007, and 85381005. Two deaths were reported during the clinical Study 85381002.

Laboratory findings

There were no major findings reported.

Safety in special populations

PF-06410293 was developed as a biosimilar to the reference product Humira; therefore, product information from Humira also applies to PF-06410293. The product information is in line with the reference product and is adequate.

Immunological events (if available)

Safety and immunogenicity profiles did not show any difference among *PF-06410293*, US-Humira, and EU-Humira treatment groups.

Safety-related to drug-drug interactions and other interactions

Drug-drug Interactions were not evaluated

Discontinuation due to AES

There were no dose reductions, temporary discontinuations or permanent discontinuations due to AEs in Studies B5381001, B5381007, or B5381005.

In study B53811002:

During TP1, eleven (11 [3.7%]) and 14 (4.7%) subjects from the PF-06410293 and adalimumab-EU arms had AEs leading to discontinuation from treatment, respectively.

During TP2, six (6 [2.1%]), 8 (5.9%) and 2 (1.5%) subjects from the PF-06410293/PF-06410293, adalimumab-EU/adalimumab-EU and adalimumab-EU/PF-06410293 treatment groups had AEs leading to discontinuations from treatment, respectively.

Post-marketing experience

Not available

3.2.3.3 Overall conclusion on clinical safety

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 EU-Humira.

3.2.4 Discussion on Clinical efficacy and safety aspects

The submitted clinical development program of Abrilada showed established comparability results with the reference. The proposed biosimilar is highly similar to the reference product (Humira) and has no clinically meaningful differences in terms of efficacy, safety, and immunogenicity. Therefore, it is justifiable to extrapolate the equivalent clinical efficacy and the comparable safety profile from the Abrilada studies in RA patients to all indications where Humira has been approved. Hence, the efficacy and safety department recommends the approval of Abrilada for all of the following submitted indications: psoriasis, RA, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, Crohn's disease, and ulcerative colitis.

4. Risk Management Plan

Table: Summary Table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious infections	Routine risk minimisation measures: • Proposed SPC Section 4.3 • Contraindications • Proposed SPC Section 4.4, Special • warnings and precautions for use Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Tuberculosis (TB)	Routine risk minimisation measures: • Proposed SPC Section 4.4, Special • warnings and precautions for use • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

	Additional risk minimisation measures: Patient Reminder Card	None
Malignancies	Routine risk minimisation measures: • Proposed SPC Section 4.4, Special • warnings and precautions for use Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Demyelinating disorders (Including MS, GBS and ON)	Routine risk minimisation measures: • Proposed SPC Section 4.4, Special • warnings and precautions for use Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Bacillus Calmette-Guérin (BCG) disease following live BCG vaccination in infants within utero exposure to adalimumab	Routine risk minimisation measures: • SPC Section 4.6 Fertility, pregnancy, and lactation Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Progressive multifocal leukoencephalopathy (PML)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Reversible posterior Leukoencephalopathy syndrome (RPLS)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Adenocarcinoma of colon in ulcerative colitis (UC) patients	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse

	Additional risk minimisation measures: None	reactions reporting and signal detection: None Additional pharmacovigilance activities: None
	Routine risk minimisation measures: • Proposed SPC Section 4.3 • Contraindications • Proposed SPC Section 4.4, Special • warnings and precautions for use Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none Additional pharmacovigilance activities:

Routine Risk Minimization Measures:

Measures to minimize the risks identified for medicines can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the patient information leaflet PIL and SPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size-the amount of medicine in a pack is chosen to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the public (e.g., with or without prescription) can help minimize its risks.

In addition to these measures, information about adverse events is collected continuously and regularly analyses, including PSUR assessment so that immediate action can be taken as necessary.

Additional Risk Minimization Measure:

1. Patient alert card.

Objectives:

To minimize the occurrence and severity of the following risks:

- Serious infections.
- Tuberculosis (TB).
- Demyelinating disorders (including MS, GBS, and ON).

- Bacillus Calmette-Guérin (BCG) disease following live BCG vaccination in infants within utero exposure to adalimumab.

4.1 Artwork and Trade Name assessment (Artwork available in appendix)

Proposed trade Name	Dosage Form
Abrilada	Solution for Inj.

Look –alike/Sound-alike (LA/SA) Error Risk Potential:

Abrilada name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP Confused Drug Name List, INN International Nonproprietary Names and USAN United States Adopted Names STEM) and the pharmaceutical characteristic of the product:

LA/SA for Product name	SFDA	Shared File/ Excel Sheet	Martindale	Stem Book 2018
Abrilada	NO	NO	NO	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name Abrilada is accepted.

Outer and Inner Package:

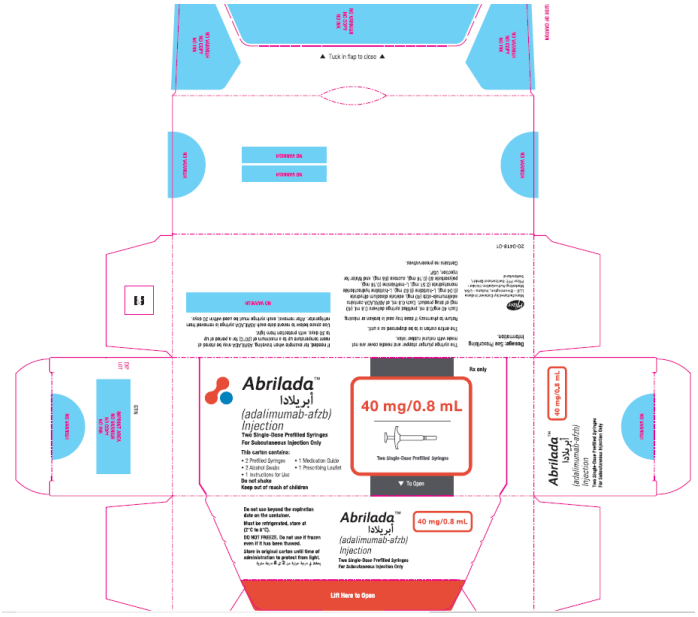
Based on the submitted data, the proposed artwork is accepted.

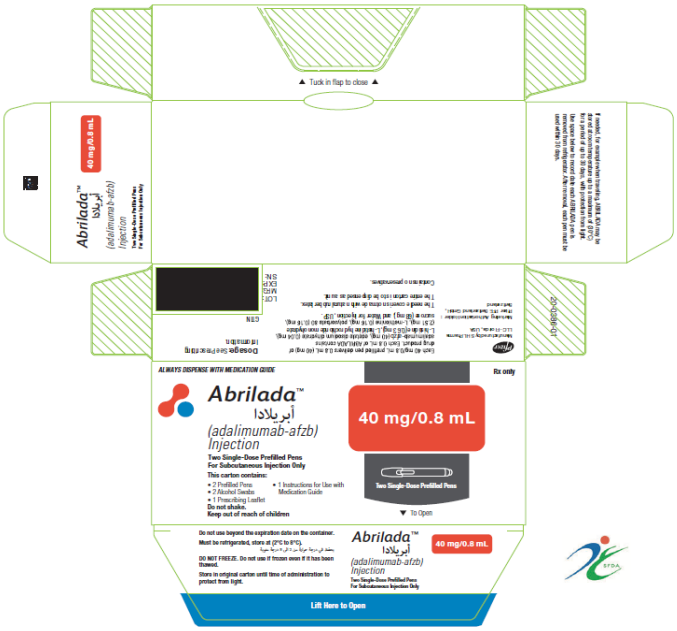
5. Overall Conclusion

Based on a review of data on quality, safety and efficacy, SFDA considered that the benefit/risk profile of Abrilada was favorable and decided to grant the marketing authorization of Abrilada for the treatment of:

- Rheumatoid Arthritis: ABRILADA is indicated for 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. ABRILADA can be used alone or in combination with MTX or other non-biologic DMARDs.
- Juvenile Idiopathic Arthritis: ABRILADA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older. ABRILADA can be used alone or in combination with MTX.
- Psoriatic Arthritis: ABRILADA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. ABRILADA can be used alone or in combination with non-biologic DMARDs.
- Ankylosing Spondylitis: ABRILADA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.
- Adult Crohn's Disease: ABRILADA is indicated for 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. ABRILADA is indicated for 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: ABRILADA is indicated for 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: ABRILADA is indicated for 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. ABRILADA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

6. Appendix


Abrilada™
أبريلادا
(adalimumab-afzb)
Injection
40 mg/0.8 mL
Rx only
Lift Here to Open


Abrilada™
أبريلادا
(adalimumab-afzb)
Injection
40 mg/0.8 mL
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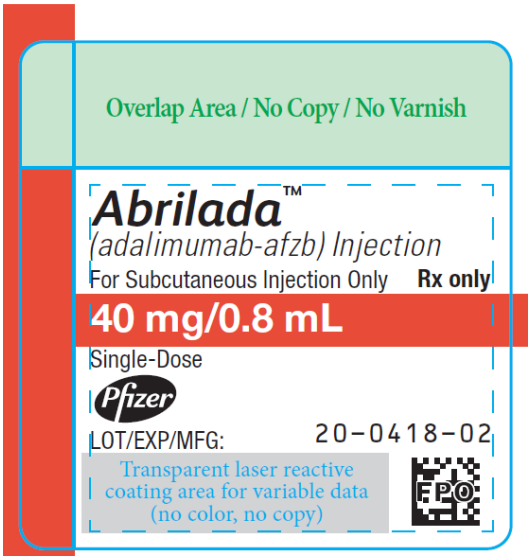
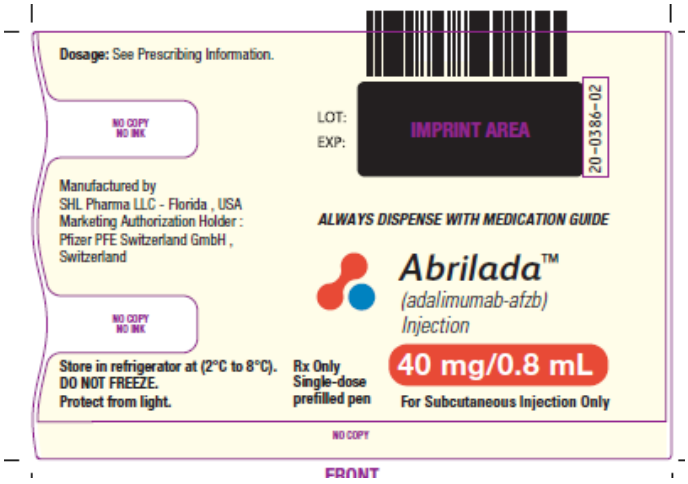
Lift Here to Open


Overlap Area / No Copy / No Varnish
Abrilada™
(adalimumab-afzb) Injection
For Subcutaneous Injection Only
Rx only
40 mg/0.8 mL
Single-Dose
Pfizer
LOT/EXP/MFG:
20-0418-02
Transparent laser reactive coating area for variable data (no color, no copy)


Dosage: See Prescribing Information.
NO COPY NO INK
LOT:
EXP:
IMPRINT AREA
20-0386-02
Manufactured by
SHL Pharma LLC - Florida , USA
Marketing Authorization Holder :
Pfizer PFE Switzerland GmbH ,
Switzerland
ALWAYS DISPENSE WITH MEDICATION GUIDE
Abrilada™
(adalimumab-afzb)
Injection
Store in refrigerator at (2°C to 8°C).
DO NOT FREEZE.
Protect from light.
Rx Only
Single-dose prefilled pen
40 mg/0.8 mL
For Subcutaneous Injection Only
NO COPY
FRONT

The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published in (SDI or Summary Saudi-PAR report).

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa