12 December 2019
EMA/2756/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AMSPARITY

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/004879/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
6-MP	6-mercaptopurine
Δ	delta or change
ACR	American College of Rheumatology
ACR20	20% improvement by American College of Rheumatology definition of improvement criteria
ADA	anti-drug antibody/antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AI	Auto-injector
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}2wk}$	area under the serum concentration-time profile from time 0 to the nominal 2-week time point
AUC_{168}	Area under the concentration-time curve from time 0 to 168 hours postdose
AUC_{inf}	area under the serum concentration-time profile from time 0 extrapolated to infinity
AUC_t and AUC_{last}	area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration
BMI	body mass index
CD	Crohn's disease, Circular Dichroism
CDC	complement dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum observed serum concentration
CPK	creatine phosphokinase
CRP	C-reactive protein
CV	coefficient of variation
DAS28-4(CRP)	Disease Activity Score-28; 4 components based on hs-CRP
DMARD	disease-modifying anti-rheumatic drugs
ECL	electrochemiluminescence
EDTA	edetate dihydrate
ELAM	endothelial cell-leukocyte adhesion molecule
ELAM-1	endothelial cell leukocyte adhesion molecule-1
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of treatment
ET	early termination
EU	European Union
EULAR	European League Against Rheumatism
F	bioavailibility
Fab	fragment antigen binding
Fc	fragment crystallizable
FcRn	fragment crystallizable neonatal receptor
FDA	Food and Drug Administration

FDA-NIH	Food and Drug Administration and National Institutes of Health
g	grams
GLP	good laboratory practices
GMR	geometric mean ratio
HMMS	high molecular mass species
HS	hidradenitis suppurativa
hs-CRP	high sensitivity C-reactive protein
IBD	irritable bowel disease
ICH	International Conference on Harmonisation
ID	identification
IgG/Ig	immunoglobulin G/immunoglobulin
ISR	injection site reaction
ITT	intent-to-treat
IV	intravenous
IWRS	individually weighted residuals
JIA	juvenile idiopathic arthritis
KA	absorption rate constant
kg	kilogram
L	liter
mAb	monoclonal antibody
mg	milligram
min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
MMP	matrix metalloproteinase
MOA	mode of action/mechanism of action
mTNF	membrane bound tumor necrosis factor
MTX	methotrexate
NAb	neutralizing antibody
NIH	National Institute of Health
NK	natural killer
NONMEM	nonlinear mixed effects model
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PFP	prefilled pen
PFS	prefilled syringe
PJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic(s)
PMAR	population modeling analysis report
PP	per protocol
PPK	population pharmacokinetics
PsA	psoriatic arthritis
PsO	plaque psoriasis
PT	preferred term
QA	quality attributes
Q/F	apparent inter compartmental clearence
RA	rheumatoid arthritis
RGA	reporter gene assay
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDAI	simplified disease activity index
SmPC	Summary of Product Characteristics
SOC	system organ class

SPR	Surface Plasmon Resonance
sTNF	soluble tumor necrosis factor
$t_{½}$	terminal elimination half-life/Apparent terminal elimination half-life/terminal half-life
TB	tuberculosis
TEAE	treatment emergent adverse event
TK	toxicokinetic
T_{max}	time of maximum observed serum concentration/Time to reach Cmax
TME	targeted medical event
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
TP	treatment period
TP1	treatment period 1
TP2	treatment period 2
TP3	treatment period 3
UC	ulcerative colitis
µg	microgram
US	United States
UV	uveitis
Vc	central volume of distribution
VCAM-1	vascular cell adhesion molecule-1
Vc/F	apparent volume of distribution of the central compartment
Vp	peripheral volume of distribution
Vp/F	apparent volume of distribution of the peripheral compartment
Vz/F	apparent volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 5 November 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Amsparity, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 July 2017.

The applicant applied for the following indications:

Rheumatoid arthritis

Amsparity in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Amsparity can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Amsparity in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Amsparity can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Amsparity is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Amsparity is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Amsparity is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Amsparity is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

Amsparity is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Amsparity is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Amsparity is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn's disease

Amsparity is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Amsparity is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Amsparity is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Adolescent hidradenitis suppurativa

Amsparity is indicated for the treatment of active moderate to severe hidradenitis suppurativa (HS) (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Uveitis

Amsparity is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric uveitis

Amsparity is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form:
  Humira, 40 mg/0.8 mL, solution for injection
  Humira, 40 mg, solution for injection in pre-filled syringe
  Humira, 40 mg, solution for injection in pre-filled pen
  Humira, 20 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: AbbVie Deutschland GmbH & Co. KG
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers: EU/1/03/256/001; EU/1/03/256/002-005; EU/1/03/256/007-010; EU/1/03/256/022

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form:
  Humira, 40 mg/0.8 mL, solution for injection
  Humira, 40 mg, solution for injection in pre-filled syringe
  Humira, 40 mg, solution for injection in pre-filled pen
  Humira, 20 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: AbbVie Deutschland GmbH & Co. KG
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers: EU/1/03/256/001; EU/1/03/256/002-005; EU/1/03/256/007-010; EU/1/03/256/022

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form:
  Humira, 40 mg, solution for injection in pre-filled syringe
- Marketing authorisation holder: AbbVie Deutschland GmbH & Co. KG
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union

- Marketing authorisation numbers: EU/1/03/256/002-005

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received Scientific Advice on 18 October 2012 (EMEA/H/SA/2416/1/2012/III), 25 April 2014 (EMEA/H/SA/2416/1/FU/1/2014/III), 24 July 2014 (EMEA/H/SA/2416/1/FU/2/2014/II), 28 January 2016 (EMEA/H/SA/2416/1/FU/3/2015/II) and 14 December 2017 (EMEA/H/SA/2416/1/FU/4/2017/III) for the development programme supporting the indication granted by CHMP. The Scientific Advice pertained to the following quality and clinical aspects of the dossier:

Quality: Analytical Methods Panel to use in support of the demonstration of analytical similarity. Cloning and Manufacture of the Master Cell Bank and Working Cell Bank. Comparability plan to support the change of the prefilled syringe used in the different clinical studies.

The main clinical aspects under consideration were:

- The design of the PK trial in healthy volunteers with emphasis in the PK/clearance measurement in the presence of anti-drug antibody and neutralising anti-drug antibody
- The design of the efficacy and safety trial in patients with moderate to severe rheumatoid arthritis including population selected and the primary endpoint, proposed margins and statistical assumptions, duration and safety database. Possibility to switch patients from the innovator product to a biosimilar and its impact on the labelling
- Extrapolation of the clinical results in moderate to severe rheumatoid arthritis to support registration in the other indications approved for the Reference Medicinal Product
- Supportive PK/PD study in either Crohn’s disease or plaque psoriasis to allow extrapolation to the full innovator label
- The design of User testing bridging for a proposed autoinjector
- The possibility to obtain a MA with one single presentation and the consequent label restriction
- The mitigation strategies to maintain the blind of the efficacy study in light of the potential changes in the Reference Product

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Simona Badoi

The application was received by the EMA on	5 November 2018
The procedure started on	29 November 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 February 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	19 February 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 February 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 March 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	23 September 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 October 2019
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	10 October 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	17 October 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	27 November 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Amsparity on	12 December 2019

2. Scientific discussion

2.1. About the product

Adalimumab, the active ingredient of Amsparity (also referred as adalimumab-Pfizer and PF-06410293) is a genetically engineered recombinant human immunoglobulin IgG1 monoclonal antibody, which binds specifically to tumour necrosis factor alpha (TNF-α) and neutralises its biological function by blocking interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration. Adalimumab belongs to the pharmacotherapeutic group "immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors" (ATC code: L04AB04).

Amsparity has been developed as a biosimilar to the reference medicinal product Humira (adalimumab) according to Article 10(4) of Directive 2001/83/EC. All the indications labelled for the EU reference product are claimed for the current biosimilar product, i.e. treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA), active enthesitis-related arthritis, axial spondyloarthritis (ankylosing spondylitis [AS], and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis (PsA), adult and paediatric plaque psoriasis (PsO), adult and paediatric Crohn's disease (CD), ulcerative colitis (UC), adult and adolescent hidradenitis suppurativa (HS), adult and paediatric non-infectious uveitis (UV).

Amsparity is presented as a 0.8 mL solution for injection, containing 40 mg adalimumab, in a single dose pre-filled syringe, pre-filled pen and vial to be administered via subcutaneous (SC) injection. Amsparity is also available as 0.4 mL single dose pre-filled syringe, containing 20 mg adalimumab, to be administered via SC injection.

2.2. Type of Application and aspects on development

This Marketing Authorisation Application is an abridged application for a similar biological medicinal product under Article 10(4) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

Similarity is claimed to Humira (adalimumab) as the reference medicinal product, which has been marketed in the European Union for over 10 years. Humira 40 mg solution for injection in a prefilled syringe was first authorised in the EU on 8 September 2003; the Marketing Authorisation Holder is AbbVie Deutschland GmbH & Co. KG.

For their development, the applicant has applied several guidelines. The most important guidance applied related to the guideline on similar biological medical products (CHMP/437/04 Rev.1), guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) and guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1). In addition to the aforementioned CHMP guidelines the applicant has complied in their development program also with the FDA guidelines to allow global development.

The applicant received CHMP scientific advice for the product development on six occasions pertaining to the quality, non-clinical, and clinical development and one qualification advice on clinical comparative studies of biologic therapies in Rheumatoid Arthritis. The pivotal study and the development programme overall were compliant with CHMP guidance/scientific advice.

The applicant has not applied for a PIP for the current development program, which is acceptable as

this is a biosimilar medicinal product.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a single-use, sterile, preservative-free solution for administration via SC injection containing 40 mg of adalimumab as active substance in 0.8 mL. For paediatric use, the solution contains 20 mg of adalimumab as active substance in 0.4 mL. The final concentration is 50 mg/mL.

Other ingredients are: L-histidine, L-histidine hydrochloride monohydrate, sucrose, disodium edetate dihydrate (EDTA), L-methionine, polysorbate 80 and water for injections.

The product is available in four presentations: single use vial (type I glass), fitted with rubber stoppers, aluminium crimps and flip off seals; single use pre filled syringe (type I glass) with a rubber plunger stopper and a needle with a needle shield for adult and paediatric use; single use pre filled pen containing a pre filled syringe. The syringe inside the pen is made from type 1 glass with a rubber plunger stopper and a needle with a needle shield.

Amsparity is developed as a biosimilar to Humira (adalimumab, AbbVie Deutschland GmbH & Co. KG).

2.3.2. Active Substance

General information

The active substance (INN: adalimumab, manufacturer's code PF-06410293) is an IgG1 kappa monoclonal antibody (mAb) expressed in Chinese Hamster Ovary (CHO) cells with two identical heavy (H) chains and two identical light (L) chains, covalently linked with four inter-chain disulfide bonds. The N-linked glycosylation consensus sequence, NST, in the CH2 region is essentially fully occupied with asialo, core-fucosylated, complex-type biantennary N-linked glycans with zero or one terminal galactose residue, abbreviated as G0F and G1F, respectively. The active substance is capable of binding to human TNF in a dose dependent manner and neutralizing its effects. TNF is a naturally occurring cytokine that promotes normal inflammatory and immune responses when bound to its receptor. However, overexpressed TNF-α has been implicated in numerous autoimmune diseases. Blocking the TNF receptors results in the inhibition of pro-inflammatory pathways leading to decreased cytokine release and reduced inflammatory cell infiltration.

Manufacture, characterisation and process controls

Manufacture and quality control (QC) testing of the active substance occurs at Wyeth BioPharma, Andover, MA, USA, which is authorized according to current GMP regulations.

Description of manufacturing process and process controls

Adalimumab active substance manufacturing process has been adequately described. The production cell line is a Chinese Hamster Ovary (CHO) cell line.

The manufacturing process for the active substance includes steps for fermentation, harvest, purification with a series of chromatography, viral inactivation/filtration and ultra-/diafiltration steps.

The formulated active substance is stored and transported under appropriate conditions. There are two possible reprocessing steps (the virus reduction filtration and final filtration). Reprocessing conditions are appropriately described. The manufacturing process, with process controls, has been clearly outlined in flow-diagrams. Overall, the manufacturing process has been adequately discussed in the dossier. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. Process parameters and controls have been appropriately presented and appropriate justification and clarification have been provided for the assignment of process parameters and their criticality. A detailed description of the container closure system is provided. Extractable/leachable and toxicological assessment studies have been performed to identify possible safety risks. The proposed container closure system is considered adequately qualified and suitable for storage of the active substance.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been provided. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Recombinant CHO cells expressing the monoclonal antibody adalimumab were established by transfection of the expression vector followed by genetic selection. Generation and testing of the expression vectors were described. A two-tiered cell banking system for Master Cell Banks (MCB), WCB and end-of-production cells (EOP) is in place. The CHO-cells are well characterised and are established according to ICH Q5A, ICH Q5B and Q5D guidelines. The cell banks are tested to be free from adventitious agents. The limit of in vitro cell age is determined and genotypic and phenotypic stability of the recombinant cell line at the limit of cell age is demonstrated. A protocol is presented for the preparation, qualification and storage of renewal of working cell banks, thus no variation is expected when a new WCB is established.

Control of critical steps and intermediates

The in-process controls, including process parameters and material attributes with acceptable ranges and in-process tests with control limits as well as the targets and normal operating ranges (NORs) for manufacturing of the active substance have been presented with their classification as critical or non-critical.

Overall, the presented process controls are deemed appropriate, and the Applicant has appropriately described the regulatory procedures (i.e. variation procedures) foreseen in case of changes introduced into IPTs. Actions taken if limits are exceeded are specified. The overall control strategy is considered satisfactory and is clearly linked to critical quality attributes (CQAs).

Process validation

The intended commercial manufacturing process for the adalimumab active substance has been validated at the intended commercial scale. The manufacturing process has been validated adequately, including removal of product- and process-related impurities, inactivation/removal of viral and adventitious agents, process intermediate hold time studies, chromatography column resin lifetime studies, UF/DF membrane re-use cycles, media and buffer hold time studies, reprocessing, and shipping qualification. Consistency in production has been shown on four independent full-scale batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests were fulfilled demonstrating that the purification process consistently produces

adalimumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

The adalimumab active substance manufacturing process was developed using the Applicant's preferred CHO host cell line and mAb cell culture and purification processes. The Applicant has employed the intended commercial process already at the earliest stages of development and all batches used for nonclinical and clinical studies were manufactured at the intended commercial launch site using the intended commercial process. Only minor changes) were introduced to the process during development to support consistency of the process. The implemented changes can be considered minor optimization to the process and the provided evidence on comparability of the processes is considered sufficient.

Characterisation

The adalimumab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of an IgG1-type antibody.

The characterisation of adalimumab active substance involved determination of structure (primary, secondary, and higher-order), post-translational modifications (N-linked glycans, disulfide bonds), charge variants, aggregation and fragmentation, and biological activity. These studies are discussed in the Section for Biosimilarity as the characterisation studies are also part of biosimilarity assessment. In order to better understand possible degradation pathways of the active substance forced degradation studies for the active substance and finished product were performed. In general, the studies included in the characterization are considered relevant and comprehensive. In addition, the Applicant has clarified that no evidence of O-glycans or meaningful levels of potentially immunogenic glycan structures was observed in the active substance.

Specification

The set of agreed specifications includes tests for appearance, protein concentration, identity, purity and impurities, biological activity and microbiological tests.

All test parameters proposed to be included in the adalimumab active substance specification have been discussed separately and justification and historical data has been provided for each parameter. Overall, the test parameters proposed to be included in the adalimumab active substance specification are considered relevant and in line with current guidance.

Most of the tests included in the release specification are also part of the shelf life specification. No differences in the acceptance criteria are foreseen.

Analytical methods

Appropriate method descriptions have been provided for all analytical methods. In general, validation for all methods has been performed adequately following ICHQ2 (R1). All predetermined validation acceptance criteria were met and all methods were considered validated for their intended use. For microbiological testing validation results are presented and these meet the requirements set in the Ph. Eur.

Batch analysis

Batches of active substance used for development studies, nonclinical studies, clinical studies, stability, and produced during process validation have been appropriately listed. Batch analyses data was

provided for development batches, Clinical Inventory/ Stability Batches and Clinical Inventory/ Process Validation Batches. The results are all within the pre-defined specifications and confirm consistency of the manufacturing process.

Reference materials

The reference standards used throughout the product development have been adequately described. The Applicant has established a two-tiered system for in-house reference material involving primary and working reference standards.

The characterisation tests and analytical procedures for establishing a new WRM were provided.

Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container when stored at the recommended storage condition.

The stability program has been designed following relevant ICH guidelines. The analytical procedures used in the stability monitoring program have been validated and their stability indicating properties have been confirmed. Most attributes, test methods and acceptance criteria in the shelf-life specification are identical to those in the release specification.

Real time stability data at long term conditions, stability data at accelerated conditions, and supportive stability data, were provided on an adequate number of batches. The data indicate that there have been no significant changes in terms of quality, purity or potency for the active substance when stored at the long term and accelerated conditions. All results were within the acceptance criteria.

Testing under stressed conditions (thermal stress and photostability stress) were also completed. The Applicant has demonstrated that the product is photolabile. The applicant has committed to complete the ongoing stability studies according to the submitted protocol. Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA

Comparability exercise for Active Substance

N.A.

2.3.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is supplied as a sterile, clear, colourless solution for subcutaneous injection administration containing adalimumab (50 mg/mL) as active substance, L-histidine and L-histidine HCl Monohydrate (buffering agents), sucrose (tonicifier), edetate disodium dihydrate (chelator), L-methionine (stabilizer), polysorbate 80 (surfactant) and water for injection (solvent).

The Amsparity solution for injection is provided in four different presentations: Vial 40 mg/0.8 mL; two prefilled syringes (PFS): 40 mg/0.8 mL and 20 mg/0.4 mL; and Prefilled Pen or auto-injector (PFP or AI) 40 mg/0.8 mL. The PFP encloses an Amsparity 40 mg/0.8 mL PFS.

The finished product does not contain any overages. Each prefilled syringe contains an overfill to assure the nominal dose is delivered.

All excipients are established pharmaceutical ingredients of compendial grade, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

Pharmaceutical development

The intent of adalimumab finished product development was to obtain a product that is both pharmaceutically acceptable and highly similar to the reference adalimumab product on a global basis. As there are five presentations of the reference adalimumab product available across various regions, this involved developing a single active substance that could be used to manufacture any of the finished products: 10, 20, 40 mg PFS, 40 mg vial and a 40 mg PFP. The formulation development program evaluated the active substance in multiple buffer and pH conditions and evaluated additional excipients to determine if the excipients are effectively stabilizing the active substance. The formulation development has been presented in detail, and the differences in the chosen formulation in respect to the originator have been presented.

The manufacturing process development has been described in detail. All finished product presentations have been manufactured at the intended commercial manufacturing facility and scale for the entirety of the clinical development program. The formulation composition and protein concentration have remained the same throughout development for all presentations. The 40 mg prefilled syringe manufactured at the intended commercial scale was used in clinical studies, along with the 40 mg prefilled pen.

The primary packaging is: a) single-use vial (type I glass), fitted with rubber stoppers, aluminium crimps and flip-off seals; b) single-use pre-filled syringe (type I glass) with a plunger stopper and a needle with a needle shield; c) single-use pre-filled pen containing a pre-filled syringe. The syringe inside the pen is made from type 1 glass with a plunger stopper and a needle with a needle shield. The primary packaging materials comply with Ph. Eur. and EC requirements. The choice of the container closure systems has been validated by stability data and is adequate for the intended use of the product.

The finished product PFP is defined as a medicinal product under Directive 2001/83/EC, as amended, as the device component forms a single integral product intended exclusively for use in combination with the PFS. Design changes to the pen and instructions for use (IFU) made during development have been presented. The Applicant presents evidence that retesting of finished product quality attributes for the finished product PFP release and PFP stability studies is not required when the testing is already performed on the corresponding PFS component of the PFP. This is considered acceptable.

Quality attributes relevant to the finished product were assessed using risk management principles for criticality for the finished product quality and for relevance to similarity within the context of the finished product target for development.

The Quality Target Product Profile (QTPP) was developed, including the product attributes relevant to similarity and expectations for pharmaceutical acceptability. The QTPP describes the finished product in terms of quality characteristics to be achieved at the end of the manufacturing process.

Manufacture of the product and process controls

The finished product manufacturing process has been satisfactorily described. It is a non-standard aseptic process normally associated with biological product manufacture. Manufacture includes formulation and fill finish activities. The material is sterile filtered, filled and sealed. has been satisfactorily described.

Clear step-by-step descriptions and flow charts of the Amsparity finished product manufacturing processes including IPCs were provided for all presentations and are considered appropriate overall.

The finished product PFP is manufactured using the PFS 40 mg. The intended manufacturing activities used to produce the final finished product PFP are simple assembly operations similar to existing processes for other pen delivery systems and are designed to ensure no impact to the PFS container closure integrity. The description of PFP manufacturing process is appropriate.

Finished product manufacturing process controls and control limits for relevant manufacturing steps. The finished product (vial and PFS presentations) manufacturing process has been validated. The validation studies for the vial and PFS presentations included: manufacturing process validation, hold times validation, aseptic filling procedure validation and shipping validation. . Overall, the finished product manufacturing process can be considered successfully validated and it can be concluded that it is capable of consistently producing sterile finished product as demonstrated by the manufacture of full scale finished product lots, all meeting the established acceptance criteria.

The validation studies for Amsparity PFP included process validation and shipping validation. The PV lots met the predetermined protocol acceptance criteria demonstrating that the assembly process produces Amsparity PFPs of consistent quality. Sufficient information of the PFP process validation has been provided.

Product specification

The specifications for Amsparity vials, PFS and PFP for intended commercial batch release include compendial and non-compendial assays: appearance, protein concentration, identity tests, purity and impurity tests, biological activity and other general tests.

The non-compendial analytical procedures used for batch release and stability studies, are largely common to both the active substance and finished product and have been described and discussed.

Overall, the batch data and justification of specification support the proposed acceptance criteria set for the specifications. The proposed specifications for Amsparity PFP include demonstrating appropriate functional performance. The batch data supports the proposed acceptance criteria set for the specifications.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data on batches of the finished product at the intended commercial scale, and including clinical batches, were provided for all presentations. The results are within specifications and confirm consistency of the manufacturing process.

Reference materials

The reference materials used for analysis of Amsparity finished product are the same as those used for the active substance.

Stability of the product

Based on available stability data for the PFS and vial a proposed shelf-life of 36 months, when stored protected from light, at the recommended temperature of 2 to 8 °C as stated in the SmPC is

acceptable. Similarly, on the basis of the available stability data for the PFP, a proposed shelf-life of 36 months when stored at 2 to 8 °C for the PFP is agreed.

A single Amsparity pre-filled syringe / pre-filled pen / vial may be stored at temperatures up to a maximum of 30°C for a period of up to 30 days. The pre-filled syringe / pre-filled pen / vial must be protected from light and discarded if not used within the 30-day period. This is supported by the accelerated and thermal cycling stability data provided.

The stability program has been designed following relevant ICH guidelines. The analytical procedures used in the stability monitoring program have been validated and their stability indicating properties have been confirmed. The parameters tested are largely the same as for release.

Real-time/real condition stability data, accelerated stability data and thermal stress study data were provided.

The Applicant has provided data that indicate that the product is photolabile. The Applicant has demonstrated that the design of the PFP, its final assembly, labelling and packaging processes, have no impact on the PFS and finished product quality. Therefore, the results and conclusions from the stability studies on the PFS are considered applicable to the quality of the finished product when stored in the PFP and used to set the overall shelf life claim of the PFP itself.

The applicant has committed to complete the ongoing stability studies according to the submitted protocol. In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Comparability exercise for finished medicinal drug product

N.A.

Adventitious agents

The Applicant has addressed both non-viral and viral contaminants.

In the intended commercial manufacturing process no material from animal or human origin is used and hence the risk of TSE contamination from the raw materials used is considered to be negligible.

The CHO cell line used for the production is well characterised. MCB, WCB and EPC have been characterised for the absence of contaminating viruses according to ICHQ5A and CPMP/BWP/268/95. Tests for viruses as well as sterility and mycoplasma have been conducted for the cell banks. A virus validation study was performed according to CPMP/BWP/268/95. Viruses for the clearance studies can be considered to represent a wide range of physico-chemical properties that demonstrates the ability of the system to eliminate viruses in general.

GMO

N.A.

Biosimilarity

The Applicant has performed an extensive comparability analysis to demonstrate biosimilarity to the reference product Humira (adalimumab, AbbVie Deutschland GmbH & Co. KG) in line with the current guidance.

Batches included

Sufficient Humira-US and Humira-EU finished product lots were purchased to support the demonstration of biosimilarity. The Applicant has provided appropriate summary tables with all Amsparity finished product batches used for demonstrating biosimilarity in quality, non-clinical, and clinical studies.

For the biosimilarity analysis, the company performed a comparability exercise including Amsparity versus Humira (EU) and Humira (US). The evaluation of the analytical biosimilarity is based on the comparison with Humira (EU) batches.

Comparability criteria

Statistical analysis was applied to attributes with moderate to very high level of potential impact to support assessment of results, and generally included assays that evaluate clinically relevant mechanism(s) of action (MoA) of the product for each indication for which approval is sought and attributes that could impact these MoA.

Method qualification

Descriptions of analytical methods data have been provided for all methods used for characterisation of the biosimilar product. Validation data is provided for the methods used also for routine release testing. In addition, qualification reports for biological assays have been provided. In general, the assays are qualified for accuracy, intermediate precision, linearity, and range. In addition, some of the assays have been qualified for specificity, and the controls used are appropriate.

Summary of results

Results from the biosimilarity exercise as presented by the Applicant are provided in Table 1 including attributes studied, analytical procedures and conclusions. Critical evaluation of biosimilarity is provided below the summary table.

Table 1 Summary of similarity conclusions

Attribute	Analytical Procedure	Similarity Conclusion
Primary Structure and Posttranslational Modifications	LC/MS/MS – Peptide Mapping with specialized bioinformatics	Identical amino acid sequence
	Peptide Mapping/ Edman Degradation	
	SEC/ESI MS	Highly similar molecular mass and posttranslational modifications at the intact molecule level
	LC/MS – Subunit Analysis	Highly similar identity and location of posttranslational modifications at the subunit/domain level
	LC/MS and LC/UV – Peptide Mapping (Lys-C)	Highly similar identity and location of posttranslational modifications at the peptide level
TNF binding to Fab domain	Inhibition of apoptosis assay	Highly similar dose-response curves and relative potency
	Binding to Target Antigen (sTNF)	Highly similar dose-response curves and relative potency
	Binding to Cell Surface Target Antigen (mTNF) by Flow Cytometry	Highly similar dose-response curves and relative % EC50
	Inhibition of TNF-induced ELAM-1 expression	Highly similar dose-dependent response curves and relative % EC50

Attribute	Analytical Procedure	Similarity Conclusion
	Binding ELISA	Lack of binding to LT-a confirmed
	Reverse signaling assay	Highly similar dose-response curves and % relative EC50
Effector function via Fc domain	Inhibition of T cell Proliferation in Mixed Lymphocyte Reaction (MLR) Assay	Highly similar dose-response curves
	Primary NK Cell ADCC Assay (158 V/V)	Highly similar dose-response curves and relative % EC50. Minor mean shift observed in PF-06410293 results was not observed in any other ADCC-related assays.
	PBMC ADCC assay (158 V/V)	Highly similar dose-response curves and relative % EC50
	PBMC ADCC assay (158 V/F)	Highly similar dose-response curves and relative % EC50
	PBMC ADCC assay (158 F/F)	Highly similar dose-response curves and relative % EC50
	FcγRIIIa Reporter Gene Assay	Highly similar dose-response curves and relative % EC50
	Binding to FcγRIIIa 158V by SPR	Highly similar sensorgrams and relative % Kd
	Binding to FcγRIIIa 158F by SPR	Highly similar dose-response curves and relative % EC50. Small mean shift in PF-06410293 due to small differences in relative % Kd resulting from small differences in ka, kd and Kd for PF-06410293 is not considered clinically relevant as no impact is observed on *in vitro* ADCC assays.
CDC Activity	CDC Assay	Highly similar dose-response curves and relative % EC50
	C1q ELISA assay	Highly similar dose-response curves and relative % EC50
Relevant to PK: FcRn Binding	Binding to FcRn by SPR	Highly similar SPR sensorgrams and relative % Kd
Not Relevant to MoA: Fcγ Receptor Binding	Binding to FcγRI, FcγRIIa, FcγRIIb, and FcγRIIIb, by SPR	Highly similar binding affinity and kinetics
N-Linked Glycan Structure: Total Afucosylation	HILIC	Significant overlap in total afucosylation levels. Mean afucosylation for PF-06410293 was slightly lower than adalimumab-US and adalimumab-EU. This observation is not considered clinically significant as no impact is observed in the *in vitro* assays associated with the ADCC mechanism of action.
N-Linked Glycan Structure: Terminal Galactosylation	HILIC	Significant overlap in terminal galactosylation levels for PF-06410293, adalimumab-US and adalimumab-EU. The maximum terminal galactosylation level of PF-06410293 was slightly higher than adalimumab-US and adalimumab-EU. Minor differences in terminal galactosylation are not considered clinically significant as no impact is observed in the binding and *in vitro* assays associated with the CDC mechanism of action.

Attribute	Analytical Procedure	Similarity Conclusion
N-Linked Glycan Structure: High Mannose	HILIC	High mannose levels in all PF-06410293 lots were lower than the licensed product. Minor differences in high mannose N-linked glycans are not considered clinically significant, low levels of high mannose are present in all products and PK similarity between PF-06410293, adalimumab-US and adalimumab-EU was demonstrated in the B5381007 clinical study.
N-Linked Glycan Structure: Sialylation	HILIC/MS	Highly similar, trace levels of sialylated N-linked glycans
N-Linked Glycan Structure	HILIC/MS	Highly similar relative proportions of major and minor level N-linked glycans
	Exoglycosidase Digestion/HILIC	Highly similar N-linked glycan structural assignments and glycosidic linkages
	Sialic Acid Assay	Highly similar, predominant sialic acid is NeuAc
Charge Heterogeneity: Acidic Species	iCE	Highly similar, significant overlap observed in acidic species levels.
Charge Heterogeneity	CEX-HPLC profile characterized by MS	Highly similar major and minor charge isoform species
	CEX-HPLC profile characterized for biological activity	Highly similar biological activity for each charge isoform species
	Carboxypeptidase B/CEX-HPLC	Highly similar charge isoform profile after removal of C-terminal lysine
Product Purity: Monomer	SE-HPLC	Highly similar, significant overlap observed in monomer levels
Product Purity: HMMS	SE-HPLC	Highly similar levels of HMMS species
Product Purity: Fragments	CGE (reducing)	The fragments level in PF-06410293 was observed to be lower than that of adalimumab-US and adalimumab-EU. A lower level of this product-related impurity is not clinically significant and is supportive of high similarity.
Product Purity: Intact IgG	CGE (Non-reducing)	Highly similar intact IgG content
Product Purity: SDS-PAGE	SDS-PAGE	Highly similar banding patterns
Disulfide Bonds	Sulfhydryl Analysis	Highly similar trace level of unpaired protein sulfhydryl groups
	LC/MS – Non-reduced Peptide Mapping (Lys-C)	Identical disulfide bond connectivity
Higher Order Structure	Far-UV Circular Dichroism (CD) Spectroscopy	Highly similar secondary structure
	Fourier Transform Infrared (FTIR) Spectroscopy	
	Near-UV CD Spectroscopy	Highly similar tertiary structure

Attribute	Analytical Procedure	Similarity Conclusion
	Intrinsic Fluorescence Emission Spectroscopy	
	Differential Scanning Calorimetry (DSC)	Highly similar thermal stability of higher order structure
	X-ray Crystallography	Highly similar crystal structures
Protein Concentration	UV spectroscopy	Highly similar protein concentration
Degradation Profile	SE-HPLC, iCE, CGE (reducing and non-reducing), cell-based bioassay, UV spectroscopy, LC/MS –Peptide mapping (Trypsin), LC/MS/MS – peptide mapping (Lys-C/trypsin),	Highly similar degradation profiles.

Critical evaluation of analytical biosimilarity

On the quality level, a comprehensive biosimilarity exercise has been performed following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012). The comparability exercise is mostly based on comparison of analytical characterization data collected during the years of pharmaceutical development. For most quality attributes, a high degree of similarity has been demonstrated.

A high degree of similarity between Amsparity and Humira-EU can be demonstrated using the following quality attributes:

- Primary structure
- Higher order structure
- Dimers, aggregations, and fragments
- Glycosylation, with the exception of total afucosylation/high mannose variants
- Charge variant profile
- Binding to both sTNF and mTNF
- C1q binding and CDC activity.

For the following quality attributes minor differences between Amsparity and Humira-EU are not expected to have significant clinical impact, however further justification and/or control was requested:

- The levels of high mannose variants differ. Based on Applicant's discussion and previous knowledge on other anti-TNF antibodies, it was agreed that the minor difference between Amsparity and Humira-EU high mannose levels is not expected to have clinical impact.
- Lower level of ADCC function correlating with lower levels of total afucosylation. This trend was not as visible in the assays that are most representative of the physical situation.

- In addition to discussion on the structure function relationships, new data on ADCC activity has been provided during the procedure. ADCC PBMC assay was performed on the V/V high affinity binding genotype. A similar trend of lower ADCC activity was observed with healthy donor PBMC V/V cells. Mostly the results are overlapping and can be accepted.
  In addition, an ADCC assay was performed also on IBD patient donor cells and the results are discussed in the non-clinical section.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The data provided support biosimilarity versus the EU reference medicinal product (Humira (EU)) at the quality level. In addition, the non-EU comparator (Humira (US)) used in pivotal clinical trials has been shown to be representative of the EU reference medicinal product.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation(s) for future quality development

N.A.

2.4. Non-clinical aspects

2.4.1. Introduction

Adalimumab used in the nonclinical studies was produced using the intended manufacturing process at the intended commercial sites and scale and represents the intended commercial product. Humira-EU 40 mg/0.8 mL solution for injection was used as a reference product. In addition, Humira-US has been used in the studies for the globally harmonised development purposes.

The nonclinical studies comprised the comparative battery of *in vitro* analyses of biological activity and a GLP-compliant 1-month repeated dose toxicity and toxicokinetic study in cynomolgus monkeys. The nonclinical *in vivo* testing strategy was designed to meet the requirements for a global development strategy.

The nonclinical development of Amsparity (PF-06410293, adalimumab-Pfizer) was done in accordance with the "Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" (EMEA/CHMP/BMWP/403543/2010) and the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

2.4.2. Pharmacology

Adalimumab is a recombinant fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) which binds to TNF and inhibits its interaction with the p55 and p75 cell surface TNF receptors, thereby neutralising the effect of TNF found in inflammatory conditions.

It is an IgG1 kappa antibody that binds, via the variable region complementarity determining regions, to both soluble TNF (sTNF) and transmembrane TNF (mTNF) with high avidity. The primary mechanism of action is binding of the fragment antigen binding (Fab) domain of adalimumab to sTNF. This results in disruption of TNF ligand-receptor signalling and inflammatory cascade, with downstream down-regulation of adhesion molecule expression and a reduction of inflammatory cell infiltration. This mechanism of action is applicable across all disease indications.

To support the biosimilarity between adalimumab-Pfizer and the reference product Humira-EU (but also Humira-US), the *in vitro* pharmacology of adalimumab-Pfizer was assessed with respect to its Fab and fragment crystallizable (fc)-based biological activity in a number of functional and binding assays.

The *in vitro* functional characterisation data are summarised in Table 1. The Fab-related functions including inhibition of TNF-induced apoptosis and endothelial leucocyte adhesion molecule-1 (ELAM-1) expression, binding to soluble and membrane bound TNFα, and reverse signalling indicate similar activity of Amsparity and Humira-EU (and Humira-US). Fc-related functions were comparatively assessed by ADCC and CDC assays and complemented with binding assays for the FcγRIa, FcγRIIa, FcγRIIIa and b, FcRn and C1q. The binding and functional activity was similar for Amsparity and Humira-EU in regards of the binding to FcγRIa, FcγRIIa, FcγRIIIb, FcRn and C1q, and CDC activity. In addition, Amsparity and Humira-EU showed similar inhibition of T-cell proliferation regardless of FcγRIIIa genotype of PBMCs.

Therefore, results from these assays demonstrated that adalimumab-Pfizer was similar to Humira-EU (and also Humira-US).

Stand-alone safety pharmacology studies were not conducted and are not required. Cardiovascular endpoints and respiration rate were evaluated in cynomolgus monkeys in the repeat dose toxicity study with adalimumab-Pfizer and Humira-EU. There were no treatment-related changes.

In vivo pharmacodynamics, secondary pharmacodynamics and pharmacodynamic drug interaction studies were not conducted and are not required.

2.4.3. Pharmacokinetics

Comparative toxicokinetic data were obtained from a 1-month repeat-dose toxicity study in cynomolgus monkeys receiving weekly SC dosing of 157 mg/kg of PF-06410293 or Humira-EU (see toxicology section 2.4.4. below).

The absence of studies evaluating the distribution, metabolism, excretion and pharmacokinetic drug interactions is consistent with CHMP guidance (Guideline on similar biological medicinal products containing monoclonal antibodies, EMA/CHMP/BMWP/403543/2010).

2.4.4. Toxicology

Toxicokinetic (TK) and anti-drug antibody (ADA) evaluations in male and female cynomolgus monkeys were conducted in support of a 1-month SC repeat-dose toxicity study with adalimumab-Pfizer and Humira-EU.

Animals received a weekly SC dose of 157 mg/kg of PF-06410293 or Humira-EU and respective vehicles. Dose selection was based on the high dose used for the 4-week study in cynomolgus monkeys for the reference product Humira. The adalimumab active substance used in the toxicity study was manufactured using the same process that is intended for market supply and is therefore representative of the intended final manufacturing process.

Comparable safety profile was demonstrated. Microscopic findings in the spleen consisted of minimally decreased cellularity of lymphoid follicles and germinal centers, which corresponded with immunohistochemistry findings of decreased CD21, IgG, and IgM positive cells. These findings were similar in incidence and severity in PF-06410293 and Humira-EU treated animals, and were consistent with previously reported expected pharmacologic activity of adalimumab in cynomolgus monkeys. The TK profiles were comparable, but there was a tendency for higher exposures (AUC_{168} and C_{max}) in animals treated with PF-06410293 in comparison to Humira-EU on day 22. The exposures were approximately 1.2–fold higher in PF-06410293 treated animals. The low number of animals/group is however limiting the value of the study to draw further conclusions.

Adalimumab-Pfizer did not elicit anti-drug antibody formation in treated monkeys. One ADA-positive animal was reported in the Humira-EU treated group. The analytical methods (ELISA) employed for determination of adalimumab concentration in the cynomolgus monkey serum were sufficiently validated. However, the ECL assay for determination of anti-adalimumab antibodies in the monkey samples may have underestimated the ADA positivity due to the drug interference and may not have fitted the purpose. Consequently, the data do not allow drawing conclusions on the similarity or dissimilarity of PF-06410293 and Humira-EU on triggering the ADA formation in cynomolgus monkeys.

Overall, these differences did not affect the safety profile of PF-06410293 in comparison to Humira-EU

Nonclinical reproductive and developmental toxicity, genotoxicity, and carcinogenicity studies were not conducted as these are not warranted when the proposed product and the reference product have been demonstrated to be highly similar through extensive structural and functional characterization and animal toxicity studies.

2.4.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) consisted in a justification for not submitting ERA studies. The active substance is a natural substance, a protein, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, adalimumab is not expected to pose a risk to the environment. This is in accordance with the CHMP Guideline on the environmental risk assessment of Assessment report EMA/CHMP/559383/2017 Page 25/111 medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.4.6. Discussion on non-clinical aspects

The characterisation studies of Fab-related functions indicate similar activity for Amsparity and Humira-EU. However, there were some differences observed in the antibody-dependent cell-mediated cytotoxicity (ADCC) activity in primary NK-cells. Although the ADCC activity effector functions are not considered to play a major role in the functionality of adalimumab, triggering of the ADCC can be mediated by the membrane bound TNF. There were some analytical differences observed in the high mannose content and afucosylated species between the adalimumab-Pfizer and Humira-EU. Lower afucosylated species content range was reported in adalimumab-Pfizer in comparison to Humira EU. In the comparative ADCC study in primary NK cells (high affinity genotype) the adalimumab-Pfizer lots were located in the lower activity range of the reference product, and the Humira-EU to the upper

range. This could be interpreted that adalimumab-Pfizer triggered less ADCC response in primary NK cells than Humira-EU. Further ADCC assays were conducted in peripheral blood mononuclear cells (PBMCs). These studies indicated similar ADCC activity in PBMCs, which in general could be considered more representative of physiological condition but is also less sensitive than the studies in NK-cells. The reporter gene assay (RGA-assay) was employed using stable Jurkat cell line expressing FcγRIIIa for analysing the similarity of triggering the early steps of ADCC pathway. In this study, adalimumab-Pfizer and Humira-EU can be considered similar in regards of triggering the early steps in ADCC pathway. There were also small differences in the FcγRIIIa –binding activities but these were not in line with the ADCC activity findings.

In order to test the potential functional effects of differences noted in high mannose N-glycan content between the adalimumab-Pfizer and Humira-EU, cellular uptake of adalimumab-Pfizer and Humira-US into rat alveolar macrophages was investigated in the absence and presence of mannan. It has been reported that therapeutic IgGs containing high-mannose glycans in the Fc region are cleared more rapidly in humans than other glycan forms. The differences in high mannose glycan species could in principle impact pharmacokinetics via differential clearance through binding to mannose-binding receptors and ADCC function through binding to FcγRIIIa. However, the uptake was similar for adalimumab-Pfizer and Humira-US. The excess mannan did not significantly inhibit the adalimumab-Pfizer or Humira-US uptake to the rat alveolar macrophages, and it was concluded that the mannose receptor was not the major receptor mediating the adalimumab cellular uptake. However, the relevance of the assay for characterisation of potential functional effects of high mannose N-glycan content differences in adalimumab-Pfizer and Humira-EU is considered low.

In conclusion, the functional characterisation studies implicated similar Fab-related activities for adalimumab-Pfizer and Humira-EU, and revealed some differences in the ADCC effector functions in primary NK-cells. In light of the pharmacokinetic differences seen between adalimumab-Pfizer and Humira-EU during the evaluation, the difference in high mannose variant and total afucosylation levels needed further discussion. The applicant was asked to further discuss the clinical impact of the observed differences in the ADCC activity and total afucosylation species content and high mannose variants between adalimumab-Pfizer and Humira-EU to serve as part of the scientific justification for extrapolation for the IBD indications, for which, the effector functions are plausible mechanisms of action of adalimumab. This question overlapped with Quality concerns. In their response, the applicant provided data from the *in vitro* ADCC PBMC assay comparing the adalimumab-Pfizer, Humira-US and Humira-EU activity using effector cells from IBD-patient donors.

Quantitative comparison of the results could not be done due to the low signal to noise ratio (possibly related to the lowered ADCC response of the IBD-patient donor cells). However, no meaningful differences between the adalimumab-Pfizer and Humira-EU (or Humira-US) in triggering the ADCC response in the IBD patient cells was noted. The clinical impact of high mannose content on the PK was clarified and is expected to be minor. It was estimated (extrapolation of the Goetze experimental data) that the decrease in the AUC for the Humira-EU and Humira-US would range from 2.1 – 2.3%, while the decrease for adalimumab-Pfizer would be ~0.4%. Thus, it can be concluded that the differences in high mannose, and its impact on the PK of adalimumab, is not expected to be significant.

In conclusion, from the nonclinical point of view, the clinical impact of the observed differences in the ADCC activity and total afucosylation level and high mannose variants between adalimumab-Pfizer and Humira-EU is solved.

There was a tendency for higher exposures (1.2 –fold higher AUC168 and Cmax) in animals treated with adalimumab-Pfizer in comparison to Humira-EU on day 22. The low number of animals / groups is however limiting the value of the study to draw further conclusions. Furthermore, these differences did

not affect the safety profile of adalimumab-Pfizer in comparison to Humira-EU. Comparable safety profile was demonstrated.

The assay for determination of anti-adalimumab antibodies may not have fitted the purpose and may have underestimated the ADA positivity due to drug interference in the monkey serum samples. Consequently, the data do not allow drawing conclusions on the similarity or dissimilarity of adalimumab-Pfizer and Humira-EU on triggering the ADA formation in cynomolgus monkeys. However, this is not further pursued from the nonclinical side taking into consideration the small number of animals in the study and comparable safety characteristics. The pharmacokinetics has been evaluated in patients in the biosimilarity programme (see Clinical aspects 2.5.).

2.4.7. Conclusion on the non-clinical aspects

During the evaluation, no major objections were identified in the nonclinical part of the dossier. The applicant clarified the differences identified in the high mannose and afucosylation levels, which could possibly reflect differences in the ADCC activity (as tested in the NK cells) and justify the lack of impact in extrapolation to all indications (e.g. IBD). It could be concluded, that there were no meaningful differences between the adalimumab-Pfizer and Humira-EU (or Humira-US) in triggering the ADCC response in the IBD patient cells. The clinical impact of high mannose content on the PK was clarified and is expected be minor.

In conclusion, the available non-clinical data support the biosimilarity between Amsparity and the Humira-EU.

2.5. Clinical aspects

2.5.1. Introduction

The clinical development programme included five studies: 3 single-dose PK studies in healthy volunteers (B5381001, B5381005, B5381007), a pivotal efficacy and safety study in moderate to severe Rheumatoid Arthritis (RA) patients (B5381002), and a single arm, prefilled pen sub-study in moderate to severe Rheumatoid Arthritis (RA) patients (B5381002b). An overview of the clinical studies is presented in Table 2.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2 Tabular overview of clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
B5381001	2 centers in 2 countries	Phase 1, double blind, randomized (1:1:1), parallel-group, single-dose, 3-arm, comparative PK study of Amsparity and adalimumab sourced from US and EU administered to healthy volunteers.	Amsparity or Humira-US or Humira-EU Route: Single-use, prefilled syringe for subcutaneous injection Dose Regimen: 40 mg [0.8 mL of a 50 mg/mL solution] on Study Day 1	• To compare the PK of Amsparity to Humira-EU, and Amsparity to Humira-US. • To compare the PK of Humira-EU to Humira-US. • To evaluate the single-dose safety and tolerability. • To evaluate the immunogenicity.	**Randomized:** Amsparity=69 Humira-US=71 Humira-EU=70 **Treated:** Amsparity=69 Humira-US=71 Humira-EU=70 **Completed:** Amsparity=68 Humira-US=71 Humira-EU=69	Single dose 28 May 2013 to 03 February 2014	Healthy females of non-childbearing potential and healthy males between the ages of 18 and 55 years, inclusive. Body Mass Index (BMI) of 17.5 to 30.5 kg/m2; and a total body weight >50 kg (110 lbs).	**Primary PK endpoints:** C_{max}, AUC_t, AUC_{inf},
B5381005	Single center	Phase 1, open-label, Randomized (1:1), single dose, parallel group, 2-arm comparability study to assess the PK of Amsparity following subcutaneous administration using a prefilled syringe (PFS) or a prefilled pen (PFP) in healthy adult subjects.	Arm A: Amsparity prefilled syringe Arm B: Amsparity prefilled pen Route: Single-use, prefilled syringe or prefilled pen for subcutaneous injection Dose Regimen: 40 mg [0.8 mL of a 50 mg/mL solution] on Study Day 1	**Primary Objective:** • To compare the single-dose PK of Amsparity administered SC with a PFP device containing the Amsparity PFS, as compared to that of the PFS, in healthy adult subjects. **Secondary Objectives:** • To evaluate the safety and tolerability of Amsparity administered with the PFP device containing the PFS, compared to	**Randomized:** Arm A=81 Arm B=83 **Treated:** Arm A=81 Arm B=83 **Completed:** Arm A=79 Arm B=83	Single dose 21 January 2016 to 22 June 2016	Healthy female subjects and/or male subjects, who, at the time of screening, are between the ages of 18 and 55 years, inclusive. Body Mass Index (BMI) of 17.5 to 32 kg/m2; and a total body weight >50 kg (110 pounds). Female subjects of childbearing potential who are willing to use a highly effective method of contraception of and women of non-childbearing potential	**Primary PK endpoints:** C_{max}, AUC_{0-2wk}

				the PFS. • To evaluate the full PK profile following a single dose of Amsparity administered with the PFP device and the PFS. **Exploratory Objective:** • To evaluate the immunogenicity of Amsparity administered with the PFP device containing the PFS, and with the PFS.				
B5381007	4 centers in 1 country	Phase 1, double blind, randomized (1:1:1), parallel-group, 3-arm, single-dose, comparative pharmacokinetic study of Amsparity and adalimumab sourced from US and EU administered to healthy male and female subjects.	Amsparity or Humira-US or Humira-EU Route: Single use prefilled syringe for subcutaneous injection Dose Regimen: 40 mg [0.8 mL of a 50 mg/mL solution] on Study Day 1	**Primary Objective** • To compare the PK of Amsparity to Humira-EU, and of Amsparity to Humira-US. **Secondary Objectives** • To compare the PK of Humira-EU to Humira-US. • To evaluate the single-dose safety and tolerability. • To evaluate immunogenicity.	**Randomized:** Amsparity=121 Humira-US=122 Humira-EU=119 **Treated:** Amsparity=121 Humira-US=119 Humira-EU=119 **Completed:** Amsparity=116 adalimumab-US=112 Humira-EU=112	Single dose 22 Sep 2014 to 17 Mar 2015	Healthy male and female subjects between the ages of 18 and 45 years, inclusive. Body Mass Index (BMI) of 19.0 to 30.5 kg/m2; and a total body weight >60 kg (132 lbs). Female subjects of childbearing potential who are willing to use a highly effective method of contraception of and women of non-childbearing potential	**Primary PK endpoints:** C_{max}, $AUC_{0\text{-}2wk}$, AUC_t, AUC_{inf}
B5381002	173 centers in 24 countries.	Multi-national, 2-armed, randomized (1:1), double-blind, parallel-group study designed to evaluate the safety, efficacy, population PK, and immunogenicity of	**TP1:** Amsparity or Humira-EU **TP2:** Amsparity/ Amsparity or Humira-EU/ Humira-EU or Humira-EU/ Amsparity **TP3:** Amsparity	**Primary Objective:** • To compare the treatment efficacy between Amsparity and Humira-EU in subjects with moderately to severely active RA who were treated with adalimumab in combination with MTX.	**TP1: Randomized:** Amsparity =297 Humira-EU=300 **Treated:** Amsparity =297 Humira-EU=299 **Completed TP1:** Amsparity =286 Humira-EU=273	Multiple dose for 18 months 25 June 2015 to 01 March 2017 Last Subject Completing Week 52 Visit	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 rheumatoid arthritis (RA) based on 2010 American College of Rheumatology (ACR)/European League	**Primary Efficacy Endpoint:** ACR20 at Week 12

		Amsparity versus Humira-EU in combination with MTX to treat subjects with moderately to severely active RA who had an inadequate response to MTX therapy.	Route: Single-use, prefilled syringe for subcutaneous injection Dose Regimen: 40 mg [0.8 mL of a 50 mg/mL solution] every other week	**Secondary Objectives:** • To evaluate the overall safety and tolerability of Amsparity and Humira-EU. • To evaluate the immunogenicity of Amsparity and Humira-EU. • To evaluate the multiple composite and individual parameters of clinical response to Amsparity and Humira-EU. • To evaluate the overall safety, tolerability and immunogenicity of Amsparity after treatment transition from Humira-EU to Amsparity. • To evaluate the population PK of Amsparity and Humira-EU. • To evaluate the PD response to Amsparity and Humira-EU.	**TP2:** **Re-randomized:** Amsparity / Amsparity =283 Humira-EU/ Humira-EU=135 Humira-EU/ Amsparity =134 **Treated:** Amsparity / Amsparity =283 Humira-EU/ Humira-EU=135 Humira-EU/ Amsparity =133 **Completed TP2:** Amsparity / Amsparity =258 Humira-EU/ Humira-EU=120 Humira-EU/ Amsparity =126 **TP3 (entered):** Amsparity / Amsparity / Amsparity =259 Humira-EU / Humira-EU / Amsparity= 121 Humira-EU / Amsparity / Amsparity =127 **Treated:** Amsparity / Amsparity / Amsparity =258 Humira-EU / Humira-EU / Amsparity= 120		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. Subjects must have received oral, subcutaneous (SC), or intramuscular (IM) methotrexate 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	

					Humira-EU / Amsparity / Amsparity =127 **Completed TP3:** Amsparity / Amsparity / Amsparity =241 Humira-EU / Humira-EU / Amsparity= 113 Humira-EU / Amsparity / Amsparity =120			
B5381002b	19 centers in 4 countries.	An open-label, single arm, prefilled pen Sub study in a subset of subjects enrolled in Study B5381002.	Amsparity Route: single-use, prefilled pen device for subcutaneous administration Dose Regimen: 40 mg [0.8 mL of a 50 mg/mL solution] every other week	**Primary Objective:** • To evaluate the success of Amsparity administration by the subject with RA or their non-healthcare professional caregiver using the PFP device. **Secondary Objectives:** • To describe the safety of Amsparity administration by the subject or their non-healthcare professional caregiver using the PFP device. • To determine the correct operation of the Amsparity PFP by examination of returned used devices.	**Screened:** Amsparity =63 **Treated:** Amsparity =50 **Completed:** Amsparity =49	Multiple dose for 10 weeks 03 October 2016 to 16 May 2017	This is the substudy of the pivotal B5381002 study and the same inclusion criteria apply.	

2.5.2. Pharmacokinetics

The pharmacokinetics (PK) and immunogenicity profiles of adalimumab-Pfizer were investigated in four clinical studies: 2 single-dose subcutaneous (SC) PK similarity studies in healthy subjects, 1 single SC dose PK comparability study using a prefilled syringe (PFS) or a prefilled pen (PFP) in healthy subjects, and 1 multi-dose clinical comparability study in subjects with moderately to severely active RA, which included an optional device substudy using a PFP.

Analytical methods

The methodologies used in the analysis of biological samples for the detection of drug concentrations (PK), antidrug antibodies (ADAs), and neutralising antibodies (NAbs) were fully validated. Furthermore, the respective assays were designed and conducted in accordance with regulatory guidance.
The following analytical methods were used: ELISA for the determination of adalimumab concentrations in human serum, Electrochemiluminescence (ECL) bridging assay for the detection of ADA and a cell-based immunogenicity assay for the detection of Nab against adalimumab in human serum from healthy subjects and RA patients.

The adalimumab concentration in the serum was determined by a validated ELISA method. In this assay, adalimumab is captured by a recombinant human TNF-α and an HRP-conjugated goat anti-human IgG antibody is used to detect the bound analyte. The use of Humira-EU as a reference standard for calibration curve preparation can be agreed as the analytical similarity from three full standard curves independently prepared from adalimumab-Pfizer, Humira-EU, and Humira-US was demonstrated. The same analytical method was used for the determination of adalimumab in the serum from healthy volunteers and patients with rheumatoid arthritis (RA). This is acceptable as the method demonstrated also selectivity for RA serum.

The validated ADA method is an ECL immunoassay based on MSD technology using a ruthenium (Ru) metal chelate as the ECL label. Affinity purified human monoclonal anti-adalimumab antibody was used as a positive control. All serum samples were screened in Tier 1 to detect the presence of binding antibodies to adalimumab. Tier 1 positive samples were analysed to confirm specificity of the response in Tier 2. Tier 2 positive samples proceeded with End Point Tier analysis (EPT Tier 3). Two methods were validated: B5387005 (using biotin and ruthenium labelled adalimumab-Pfizer) and B5387006 (using biotin and ruthenium labelled Humira-EU). A one-assay approach, using labelled adalimumab-Pfizer, was chosen for subsequent studies due to high cross-reactivity (>95%) for ADA-positive samples between the two assay methods observed in study B5381001. This is agreed. Following request on positive controls, the applicant has presented additional method development data. The positive controls used are suitable to monitor assay performance. No matrix interference was observed using normal or RA serum. The absence of interference by lipemic or haemolysed plasma samples was also demonstrated.

The validated cell-based method was used for the evaluation of neutralising capacity of antibodies present in ADA-positive samples. Two methods were validated: B5387002 (detection of neutralising anti-adalimumab-Pfizer antibodies using adalimumab-Pfizer) and B5387004 (detection of neutralising anti-Humira-EU antibodies using Humira-EU). A one-assay approach, using adalimumab-Pfizer, was chosen for subsequent studies due to high cross-reactivity (>95%) for NAb-positive samples between the two assay methods observed in study B5381001. The drug tolerance of the assay has been adequately discussed and justified by the applicant.

Overall, the analytical methods used in each study were validated in line with the EMA bioanalytical method validation guidelines.

Clinical study B5381001 in healthy subjects

The study was a double-blind (Sponsor-open), randomised (1:1:1), parallel group, 3-arm, single-dose, PK similarity study of adalimumab-Pfizer and adalimumab sourced from the US and EU administered SC in the lower abdomen by a PFS to healthy adult subjects.

The objectives of the study were:

- To compare the PK of adalimumab-Pfizer to Humira-EU, and adalimumab-Pfizer to Humira-US (primary objective).
- To compare the PK of Humira-EU to Humira-US.
- To evaluate the single-dose safety and tolerability.
- To evaluate the immunogenicity.

The test product was adalimumab-Pfizer (40 mg of adalimumab in a PFS; open label supply) and the reference/comparator products were Humira-EU (40 mg of adalimumab in a PFS) and Humira-US (40 mg of adalimumab in a PFS).

A total of 210 healthy subjects (209 males, 1 post-menopausal female; aged 18-54 years; BMI 17.5 to 30.5 kg/m^2) were randomised to 1 of the 3 study treatment groups. The demographic data were generally comparable in the studied treatment groups. Sixty-nine (69) subjects received adalimumab–Pfizer, 70 subjects received Humira-EU and 71 subjects received Humira-US. Two (2) subjects discontinued from the study due to withdrawal by subject (1 subject in the adalimumab-Pfizer group and 1 subject in Humira-EU group). The discontinued subject in the Humira-EU group was still evaluable in the PK population. Eleven (11) subjects were excluded from the primary PK analysis (3 subjects in the adalimumab-Pfizer group, 4 subjects in the Humira-US group, and 4 subjects in the Humira-EU group).

Of these 11 subjects, 2 subjects were excluded because the measured serum concentration of adalimumab in the pre-dose sample was greater than 5% of the C_{max} for each of the subjects. The study was a parallel group study in healthy subjects. Consequently, clarification was needed for the high adalimumab concentrations in pre-dose samples. The applicant tried to find the reason for the pre-dose adalimumab concentrations > 5% of the C_{max}; however, no reason could be found. The amount of subjects having the high pre-dose adalimumab concentrations was small and the subjects were in different study groups, so it can be considered that the exclusion of these subjects from the primary PK analysis did not affect the results. An additional 9 subjects were excluded because their PK profiles exhibited an insufficient terminal phase, due to missing concentrations at later time points (PK samples were not collected at these time points) or because of the impact of ADA on the terminal phase. For each subject, the terminal phase was considered sufficient if the profile showed: 1) measurable concentrations to at least the 504-hour time point; and 2) measurable concentrations at a minimum of 3 time points after the observed T_{max}.

Blood samples for PK analysis were collected at 0 (pre-dose), and at 3, 12, 24, 48, 72, 96, 120, 144, 168, 192, 264, 336 (= 2 weeks), 504, 672, 840, 1008 h (i.e. 42 days/6 weeks) post-dose. Blood samples were collected for determination of ADA and NAbs to adalimumab at day 1 (pre-dose), day 15, day 29, day 43, day 71 and at extended follow-up. The applicant was advised by the CHMP that the sampling time period should be extended to at least 10 weeks; however, the advice was not followed. Consequently, there existed almost 50% of subjects (N =39 [59%] in the adalimumab-Pfizer group, N = 30 [45%] in the Humira-EU group and n =25 [37%] in the Humira-US group), whose AUC_t did not cover at least 80% of AUC_{inf} (i.e. the late elimination phase of the PK profile was not optimally characterised).

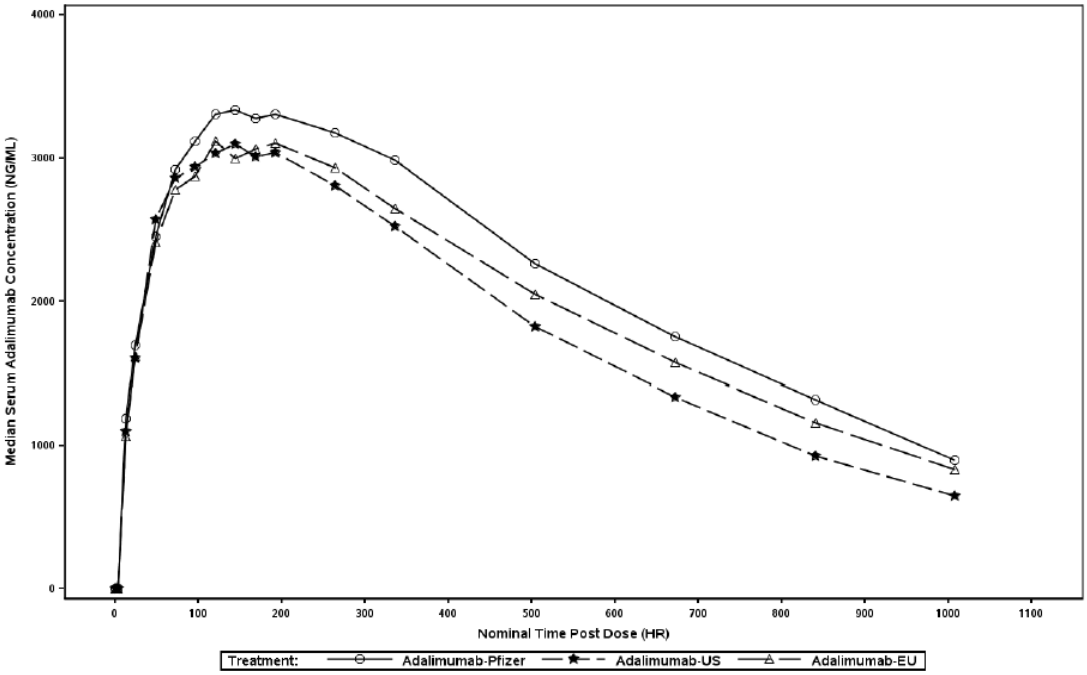
The PK parameters included: C_{max}, T_{max}, $AUC_{0\text{-}2wk}$, and AUC_t; primary PK parameters were not pre-specified in the protocol. In addition, if data permitted, AUC_{inf}, CL/F, V_z/F and $t_{½}$ were also estimated. The PK parameters were summarised using descriptive statistics according to treatment group. A one-way analysis of variance (ANOVA) with treatment as a factor was performed for each natural log transformed PK parameter ($AUC_{0\text{-}2wk}$, AUC_t, AUC_{inf} or C_{max}). PK similarity for a given test-to-reference comparison was considered 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% bioequivalence window.

Exploratory analysis was performed to examine the relationship between weight and PK parameters. Analysis of covariance (ANCOVA) with treatment as factor and baseline weight as covariate was used for this analysis. The 90% CI between 2 treatment groups was constructed for C_{max}, $AUC_{0\text{-}2wk}$, AUC_t, and AUC_{inf} in the same way as ANOVA.

Additional exploratory PK analysis was planned for assessing potential effects of ADA at low drug concentrations at 1680 hours; however, due to the high rate of ADA observed, and the small number of subjects (n = 16-25/group) with measurable concentrations at 1680 hours, there were insufficient data to perform the analysis. Descriptive summary of PK parameters (day71) is, however, presented and the results are in accordance with other PK results (i.e. the C_{max} and AUCs with adalimumab-Pfizer are slightly higher than with Humira).

PK results

The shape of concentration profiles for the test and the reference products can be considered similar; however, the median concentrations from 48-hour post dose until the end of the sampling period were higher in the adalimumab-Pfizer group than in the reference/comparator product groups (Figure 1).



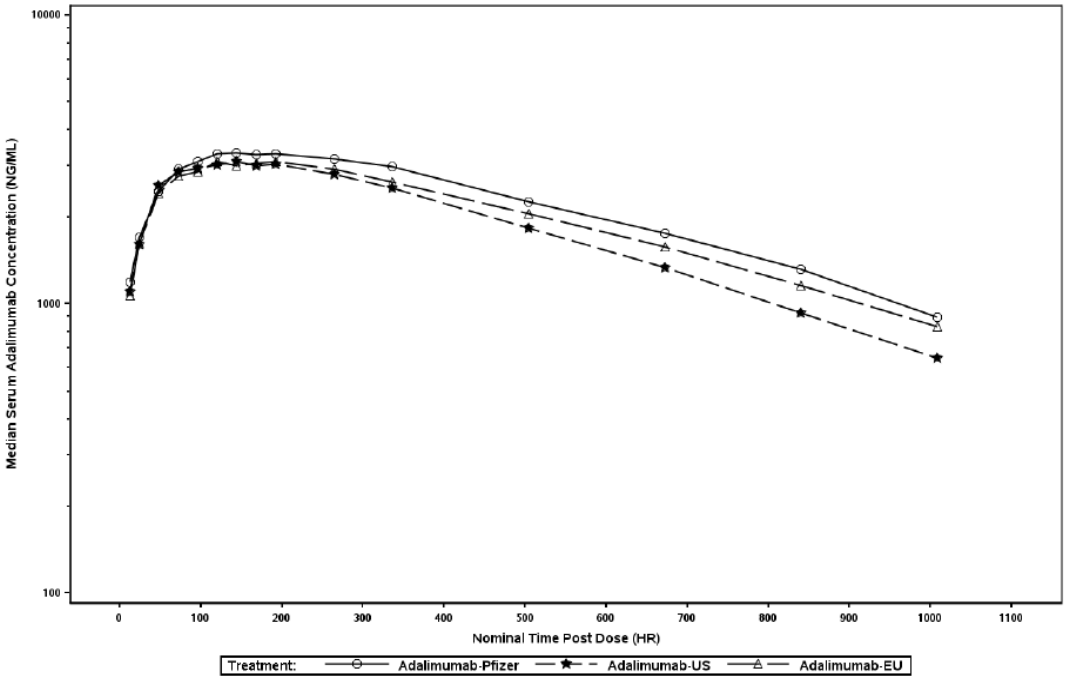


Figure 1 Median serum concentration (ng/ml) versus time (h) profiles of adalimumab-Pfizer, Humira-US and Humira-EU on linear scale and semi-logarithmic scale (PP analysis set)

Consistent with the median concentration-time profiles, the mean C_{max}, $AUC_{0\text{-}2wk}$, AUC_t and AUC_{inf} estimates were slightly higher for adalimumab-Pfizer than for Humira-EU and Humira-US. The inter-subject variability for each of the PK parameters was similar across the 3 study drugs, with %CV values of 30% to 31% for C_{max}, 31% to 32% for $AUC_{0\text{-}2wk}$, 30% to 33% for AUC_t, and 39% to 43% for AUC_{inf} (Table 3).

Table 3 Mean (±SD) PK Parameter estimates for Adalimumab-Pfizer, Adalimumab-US, and Adalimumab-EU (Day 1-43, PP Population)

Parameters (units)	Adalimumab-Pfizer (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
$AUC_{0\text{-}2wk}$ (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

a. T_{max} is reported as median.

The PK similarity between adalimumab-Pfizer and Humira-EU (and also between adalimumab-Pfizer and Humira-US) was demonstrated in C_{max} and $AUC_{0\text{-}2wk}$; however, in AUC_t and AUC_{inf} the PK similarity was not formally met (Table 4). Exposure to adalimumab (in terms of mean AUCs and C_{max}) was numerically systemically higher in adalimumab-Pfizer treatment group than in Humira-EU and Humira-US. The test-to-reference ratios of adjusted means in all exposure indicating parameters were above 100% and the 90% CIs for the test-to-reference of AUCs exclude 100% (the 90% CI adalimumab-Pfizer 100.1-127.8% vs Humira-EU, 109.8-140.1% vs Humira-US).

Table 4 Summary of statistical comparisons of PK exposure parameters between test and reference products (Day 1-43, PP Analysis Set)

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means	90% CI for Ratio[a]
	Test	Reference		
Adalimumab-Pfizer (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
Adalimumb-Pfizer (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

Statistical analysis was performed on the log-transformed parameters. Values presented in the table had been back-transformed from the log scale to the original scale.
a. The ratios (and 90% CIs) are expressed as percentages.

In the exploratory analysis, in which the weight was used as a covariate, the point estimates for AUCs and C_{max} were still above 100%; however, the 90% CIs for the C_{max}, AUC_{0-2wk}, AUC_t and AUC_{inf} were within 80.00-125.00% (including 100.00%) in comparison of adalimumab-Pfizer and Humira-EU. In the comparison of AUCs between adalimumab-Pfizer and Humira-US and Humira-EU and Humira–US, the 90% CIs were all above 100% (the upper limit being even > 125.00%).

The percentage of ADA was high (85.5% in the adalimumab-Pfizer and 90% in Humira-EU; see section 2.7. Clinical safety). Differences in the percentage of ADA and NAb, and onset ADA formation time between studied products were thought by the applicant to contribute to the failure of the AUC_t to meet the PK similarity criteria. ADA formation against adalimumab is known to be accompanied by increased clearance and reduced exposure (and possible loss of efficacy) and in this study, the mean apparent clearance (CL/F) values were slightly higher and AUCs were slightly lower with Humira-EU and Humira-US than with Amsparity.

Clinical study B5381007 in healthy subjects

This study was a double-blind (Sponsor-open), randomised (1:1:1), parallel-group, 3-arm, single-dose, definitive PK similarity study of adalimumab-Pfizer and adalimumab sourced from the US and EU administered SC in the lower abdomen by a PFS to healthy adult subjects.

This study was performed because PK comparability between Amsparity and Humira-EU could not be unambiguously shown in study B5381001. Scientific advice was received from CHMP. CHMP considered that another single-dose study in healthy subjects will add some evidence to the question on whether differences in immunogenicity and PK measures in the study B5381001 were real, or a play of chance. This study was designed based on observed data from the clinical study B5381001. Table 5 shows the main study design differences between studies B5381001 and B5381007.

Table 5 Comparison of study design differences between studies B5381001 and B5381007

	B5381001	B5381007
Planned sample size	210 (70 per treatment arm) (Power calculation based on anticipated maximal CV of 30%)	360 (120 per treatment arm) (Power calculation based on CV of 45%, from observed B5381001 maximal CV of 43%)
PK sampling duration	42 days	49 days
Stratification at randomization	No	Yes (randomization stratified by 3 body weight groups based on Day 0 body weight: <75 kg, 75 to <90 kg, and ≥90 kg)
Subject eligibility	Healthy males Postmenopausal females Non-childbearing potential females	Healthy males Non-childbearing potential females Childbearing potential females
Age range	18 - 55 years	18 - 45 years
BMI	17.5 - 30.5 kg/m^2, inclusive	19.0 - 30.5 kg/m^2, inclusive
Total body weight	>50 kg	>60 kg

The study design of B5381007 was improved by increasing sample size, the PK sampling period was extended to 49 days (being still too short), the randomisation was stratified by 3 weight categories and the heterogeneity was reduced by narrowing age and weight ranges.

Primary objective was to compare the PK of adalimumab-Pfizer to Humira-EU, and of adalimumab-Pfizer to Humira-US.

Secondary objectives were as follows:

- To compare the PK of Humira-EU to Humira-US.
- To evaluate the single-dose safety and tolerability.
- To evaluate immunogenicity.

The test product was adalimumab-Pfizer (40 mg of adalimumab in a PFS) and the reference/comparator products were Humira-EU (40 mg of adalimumab in a PFS) and Humira-US (40 mg of adalimumab in a PFS).

A total of 362 healthy subjects were randomised to 1 of the 3 study treatment groups. The number of subjects who received the study drugs was 359 (226 males and 133 females; aged between 18-45 years; BMI 19.5-30.5 kg/m^2). One hundred and twenty-one (121) subjects received adalimumab–Pfizer, 119 subjects received Humira-EU and 119 subjects received Humira-US. Three (3) subjects in the Humira-US group were randomised but did not receive any study treatment. Following dosing, 19 subjects discontinued before the end of the study, including 5 subjects in the adalimumab-Pfizer group and 7 subjects in both the Humira-US group and the Humira-EU group. Forty-eight (48) dosed subjects were excluded from the primary PK analysis (15 subjects in the adalimumab-Pfizer group, 18 subjects in the Humira-US group, and 15 subjects in the Humira-EU group). There were 4 subjects excluded from the primary PK analysis, because the serum drug concentration in the pre-dose sample was >5% of the C_{max}. The study was parallel group study in healthy subjects. Consequently, clarification was needed for the high adalimumab concentrations in pre-dose samples. The applicant tried to find the reason for the pre-dose adalimumab concentrations > 5% of the C_{max}; however, no reason could be found. The number of subjects having the high pre-dose adalimumab concentrations was small and the subjects were in different study groups, so it can be considered that the exclusion of these subjects from the primary PK analysis did not affect the results.

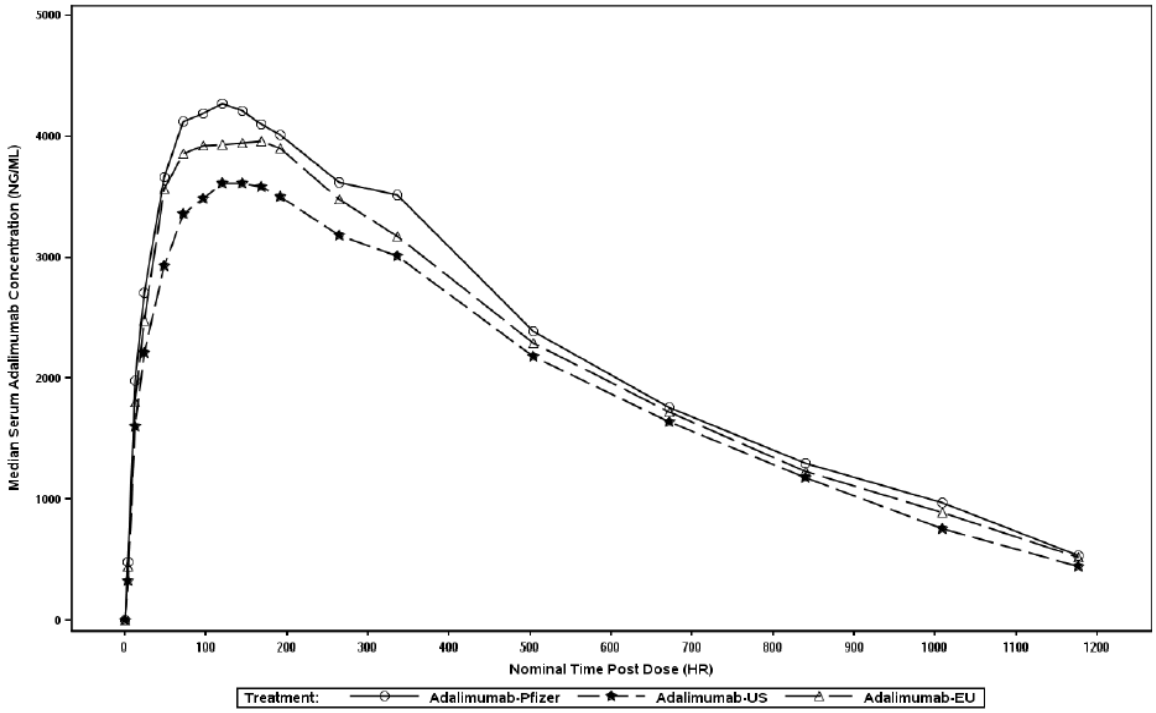
Blood samples for PK analysis were collected at 0 (pre-dose), and at 3, 12, 24, 48, 72, 96, 120, 144, 168, 192, 264, 336 (= 2 weeks), 504, 672, 840, 1008 and 1176 h (i.e. 50 days/~ 7 weeks) post-dose. Blood samples were collected for determination of ADA and NAbs to adalimumab at day 1 (pre-dose), day 15, day 29, day 43, day 50 and 71 and at follow-up.

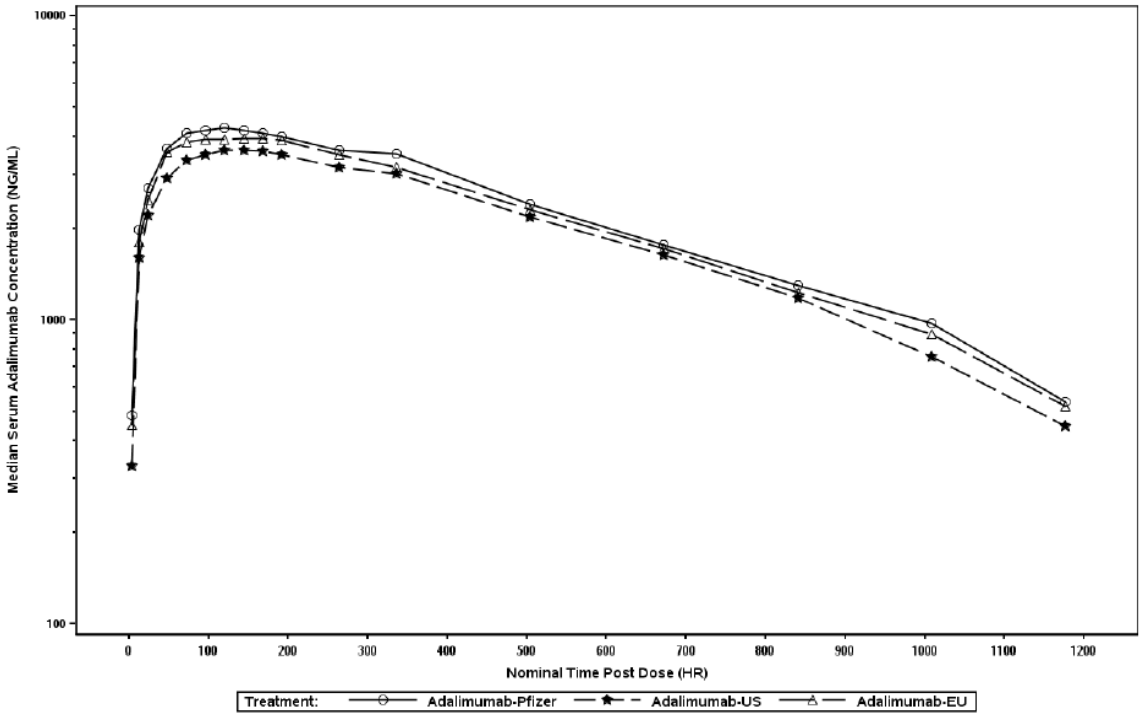
The primary PK parameters included: C_{max}, T_{max}, $AUC_{0\text{-}2wk}$, and AUC_t. In addition, if data permitted, AUC_{inf}, CL/F, V_z/F and $t_{½}$ were also estimated. The statistical methods and analyses were the same as in the study B5381001 (except the exploratory analysis using weight as a covariate, see above).

PK Results:

Among the 359 subjects receiving the assigned study drug, 311 (106 in adalimumab-Pfizer, 101 in Humira-US and 104 in Humira-EU) met the PP criteria and were eligible for the primary analysis for the PK similarity determination.

The 3 study drugs exhibited a comparable PK profile, which was characterised 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 (Figure 2).





Summary statistics were calculated by setting concentration values below the lower limit of quantification to 0.
The lower limit of quantification was 250 ng/mL.

Figure 2 Medium serum adalimumab concentration (ng/ml) –time (h) profiles of adalimumab-Pfizer, Humira-US and Humira-EU following a single SC 40 mg dose in health subjects on linear scale and semi-logarithmic scale (PP analysis set)

A descriptive summary of PK parameters for adalimumab-Pfizer, Humira-US and Humira-EU is presented in Table 6. The mean C_{max}, $AUC_{0\text{-}2wk}$, AUC_t and AUC_{inf} estimates were similar among the 3 study drugs, with estimates of these parameters for adalimumab-Pfizer being slightly higher.

The inter-subject variability for each of the PK parameters, though considerable, was similar across the 3 study drugs, with %CV values of 28-29%, 26-29%, 29-33%, and 33-40% for C_{max}, $AUC_{0\text{-}2wk}$, AUC_t and AUC_{inf}, respectively.

Table 6 Mean (±SD) PK parameter estimates for adalimumab-Pfizer, Adalimumab-US, and Adalimumab-EU (PP Population)

Parameters (Units)	Adalimumab-Pfizer	Adalimumab-US	Adalimumab-EU
	N = 106	N = 101	N = 104
N^1, N^2	106, 103	101, 99	104, 102
C_{max} (µg/mL)	4.53 ± 1.27	4.04 ± 1.18	4.09 ± 1.17
T_{max} (h)	120 (48, 362)	144 (48, 363)	132 (24, 336)
$AUC_{0\text{-}2wk}$ (µg.h/mL)	1254 ± 348.01	1101 ± 289.57	1130 ± 332.50
AUC_t (µg.h/mL)	2586 ± 858.85	2281 ± 705.92	2392 ± 697.93
AUC_{inf} (µg.h/mL)	3113 ± 1254.0	2748 ± 1078.8	2886 ± 965.4
CL/F (mL/h)	15.27 ± 6.91	16.80 ± 6.29	15.76 ± 6.45
V_z/F (mL)	6422 ± 2131.0	7095 ± 2347.4	7244 ± 3295.9
$t_{½}$ (hr)	351.5 ± 188.78	346.2 ± 204.61	362.4 ± 200.83

Arithmetic mean ± SD for all except: median (range) for T_{max}

Consistent with the serum drug concentration-time profiles and the PK parameter summary statistics, the mean numerical values in all exposure indicating PK parameters (i.e. C_{max}, AUCs) were slightly higher in the adalimumab-Pfizer group than in the Humira-EU and Humira-US group (Table 7). All 90% CIs for test-to-reference ratios of C_{max}, $AUC_{0\text{-}2wk}$, AUC_t and AUC_{inf} were within the pre-specified

acceptance window of 80.00% to 125.00% (in comparison of adalimumab-Pfizer and Humira-EU). The biggest differences were in the C_{max} and AUC_{0-2wk} values, in which, the 90% CIs for test-to-reference ratios did not include 100%, but were above 100%. There existed many subjects, whose AUC_t did not cover at least 80% of $AUC_{inf;}$ however, the amount of these subjects (N = 23 [22%] in the adalimumab-Pfizer group, N =34 [33%] in the Humira-EU group and N = 22 [22%] in the Humira-US group i.e. total amount > 20%) was smaller than in the study B5381001 (almost 50%). The secondary PK endpoints were quite comparable across treatment groups.

The similarity in PK between Humira-EU and Humira-US was demonstrated. The 90% CIs for the primary PK parameters were all within 80.00-125.00% (including 100.00%).

Table 7 Summary of statistical comparisons of PK exposure parameters (C_{max}, AUC_{0-2wk}, AUC_t, and 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		
Adalimumab-Pfizer (Test) vs Adalimumab-EU (Comparator)				
C_{max} (µg/mL)	4.344	3.901	111.36	103.97 – 119.27
AUC_{0-2wk} (µg.h/mL)	1199	1072	111.88	104.19 – 120.15
AUC_t (µg.h/mL)	2430	2275	106.80	98.76 – 115.49
AUC_{inf} (µg.h/mL)	2866	2718	105.44	96.43 – 115.29
Adalimumab-Pfizer (Test) vs Adalimumab-US (Comparator)				
C_{max} (µg/mL)	4.344	3.891	111.64	104.18 – 119.64
AUC_{0-2wk} (µg.h/mL)	1199	1064	112.73	104.92 – 121.12
AUC_t (µg.h/mL)	2430	2172	111.87	103.39 – 121.05
AUC_{inf} (µg.h/mL)	2866	2556	112.12	102.47 – 122.68
Adalimumab-EU (Test) vs Adalimumab-US (Comparator)				
C_{max} (µg/mL)	3.901	3.891	100.25	93.52 – 107.47
AUC_{0-2wk} (µg.h/mL)	1072	1064	100.76	93.74 – 108.30
AUC_t (µg.h/mL)	2275	2172	104.75	96.77 – 113.38
AUC_{inf} (µg.h/mL)	2718	2556	106.34	97.17 – 116.37

Statistical analysis was performed on the log-transformed parameters. Values presented in the table have been back-transformed from the log scale to the original scale.
a. The ratios (and 90% CIs) are expressed as percentages.

In the study B5381007, the percentage of ADAs/NAbs in the adalimumab-Pfizer group was higher than in the Humira-EU group indicating that the Applicant's argument that adalimumab-Pfizer may be less immunogenic (on the basis of the ADA/NAb results in the study B5381001 and B5381007) is not fully confirmed (see the details of ADA/NAb results in relation to PK from section 2.7. Clinical safety). However, it is accepted, that seemingly lower immunogenicity in the 2 studies (in the failed PK study and the study in RA patients) plays some role in the slightly higher exposures seen in adalimumab-Pfizer group.

Clinical study B5381005 in health subjects (PFS compared to PFP)

This study was a randomised, open-label, single-dose, parallel group, 2-arm, phase I comparability study to assess the PK of adalimumab-Pfizer following SC administration using a PFS or a PFP in healthy adult subjects.

Primary objective was to compare the single-dose PK of adalimumab-Pfizer administered SC with a pre-filled pen (PFP) device as compared to that of the pre-filled syringe (PFS), in healthy adult subjects.

Secondary objectives were:

- To evaluate the safety and tolerability of adalimumab-Pfizer administered with the PFP device compared to the PFS.
- To evaluate the full PK profile following a single-dose of adalimumab-Pfizer administered with the PFP device and the PFS.

Exploratory objective was to evaluate the immunogenicity of adalimumab administered with the PFP device and with the PFS.

The randomisation was stratified by the 3 body weight groups (i.e. > 50 kg but ≤ 60 kg, > 60 kg but ≤ 80 kg and > 80 kg).

Blood samples were collected at 0 h, 3 h, 8 h, 12 h, 24 h, 48 h, 72 h, 96 h, 144 h, 168 h (= 1 week), 192 h, 264 h, 336 h (= day 15), 504 h (= day 22), 672 h (= day 29), 840 h (=day 36), 1008 h (~ 6 weeks; i.e. at the end of study). The sampling time for PK was also in this study too short to capture the terminal elimination phase.

Primary PK endpoints were C_{max} and AUC_{0-2wk} for demonstration of PK comparability, because the applicant had an opinion that differences in the delivery devices were not anticipated to impact the terminal phase of the PK profiles.

Other PK endpoints were T_{max}, AUC_t. In addition, if data permitted, AUC_{inf}, CL/F, V_z/F and $t_{½}$ were also estimated.

Generally, in the device comparison studies, the primary PK parameters were the same as the ones used in the PK comparison studies of the products in healthy subjects i.e. AUC_{inf} and C_{max} in case of SC administration (often also AUC_{last}); however, it can be accepted that the selected PK parameters were enough to find differences between the studied devices.

PK results

A total of 163 subjects (80 subjects in the PFS arm and 83 subjects in the PFP arm) were included in the PP population. Forty-eight (48) and 58 subjects in the PFS and PFP arm, respectively, had a well-defined disposition terminal phase and therefore, estimation of AUC_{inf}, CL/F, V_z/F and $t_{1/2}$ was performed for those subjects.

For the PK comparisons between the 2 device study arms, the 90% CIs for the test-to-reference ratios of primary (C_{max} and AUC_{0-2wk}) PK endpoints were within the pre-specified acceptance window of 80.00% to 125.00% (Table 8).

Table 8 Summary of Statistical Comparisons of PK Exposure Parameters (C_{max}, AUC_{0-2wk}, AUC_{last}, and AUC_{inf}) Between Test and Reference Treatment Arms

	Adjusted Geometric Means		Ratio (Test/Reference)	
Parameter (units)	**Test**	**Reference**	**of Adjusted Means[a]**	**90% CI for Ratio[a]**
		PFP (Test) versus PFS (Reference)		
C_{max} (µg/mL)	4.454	4.134	107.74	99.16 – 117.06
AUC_{0-2wk} (µg.hr/mL)	1150	1097	104.89	95.76 – 114.89
AUC_{last} (µg.hr/mL)	2042	2101	97.23	86.75 – 108.98
AUC_{inf} (µg.hr/mL)	2203	2154	102.27	91.12 – 114.78

a. The ratios (and 90% CIs) were expressed as percentages.

The concentration profiles for adalimumab-Pfizer administered by PFP and PFS were quite similar; however, between 48 h and 192 h, the median concentrations of adalimumab-Pfizer administered by PFP were slightly higher (Figure 3).

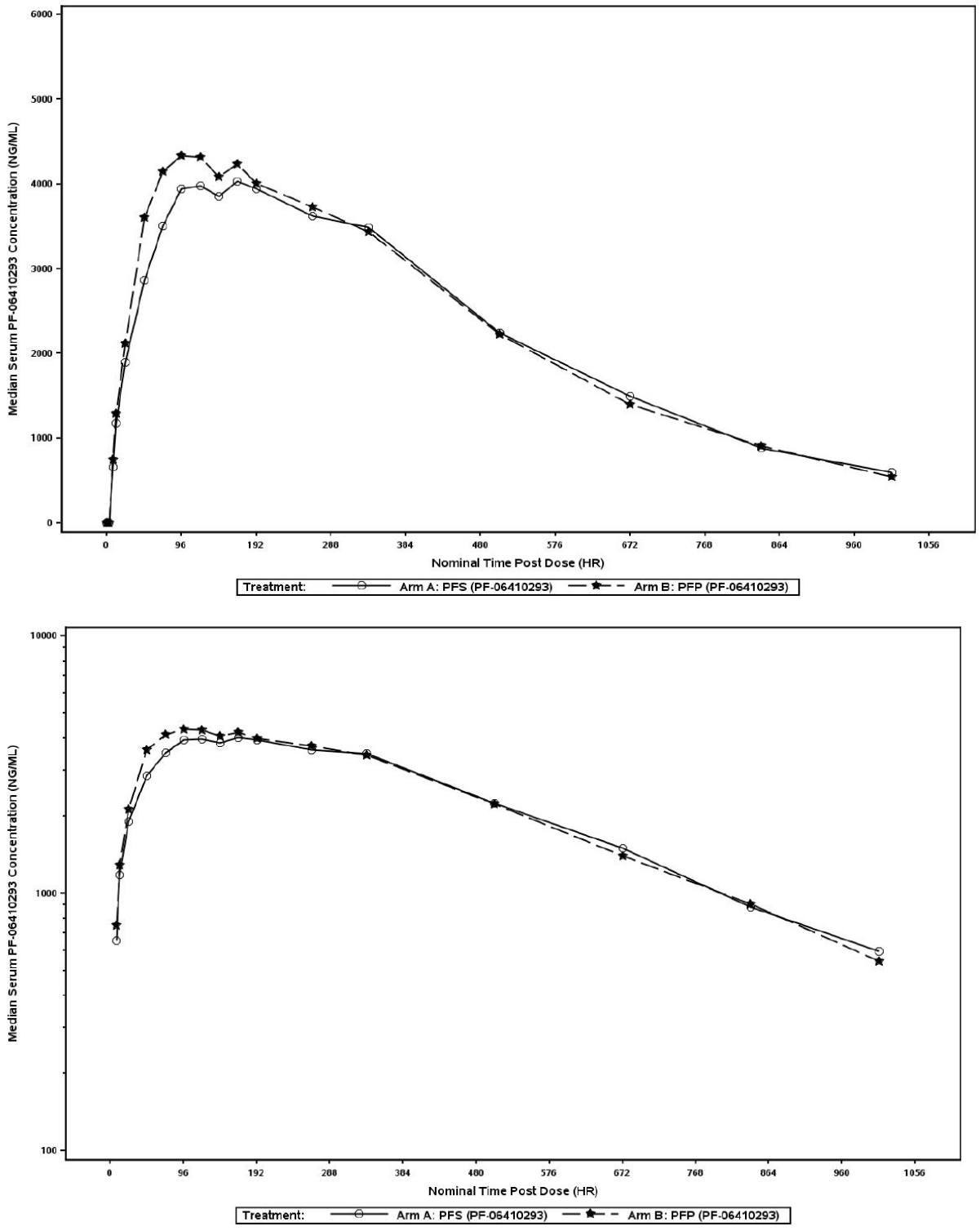


Figure 3 Median serum concentration (ng/ml)-time (h) profiles of adalimumab-Pfizer following SC administration of 40 mg dose using a PFS or PFP in healthy subjects on linear scale and semi logarithmic scale (PP population)

The T_{max} ranges also differed slightly between devices (for PFS T_{max} range 48-674 h, median T_{max} 166 h and for PFP 45-336 h, median T_{max} 142 h). The sampling period of 6 weeks was too short to accurately characterise the elimination phase and consequently, for 32 and 25 subjects in the PFS and PFP, respectively, the elimination phase could not be estimated; however, the mean/median concentration profiles for PFP and PFS seem to be almost similar in the elimination phase and consequently, the PK

similarity between PFP and PFS following administration of a 40 mg SC adalimumab-Pfizer dose in healthy adult male and female subjects is considered demonstrated.

The clinical phase III study in RA patients (B5381002) included also a sub-study, in which 50 patients in 19 study sites switched to receive adalimumab-Pfizer injections with PFP for 3 months (6 injections). The results of this sub-study were that PFP device was safe, quite easy to learn to use correctly and it was also preferred by patients.

Clinical study B5381002 in patients with moderately to severely active RA who have had an inadequate response to MTX

This study was a multi-national, 2-arm, randomised (1:1), double-blind, parallel-group study designed to evaluate the safety, efficacy, population PK, and immunogenicity of adalimumab-Pfizer versus Humira-EU administered SC in the abdomen or thigh by a PFS, both in combination with methotrexate (MTX) to treat subjects with moderately to severely active RA who had an inadequate response to MTX therapy.

The study is described in Chapter 2.6.1. Main study. The PK results are summarised below.

The evaluation of PK of Amsparity to Humira-EU was a secondary objective in this clinical study. The serum drug concentrations were measured in treatment periods 1 and 2 (TP1 and TP2). In addition, population PK assessment was planned with the drug concentration-time data from TP1 (prior to the week 26 injection) using a nonlinear mixed effect modelling approach in accordance with regulatory guidance. The population PK analysis was reported separately, in a population modelling analysis report (PMAR).

PK results

The applicant stated that mean and median serum concentration data should be interpreted with caution due to sampling and dosing deviations, likely introducing additional inter-subject variability and it is true that there were a lot of deviations in relation to the PK sampling. The mean serum concentrations were slightly higher for the Amsparity group than Humira-EU group throughout the whole study (Table 9 and Table 10).

Table 9 Serum trough concentration (ng/ml) of adalimumab-Pfizer and Humira-EU at different time points in TP1 (PK population dataset)

Time point	Statistics	adalimumab-Pfizer N =297	Humira-EU N =299
Day 1	n Mean (SD) CV% Min, Max	295 104.8 (1125) 1073 0.00, 15800	295 187.3 (1372.7) 733 0.00, 17700
Day 8 ~ week 1	n Mean (SD) CV% Min, Max	288 3756 (1830) 49 0.00, 11300	294 3488 (1938) 56 0.00, 16300
Day 15 ~ week 2	n Mean (SD) CV% Min, Max	293 3349 (1601) 48 0.00, 10800	296 3025 (1730) 57 0.00, 12800
Day 43 ~ week 6	n Mean (SD) CV% Min, Max	293 6205 (3526) 57 0.00, 21300	292 5526 (3249) 59 0.00, 19000
Day 85	n Mean (SD)	292 7575 (4725)	286 6531 (4303)

~ week 12	CV% Min, Max	62 0.00, 22300	66 0.00, 18700
Day 183 ~ week 26	n Mean (SD) CV% Min, Max	286 8244 (5495) 67 0.00, 26800	271 7190 (5402) 75 0.00, 28700
EOT/ET/Day 547	n Mean (SD) CV% Min, Max	8 3708 (4060) 110 0.00, 10200	18 2333 (2888) 124 0.00, 9710
Follow-up /Day 575	n Mean (SD) CV% Min, Max	1 304 304, 304	2 1085 (1534) 141 0.00, 2170

N =number of subjects in the PK population n = number of observations
CV% = coefficient of variation; SD = standard deviation

Table 10 Serum trough concentration (ng/ml) of adalimumab-Pfizer/adalimumab-Pfizer, Humira-EU/Humira-EU and Humira-EU/adalimumab-Pfizer at different time points in TP2 (PK population dataset)

Timepoint	Statistics	adalimumab-Pfizer/adalimumab-Pfizer N = 283	Humira-EU/Humira-EU N = 135	Humira-EU/adalimumab-Pfizer N = 133
Day 183 ~ week 26	n Mean (SD) CV% Min, Max	281 8346 (5464) 65 0.00, 26800	133 7058 (5174) 73 0.00, 28700	130 7557 (5493) 73 0.00, 20500
Day 211 ~ week 30	n Mean (SD) CV% Min, Max	276 8314 (5729) 69 0.00, 31000	131 6831 (5147) 75 0.00, 31800	131 7626 (5336) 70 0.00, 19300
Day 253 ~ week 36	n Mean (SD) CV% Min, Max	266 8066 (5297) 66 0.00, 25800	123 7063 (5234) 74 0.00, 21800	128 8198 (5628) 69 0.00, 23800
Day 365 ~ week 52	n Mean (SD) CV% Min, Max	259 7491 (4947) 66 0.00, 22100	122 6252 (5055) 81 0.00, 30800	126 8157 (5649) 69 0.00, 22600
EOT/ET/Day 547	n Mean (SD) CV% Min, Max	22 4730 (4747) 100 0.00, 15400	11 3321 (2536) 76 0.00, 7590	5 6698 (7528) 112 0.00, 18600
Follow-up/Day 575	n Mean (SD) CV% Min, Max	7 1079 (2538) 235 0.00, 6820	5 827 (944) 114 0.00, 2280	2 2815 (2227) 79 0.00, 4390

There existed considerable overlap in serum concentrations between the studied groups and the variation in the concentrations was high (CVs ranging from 48-75% in TP1 and 65-81% in TP2). The PK data (i.e. trough concentrations) received from this study support the same phenomenon, which was also seen in the PK studies i.e. with adalimumab-Pfizer the serum concentrations are slightly higher than with Humira-EU. The applicant was requested to perform direct comparison of the trough concentrations between adalimumab-Pfizer and Humira-EU, presenting point estimates and 90% CIs. This comparative analysis was asked to be provided for all visits where the PK measurements were done. In addition, the same was asked to be provided for ADA-positive and ADA-negative subgroups separately. The applicant performed the direct comparison of the trough concentrations between adalimumab-Pfizer and Humira-EU, as requested.

In ADA-positive subjects, on days 15 and 43, the 90% CI included 1.00; however, the upper limits were over 1.25. On days 85 and 183, the 90% CI range was wide. The lower limits were < 0.80 and upper limits > 1.25. In addition, the CV% was high in both study groups at every studied time points.

In ADA-negative subjects, the 90% CI was between the BE range i.e. 0.80-1.25 (including 1.00) and the CV% was much lower than in ADA-positive subjects.

The 90% CIs for all subjects were as follows: on day 15, the lower limit was > 1.00 and the upper limit was 1.25. In all other time points, the lower limit was < 1.00 (the range including 1.00); however, the upper limit was > 1.25. The CV%s were quite high in both study groups.

The trough concentrations were similar levels in ADA negative subjects between the studied treatments. The mean trough concentrations in ADA-positive subjects were much lower than in ADA-negative subjects and the variability in the trough concentrations were very high in both treatments. The geometric mean ratios of trough concentrations were higher on days 15, 43 and 183 in adalimumab-Pfizer group and on day 85 in Humira-EU group. The slightly higher mean trough concentrations in ADA-positive and in ADA-negative subjects in the adalimumab-Pfizer group impact on the trough concentrations in all subjects. The mean trough concentrations were slightly higher in the adalimumab-Pfizer group than in the Humira-EU group; however, the variability in trough concentrations was high and it can be considered that the differences in trough concentrations are not clinically relevant.

The mean steady-state trough concentrations (i.e. ~ 5-8 µg/ml) were at the same level as informed in the Humira SmPC in RA patients with MTX.

Root cause investigations before the marketing authorisation application (MAA) submission

Before submission of the MAA, extensive root cause examinations were done by the applicant to find reasons for slightly higher concentrations of adalimumab-Pfizer compared to the Humira-EU and Humira-US. The investigations included as follows:

- sensitivity analyses with protein content adjusted PK parameters
- ADA/NAb result in relation to the PK
- extensive evaluation of quality attributes related to the similarity and their potential impact on activity, PK/PD, safety and immunogenicity.

Including the protein-content in the comparisons had only minimal impact on the PK parameter ratios and corresponding 90% CIs compared to the original comparisons. The percentage and minimum/maximum titres of ADAs and NAbs appeared rather similar across all treatment arms; however, some inconsistencies in immunogenicity patterns between studies are evident. Some differences in the early PK parameter ratios may represent, at least in part, the contribution from the difference in the percent of molecules with high mannose species. The Humira reference/comparator products have higher mannose glycoform levels, which may contribute to faster clearance than with the test product.

Population PK analyses

Two population PK analysis reports were presented in the dossier: One for data from studies B5381001 and B5381007 (single dose in healthy subjects; dense PK sampling) and another for data from study B5381002 (multiple doses in RA patients; sparse PK sampling).

The PPK model for healthy subjects was a two-compartment model with absorption lag-time, first order absorption and first order elimination. A body weight based allometric function with fixed values

(0.75 for CL/F and Q/F, 1 for Vc/F and Vp/F) was applied to clearance and distribution parameters. Adalimumab-Pfizer was estimated to have an approximately 8% lower CL/F than Humira-EU (bootstrap 95% CI 1.57% - 10.20%), which is in line with the observed higher AUC values of adalimumab-Pfizer in studies B5381001 and B5381007. The other identified covariates on CL/F, i.e. increased clearance in subjects with anti-drug antibodies (parameterised as time-varying ADA titer) and decreased clearance with increasing serum albumin level, are biologically plausible and previously reported in the literature. No major deficiencies in the model were identified and it is appropriate for describing the PK of adalimumab after a single SC injection in healthy subjects. However, the population PK analysis for healthy subjects was an exploratory analysis, which is not considered to be relevant in concluding whether adalimumab-Pfizer is biosimilar with Humira.

For RA patients, independent PPK models were developed for each product (adalimumab-Pfizer and Humira-EU). These models had several uncertainties and it cannot be concluded that the presented models adequately describe the pharmacokinetics of adalimumab-Pfizer and Humira-EU in patients with moderately to severely active RA. Clarifications in regard with the models are not requested, however, because PPK modelling is not considered to be relevant in concluding whether adalimumab-Pfizer is biosimilar with Humira.

2.5.3. Pharmacodynamics

No pharmacodynamic (PD) data were evaluated in the Phase 1 bioequivalence studies in healthy volunteers since the validated PD markers do not exist for the efficacy of TNF-α inhibitors. Regarding the primary PD a set of non-clinical *in vitro* and *in vivo* studies have been performed. The studies on secondary PD have not been provided and neither been required according to the EMA guideline (EMA/CHMP/BMWP/403543/2010).

hs-CRP

Hs-CRP (High sensitivity C-reactive protein) was among the biochemistry parameters investigated in the clinical efficacy and safety study in RA patients (B5381002). No clinically significant differences were revealed in the reached hs-CRP levels. See section 2.6. Clinical efficacy for the outcome of the hs-CRP analysis.

Vectra-DA

In addition, exploratory biomarker endpoints included Vectra-DA [MBDA disease activity] score and individual Vectra-DA components up to Week 26 (TP1) in ITT population in study B5381002. Vectra-DA score was measured at Week 0, 6, 12, and 26. Vectra-DA is composed of 12 biomarkers (VCAM-1, TNFR-I, IL-6, EGF, VEGF, YKL-40, MMP-1, MMP-3, resistin, leptin, SAA, and CRP). Multi-biomarker disease activity (MBDA) score was calculated using a proprietary validated algorithm to provide a score, on a scale of 1 to 100.

Serum levels of total rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti-CCP) were evaluated as additional biomarker assessments.

Mean Vectra-DA score showed similar high baseline disease activity with a mean (SD) Vectra-DA of 57.2 (14.44) for the adalimumab-Pfizer arm and 58.3 (15.34) for the Humira-EU arm, and 78.45% and 81.67% of subjects were in the high Vectra-DA score category (>44) at baseline for the adalimumab-Pfizer and Humira-EU arms, respectively.

The Vectra-DA scores were similar between the 2 treatment arms at each study visit up to Week 26. Mean changes from baseline were similar between treatment arms in the ITT population. Mean (SD) Vectra-DA scores decreased by 11.9 (14.02) and 12.4 (13.82) at Week 6 in the adalimumab-Pfizer and

Humira-EU arms, respectively, with minimal additional change to Week 12; and decreased by 14.3 (16.57) and 15.5 (17.56) at Week 26, as compared to the baseline values.

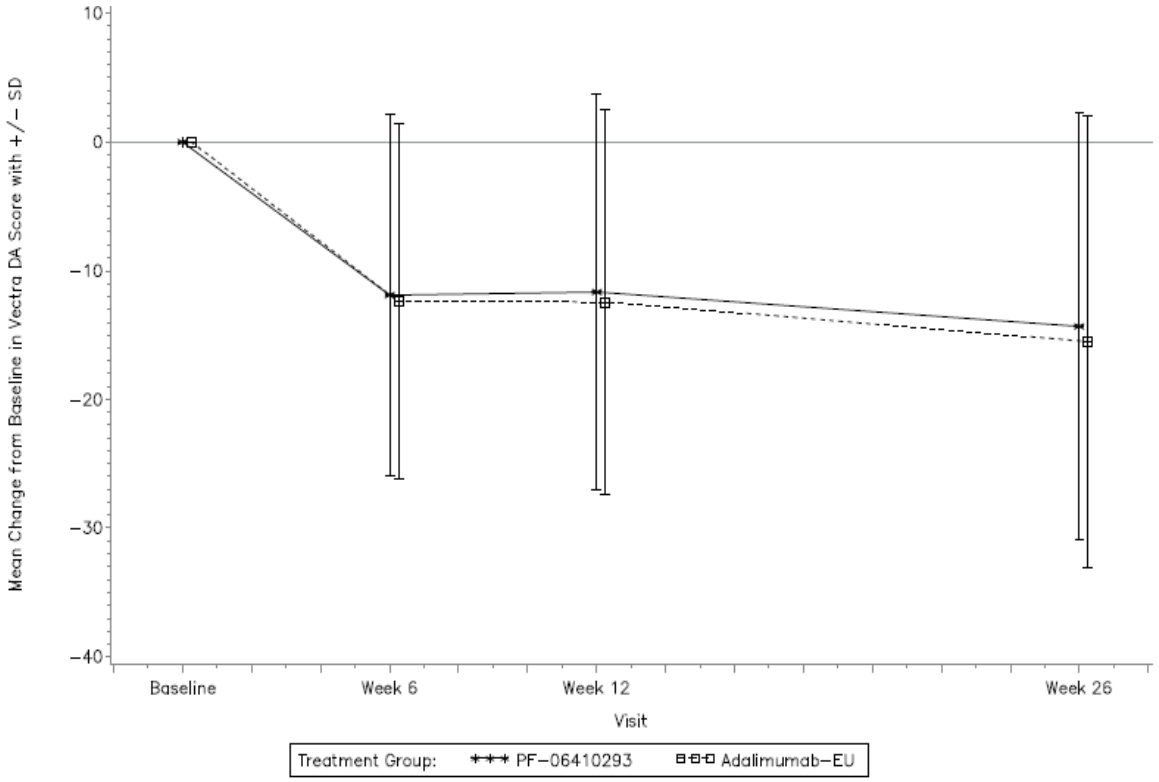


Figure 4 Mean (± SD) change from baseline in Vectra-DA score over time up to week 26, ITT population – TP1 (B5381002 study)

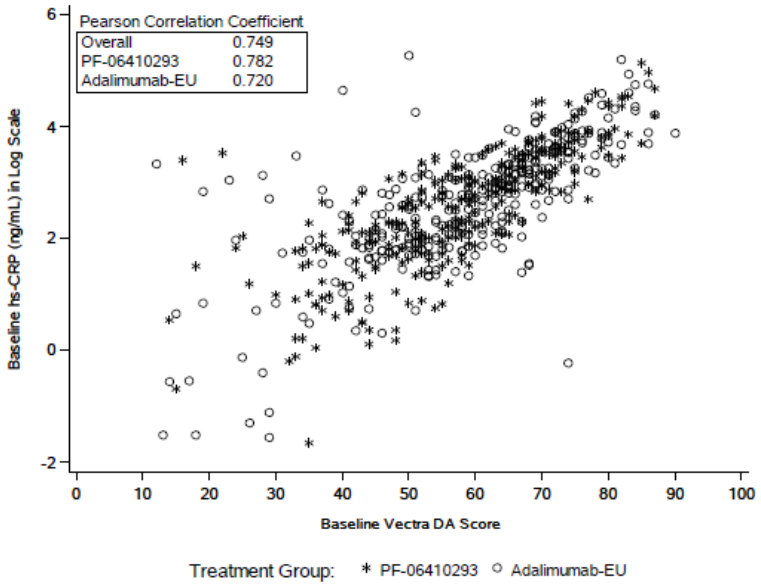


Figure 5 Baseline Vectra DA score versus baseline hs-CRP (mg/L) (Log scale)

2.5.4. Discussion on clinical pharmacology

The PK of Amsparity was compared to Humira-EU in three clinical studies (studies B5381001, B5381007 and B5381002).

Studies B5381001 and B5381007 in healthy subjects were PK studies, in which adalimumab was administered 40 mg SC as a single-dose. Study B5381002 was performed in RA patients and adalimumab was administered 40 mg SC every other week up to week 78. The administration device was the PFS in all these studies; except the clinical study B5381002 has an additional sub-group study with PFP. In addition, PK of adalimumab-Pfizer was evaluated in one clinical study (B5381005), in where the adalimumab was administered from the PFP or PFS in healthy subjects.

The development programme to demonstrate the PK similarity between adalimumab-Pfizer and Humira was in general adequate; however, all recommendations given by the CHMP were not followed (e.g. duration of PK sampling time in PK comparability studies).

PK study B5381001

The study B5381001 was performed in healthy subjects to establish comparability between adalimumab-Pfizer and Humira-EU and Humira-US in terms of C_{max}, AUC_{0-2wk}, AUC_t and AUC_{inf}. The applicant was advised by the CHMP before the study conduction that the sampling time period should be extended to at least 10 weeks; however, the advice was not followed, and the sampling time period was only up to 6 weeks. Consequently, there existed a lot of subjects (almost 50%) whose AUC_t did not cover at least 80% of AUC_{inf} and consequently, the whole PK profiles including the late elimination phase can be considered not optimally characterised.

The PK similarity between adalimumab-Pfizer and Humira-EU was demonstrated in C_{max} and AUC_{0-2wk}; however, in AUC_t and AUC_{inf} the PK similarity was not formally met. All exposure indicating mean PK parameters (i.e. AUCs and C_{max}) were numerically higher in adalimumab-Pfizer treatment group than in Humira-EU and Humira-US. The test-to-reference ratios of adjusted means in all exposure indicating parameters were above 100% and the 90% CIs for the test-to-reference of AUC_t and AUC_{inf} excluded 100%. In the exploratory analysis, in which the weight was used as covariate, the point estimates for AUCs and C_{max} were above 100%; however, the 90% CIs for the primary PK parameters were within 80.00-125.00% (including 100.00%) in comparison of adalimumab-Pfizer and Humira-EU. In the comparison of AUCs between adalimumab-Pfizer and Humira-US and Humira-EU and Humira–US the 90% CIs were all above 100% (the upper limit being even > 125.00%).

The percentage of ADA was high (85,5% and 90% in adalimumab-Pfizer and Humira-EU; see results from Chapter 2.7. Clinical safety) and differences in the percentage of ADA and NAb, and ADA onset time between studied products was thought by the applicant to contribute to the failure of the AUC_t to meet the PK similarity criteria. ADA formation against adalimumab is known to be accompanied by increased clearance (CL) and reduced exposure (and possible loss of efficacy) and in this study, the mean CL and AUCs were slightly lower with the reference/comparator products than with the test product.

Pivotal PK study B5381007

This additional single-dose PK study in healthy subject was conducted upon request from CHMP during scientific advice. The aim was to clarify if the differences in immunogenicity and PK measures in the first study B5381001 were real, or a play of chance.

The study design of B5381007 was improved by increasing sample size (based on an observed inter-individual variability of 43% for AUC_{inf} in the study B5381001). The randomisation was stratified by 3 weight categories and the heterogeneity was reduced by narrowing age and weight ranges. The

sampling period for PK was expanded from 6 weeks to 7 weeks. The sampling period was still too short and there exist many subjects, whose AUC_t did not cover at least 80% of AUC_{inf}; however, the amount of these subjects (> 20%) was smaller than in the study B5281001. Also in this study, it can be noted that the characterisation of the whole PK profiles was not optimal. In the study B5381007, the biosimilarity in PK can be considered formally met between adalimumab-Pfizer and Humira-EU (and also between adalimumab-Pfizer and Humira-US; all 90% CIs for test-to-reference ratios of C_{max}, AUC_{0-2wk}, AUC_t and AUC_{inf} were within the pre-specified acceptance range of 80.00% to 125.00%) and the results from this study can be considered to support the biosimilarity in PK. The point estimates in exposure indicating PK parameters, however, were all above 100% i.e. adalimumab-Pfizer concentrations were slightly higher than the concentrations of the reference/comparator products. The biggest differences between adalimumab-Pfizer and Humira-EU were in the C_{max} and AUC_{0-2wk} values, in which the 90% CIs for test-to-reference ratios did not include 100%, but were above 100%. The 90%CIs for test-to-Humira-US ratios in primary PK parameters were all above 100%.

In the study B5381007 the percentage of ADAs/NAbs in the adalimumab-Pfizer group was higher than in the Humira-EU group indicating that the applicant's argument that adalimumab-Pfizer may be less immunogenic (on the basis of the ADA/NAb results in the study B5381001 and also in the study B5381002) may be questioned. However, it is accepted, that seemingly lower immunogenicity in the 2 studies (in the failed PK study and the study in RA patients) possibly plays some role in the slightly higher exposures seen in the adalimumab-Pfizer group.

There were discrepancies in the reported protein contents of the batches used in the studies B5381001 and B5381007. Upon request, the applicant adequately clarified the reasons for the differences in the reported protein contents of the batches used in the studies B5381001 and B5381007 and the correct protein contests of the batches were presented. In addition, the appropriate certificates of analysis for protein concentrations (CoAs) and test reports were provided by the applicant.

Two subjects in the study B5381001 and 4 subjects in the study B5381007 were excluded from the primary PK analysis, because the serum drug concentration in the pre-dose sample was >5% of the C_{max}. The studies were parallel group studies in healthy subjects. Consequently, clarification was needed for the high adalimumab concentrations in pre-dose samples. The applicant tried to find the reason for the pre-dose adalimumab concentrations > 5% of the C_{max}; however, no reason was identified. The number of subjects having high pre-dose adalimumab concentrations was small and the subjects were in different study groups, hence, it can be considered that the exclusion of these subjects from the primary PK analysis did not affect the results.

Clinical study B5381002 in RA patients with MTX

The mean serum concentrations (adalimumab trough concentrations) were slightly higher for the adalimumab-Pfizer group than Humira-EU group throughout the whole study. It can be agreed that there existed considerable overlap in serum concentrations between the studied groups and the variation in the concentrations was high (CVs ranging from 48-75% in TP1 and 65-81% in TP2). The steady-state mean trough concentrations were at the similar level (i.e. ~ 5-8 µg/ml) as reported in RA patients with MTX in the Humira SmPC. Consequently, although the mean adalimumab concentrations were slightly higher with adalimumab-Pfizer than with Humira-EU, the differences in concentrations would not be expected to have any clinically significant impact on efficacy and safety. Upon request, the applicant performed direct comparison of the trough concentrations between adalimumab-Pfizer and Humira-EU, presenting point estimates and 90%CIs. The results confirmed the earlier conclusion that the differences in trough concentrations are not clinically relevant.

Clinical device comparison study B5381005

The equivalence in absorption phase between PFP and PFS in administration of 40 mg SC was demonstrated and also the 90%CIs for the ratios of the geometric means (PFP/PFS) for AUC_{inf} and AUC_{last} were within the limits of 80.00% to 125.00% (including 100.00). Consequently, the PK similarity between PFP and PFS following administration of a 40 mg SC adalimumab-Pfizer dose in healthy subjects can be considered demonstrated.

Population PK analyses

One population PK analysis for healthy subjects and another for RA patients was presented in the dossier. These exploratory analyses are not considered to be relevant in concluding whether adalimumab-Pfizer is biosimilar with Humira.

Root cause investigations before the MAA submission

Based on the root cause investigations (see Chapter 2.4.3. Pharmacokinetics) there are a number of factors that may have contributed to the variable results obtained for the terminal elimination PK parameters in PK studies B5381001 and B5381007. These factors most likely represent a combination of study design factors, including powering limitations for study B5381001, and small differences in immunogenicity across the 2 studies. The high mannose N-linked glycans and protein concentration of the clinical batches might have had an additive effect contributing to the slightly higher PK parameters and trough concentrations observed in the clinical studies.

Other issues

No clinical studies in special populations and no *in vitro* or *in vivo* drug-drug-interaction studies were conducted with adalimumab-Pfizer and this is acceptable.

In the proposed adalimumab-Pfizer SmPC the PK text in the Section 5.2 "Pharmacokinetic properties" was taken straight from the Humira SmPC. If the adalimumab-Pfizer and Humira are considered to be biosimilar it is acceptable to use Humira SmPC text.

2.5.5. Conclusions on clinical pharmacology

The mean concentrations were slightly higher with adalimumab-Pfizer compared to the Humira-EU in all clinical studies. The sampling times for characterisation of the whole PK profiles of studied products in the clinical studies B5381001, B5381005 and B5381007 were too short. However, the biosimilarity of adalimumab-Pfizer to Humira-EU are supported by the PK data from the studies B5381007 (although the point estimates were above 100%) and B5381002 (although the means of trough concentrations were slightly higher for adalimumab-Pfizer compared to Humira-EU). The steady-state mean trough concentrations were in the same level (~ 5-8 µg/ml) in the study B5381002 as reported for RA patients with MTX in the Humira SmPC. The slightly higher concentrations with adalimumab-Pfizer compared to the Humira-EU can be considered clinically non-relevant.

Also, the PK data including the weight as covariate in clinical study B5381001 supports the biosimilarity of adalimumab-Pfizer.

No specific PD biomarkers are available for TNF-α functional studies and the data provided has been based on non-clinical primary pharmacodynamic studies. This is approvable since the question here is about biosimilar development and not of a novel treatment entity. The applicant has attached hs-CRP data, which did not reveal clinically significant differences in the reached hs-CRP levels. The descriptive data from the Vectra-DA analysis, which was composed of 12 biomarkers showed similar high baseline disease activity between adalimumab-Pfizer and Humira-EU. The scores were similar between the 2

treatment arms at each study visit up to week 26.

In conclusion, the available PK/PD data support biosimilarity between Amsparity and the reference product Humira-EU.

2.6. Clinical efficacy

2.6.1. Main study (B5381002)

The main study (B5381002) was a multi-national, 2-arm, randomised, double-blind, parallel group study designed to evaluate the efficacy, safety, population PK, and immunogenicity of PF-06410293 versus adalimumab-EU in combination with methotrexate (MTX) to treat subjects with moderately to severely active RA who had an inadequate response to MTX therapy. This study was also designed to evaluate clinical response, safety and immunogenicity after study drug transition (randomised blind single transition) from adalimumab-EU to PF-06410293 after 6 or 12 months of adalimumab-EU treatment. The study design is presented in Figure 6.

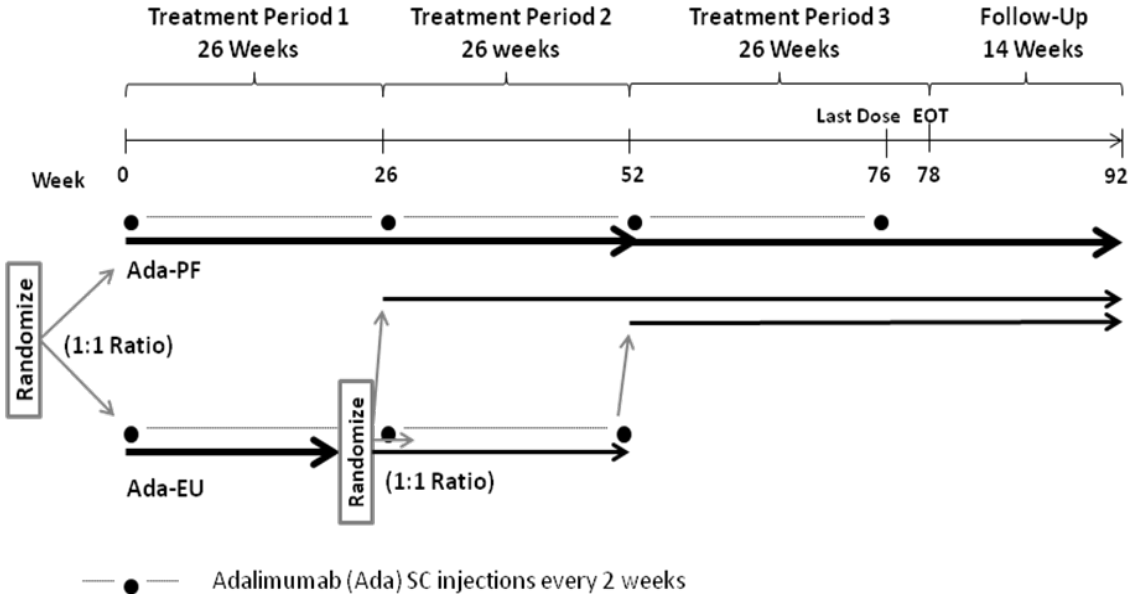


Figure 6 Study design

Methods

Study Participants

Main criteria for inclusion:

1. Male or female subjects aged 18 years or older at the time of informed consent.
2. 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.
3. Met Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA.
4. Moderately to severely active RA disease

5. Subjects had to have received oral, subcutaneous (SC), or intramuscular methotrexate for at least 12 weeks and been on a stable dose for at least 4 weeks prior to first dose of study drug. No current or prior treatment with adalimumab or lymphocyte depleting therapies (e.g., rituximab, Campath). Subjects may have received up to 2 doses of one biologic therapy (any type), including an anti-TNF inhibitor biologic agent (other than adalimumab), enrolling after a washout period of at least 12 weeks or 5 half-lives prior to the first dose of study drug, whichever is longer.
6. If receiving an oral corticosteroid, subject must be on a stable dose of ≤10 mg/day of prednisone (or equivalent) for at least 4 weeks prior to the first dose of study drug.
7. Subject must not receive any IM or intra-articular (IA) corticosteroids within the 4 weeks prior to the first dose of study drug.
8. If receiving an oral or topical non-steroidal anti-inflammatory drug (NSAID)/Cox-2 inhibitor, subject must be on a stable dose of only one NSAID/Cox-2 inhibitor drug for at least 4 weeks prior to the first dose of study drug at a dosage less than or equal to the maximum recommended dose in the product information. In addition, a cardiovascular dose of aspirin (≤325 mg/day) is permitted.

Main criteria for exclusion:

1. Pregnant females and breastfeeding females.
2. Clinically significant laboratory abnormalities at screening, including but not limited to inadequate bone marrow, liver, renal and immune system function.
3. History of severe allergic or hypersensitivity or anaphylactic reaction to a biologic drug or to active or inactive components of the study drug.
4. History of any other autoimmune rheumatic diseases other than RA.
5. Evidence or history of nervous system demyelinating diseases (including multiple sclerosis, optic neuritis, Guillain-Barré syndrome). History of seizure disorder requiring treatment in the previous 5 years prior to screening.
6. Evidence of untreated or inadequately treated latent or active TB.
7. Evidence of uncontrolled, clinically significant diseases, including moderate or severe heart failure (NYHA Class III/IV) or malignancy in the previous 5 years.
8. Chest radiography with evidence of active TB, fungal infections, or other clinically significant abnormalities.
9. Evidence or history of a malignancy within the past 5 years.
10. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that would make the subject inappropriate for entry into this study.
11. Known or screen test positive for human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus (HCV).
12. History of infection (severe).
13. May have received no more than 2 doses of one biologic therapy (other than adalimumab or lymphocyte depleting therapy).

14. Exposure to any live vaccines within 4 weeks prior to administration of the first dose of study drug
15. Any second DMARD must be washed out prior to the first study dose.

Treatments

The study treatment was provided through 3 treatment periods.

- Treatment period 1 (TP1) began with the first dose of study drug at Week 0 (Day 1) and concluded with the completion of Week 26 pre-dose assessments. Subjects were blindly randomised into adalimumab-EU and PF-06410293 in a 1:1 ratio.
- Treatment period 2 (TP2) began with the study drug dosing for Week 26, and concluded with the completion of Week 52 pre-dose assessments. At the beginning of TP2, eligible subjects from the adalimumab-EU arm were blindly re-randomised in a 1:1 ratio to remain on adalimumab-EU or transition to PF-06410293. Week 52 was the end of the blinded treatment periods in this study.
- Treatment period 3 (TP3) began with Week 52 study drug dosing, with last study drug dosing scheduled on Week 76 and the end of treatment (EOT) visit on Week 78. At the beginning of TP3, all the remaining subjects on adalimumab-EU were switched to PF-06410293 (open label).
- Follow-Up Period: 16 weeks after the last dose of study drug (up to Week 92).

Investigators remained blinded to treatment assignments during TP1 and TP2 until the final study database lock.

Following the first abdominal injection at the site, the study subjects self-administered 40 mg SC Amsparity or Humira-EU in a prefilled syringe (PFS) on a regular day of the week every other week throughout the study treatment periods. The treatment was according to the reference product labelling.

The subjects received the stable background regimen of oral or intramuscular methotrexate (10 to 25 mg per week). Subjects were also required to receive a stable background dose of oral folate.

Subjects could also have been treated with additional concomitant therapies including low dose oral corticosteroids, 1 non–steroidal anti-inflammatory drug (NSAID) or cyclooxygenase–2 (COX–2) inhibitor, and non–opioid and allowed opioid analgesics, if meeting the study inclusion criteria and not meeting any exclusion criteria.

Objectives

The primary objective of Study B5381002 was to compare the treatment efficacy (ACR20 at Week 12) between Amsparity and Humira-EU. The hypothesis tested was the equivalence between the treatments.

The secondary objectives were: to evaluate the overall safety (including immunogenicity) and tolerability; to evaluate the multiple composite and individual parameters of clinical response; to evaluate the overall safety, tolerability and immunogenicity; to evaluate the population pharmacokinetics (PK) and pharmacodynamic (PD) response.

Outcomes/endpoints

The primary efficacy endpoint was ACR20 (20% improvement by American College of Rheumatology definition of improvement criteria) at Week 12.

The secondary efficacy endpoints 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 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 $\leq$ 2.6) at Week 12 and other time points (Weeks 2, 4, 6, 8, 18 and 26).
- Proportion of subjects with ACR/EULAR (European League Against Rheumatism) remission at Week 12 and other time points (Weeks 2, 4, 6, 8, 18 and 26).

Sample size

This study planned to enrol 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% confidence interval (CI) for the observed difference in ACR20 response rates fell within the equivalence margin of (-14%, 14%) in ITT population. The power calculation assumed the expected Week 12 ACR20 response rates for PF-06410293 and adalimumab-EU to both be 60.0%. Sample size was calculated using the method provided in Chow, et al (2008)[1].

The sample size was higher than planned, 596 subjects were enrolled.

The equivalence margin was derived using a meta-analysis of historical published study data from 4 studies (Keystone 2004[2], Weinblatt 2003[3], Kim 2017[4], Chen 2009[5]). This margin was also derived to demonstrate ≥50% preservation of the historical Week 12 ACR20 response rate difference based on the lower bound of the 2-sided 95% CI for Humira as compared with placebo, in RA subjects with inadequate response to MTX. The equivalence margin was endorsed by CHMP.

[1] Chow SC, Shao J, Wang H. Sample size calculations in clinical research, second edition. Boca Raton: Taylor & Francis. 2008:1–358.
[2] Keystone EC, Kavanaugh AF, Sharp JT, 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;50:1400–1.
[3] Weinblatt ME, Keystone EC, Furst DE 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 Jan;48(1):35-45
[4] Kim H-Y, Lee S-K, Song YW, 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 J Rheumatol 2007;10:9–16.
[5] Chen DY, Chou SJ, Hsieh TY, 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 Formosan Med Assoc 2009;108(4):310-9.

Randomisation

On Day 1, prior to study drug dosing, subjects were randomised in a 1:1 ratio into 1 of 2 treatment arms to receive Amsparity or Humira-EU. Randomisation was stratified by geographic region ([North America, and Western Europe]; Japan; [South Korea and Taiwan]; Latin America; Rest of the World).

A second randomisation was performed prior to dosing at Week 26 for all subjects who were continuing into TP2; subjects with insufficient disease response were withdrawn from further study treatment at the end of TP1 and were not re-randomised. At the time of the second randomisation, all subjects received a new randomisation code. Only subjects initially randomised to the Humira-EU treatment arm were potentially impacted, as these subjects were blindly re-randomised in a 1:1 ratio to either remain on Humira-EU or to switch Amsparity starting with the Week 26 dose. All subjects were to receive open label treatment with Amsparity starting at Week 52.

Blinding (masking)

Amsparity or Humira-EU PFS were supplied packaged as blinded supplies in which the external packaging cartons for Amsparity and Humira-EU appeared identical and were identifiable with a unique study drug container number. The study drug was labelled such that the subject and study staffs were unable to determine from the dispensed syringe packaging which treatment was assigned to the subject.

Subject unique identifiers were associated with their randomisation and re-randomisation schedules and treatment assignments, and were retained centrally throughout the study. The pharmacist or approved representative who dispensed the study drug remained blinded to the assigned study drug(s) in TP1 and TP2 of the study. The study subjects, investigators, site staff, pharmacist, and Sponsor's personnel directly involved in the study conduct remained blinded to the individually weighted residuals (IWRS) treatment assignments in TP1 and TP2 throughout the study conduct. The only exception was when unblinding was required in the event of an emerging safety issue.

Statistical methods

The Intent-to-treat population (ITT) was defined as all subjects who were randomised to study treatment. The ITT population was used as the primary analysis population. This population was used for subject accountability and all efficacy analyses.

The per protocol (PP) population was defined as all subjects who were randomised and received the study treatment as planned up to Week 12, had a Week 12 evaluation, and had no major protocol deviations.

The primary efficacy endpoint was the proportion of subjects achieving a 20% or greater improvement in ACR clinical response at Week 12. The proportion of subjects achieving ACR20 response rate at Week 12 was analysed by calculating a point estimate with 95% CIs for the difference between the 2 treatment arms. The 95% CI was calculated using two different methods: Farrington-Manning score statistic and an unconditional approach. Neither of the methods was considered primary.

The primary analysis for ACR20 was performed with the missing data imputed using a non-responder imputation method. This method imputed missing ACR20 response at Week 12 as 'non-response; it also set to 'non-response' those ACR20 responses observed at Week 12 for subjects who discontinued treatment prior to Week 12.

Results

Participant flow

There were 1231 subjects screened for the study. Then, 597 subjects were randomised and 559 completed TP1. A total of 584 subjects (291/297 vs. 293/300 in adalimumab-Pfizer and Humira-EU groups respectively) completed Week 12 (primary endpoint) and 551 subjects entered TP2 of whom 504 completed TP2 (Table 11, Table 12).

Table 11 Subject disposition, ITT population – TP1

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)

Table 12 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)

The ITT population is defined as all subjects who were re-randomised to TP2.
One Subject treated with adalimumab-EU/adalimumab-EU and one treated with PF-06410293/PF-06410293 withdrew from treatment due to AEs and completed the follow-up per protocol, but were incorrectly recorded as "Discontinued from Study" due to AEs on the end of study page.
a. One subject was re-randomised but never received any treatment in TP2. This subject's final dose of study treatment was in TP1, and this subject should not have been re-randomised into TP2.

Recruitment

First subject first visit in study B5381002 was on the 25th of June 2015. Last subject completing week 26 visit was on the 31st of August 2016 and the last subject completing week 52 visit was on the 1st of March 2017.

Conduct of the study

Amendments

Six protocol amendments were implemented globally or locally, out of which numbers 4-5 were implemented after the study start. These latest amendments 4 and 5 affected the patients screening, inclusion/ exclusion criteria, and concomitant treatment.

The applicant clarifies the impact of protocol amendments 4 and 5 on proper study conduct.

Protocol 4 amendments having an impact on subject enrolment included beta-D-glucan testing to exclude patients with an invasive fungal infection and anti-double stranded deoxyribonucleic acid (DNA) (anti-dsDNA) anti-dsDNA antibody testing in Japanese subjects to exclude lupus, lupus-like syndromes, hepatitis, or other conditions associated with the presence of anti-dsDNA antibodies (other than rheumatoid arthritis [RA]). The latter testing was scheduled in Screening, Week 26, Week 52 and Week 78. Only one subject developed anti-dsDNA antibodies at screening with reported lupus-like syndrome, which resolved on Study Day 443. Regarding the former the applicant claims the given eligibility criteria to have no impact on study conduct.

Protocol amendment 5 contained the allowance of inclusion of subjects with past medical history of seizures, not present in recent 5 years, inclusion of subjects with Hepatitis B surface antibody (HBsAb) and Hepatitis B core antibody (HBcAb), and inclusion of subjects who were previously treated for latent TB after at least 4 weeks of treatment to be enrolled. According to the applicant these enrolment criteria did not have any impact on study conduct.

Based on the Applicants response the baseline DAS28-CRP prior and after the protocol Amendment 5 in 577 and 20 patients, respectively, did not deviate significantly on median and mean values. The 3 Japanese patients who were excluded based on Amendment 5 were not assessed for the RA status. Their exclusion is not expected to affect the overall outcome of the trial. Based on these data the introduction of the Amendment 5 is not expected to interfere with the main study results.

Protocol deviations

A total of 30 (10.1%) subjects in the Amsparity arm and 46 (15.3%) subjects in the Humira-EU arm were excluded from the PP population. The most frequent reasons for exclusion were not receiving complete investigational product up to Week 12 and failure to meet inclusion/exclusion criteria.

Three subjects in Humira-EU group received incorrect study drug and 1 subject did not receive all 6 injections before Week 12 evaluation. Also, few protocol violations before Week 12 in the use of prohibited concomitant biologic medication and required concomitant MTX as well as in the protocol for joint count measurement occurred.

The applicant clarified that the three subjects in the Humira-EU treatment arm who received incorrect study drug and 1 subject in the Humira-EU treatment arm that did not receive all 6 injections before the Week 12 evaluation were excluded from the PP population. The sensitivity analysis in the PP population did not show different result to the ITT population these protocol violations are not considered to have an impact on the overall study outcome.

In general, no significant difference in numbers of protocol violations were seen between compared groups.

GCP inspection

A routine GCP inspection was performed at three investigator sites for study B5381002. Overall, twelve major findings and a number of minor findings were reported by the inspectors from all three sites. No critical findings were reported at any site. The inspection team considered that the trial was performed in compliance with ethical and GCP principles and the data from the inspected sites was considered by the inspectors to be of sufficient quality. The CHMP considered that the GCP findings reported did not impact on the study results and conclusions.

Baseline data

Demographics characteristic at baseline for TP1 and TP2 (ITT population) are summarised in Table 13 and Table 14 .

Table 13 Demographic Characteristics at Baseline, ITT Population – TP1

	PF-06410293 N=297	Adalimumab-EU N=300	Total N=597
Gender, n (%)			
Female	241 (81.1)	229 (76.3)	470 (78.7)
Male	56 (18.9)	71 (23.7)	127 (21.3)
Age (years)			
Mean (SD)	51.5 (13.6)	53.5 (12.9)	52.5 (13.2)
Median (range)	54.0 (19-80)	55.0 (18-79)	54.0 (18-80)
Weight (kg)			
n (%)	297 (100.0)	299 (99.7)	596 (99.8)
Mean (SD)	74.7 (17.5)	76.2 (20.8)	75.4 (19.2)
Median (range)	72.3 (38.0-132.0)	74.0 (41.9-178.2)	73.0 (38.0-178.2)
Body Mass Index (kg/m^2)			
n (%)	295 (99.3)	297 (99.0)	592 (99.2)
Mean (SD)	27.5 (6.1)	28.1 (7.3)	27.8 (6.7)
Median (range)	26.9 (16.0-52.9)	27.0 (16.3-59.7)	26.9 (16.0-59.7)
Race, n (%)			
White	261 (87.9)	256 (85.3)	517 (86.6)
Black	6 (2.0)	9 (3.0)	15 (2.5)
Asian	16 (5.4)	17 (5.7)	33 (5.5)
Other	14 (4.7)	18 (6.0)	32 (5.4)
Ethnicity, n (%)			
Hispanic/Latino	25 (8.4)	29 (9.7)	54 (9.0)
Not Hispanic/Latino	272 (91.6)	271 (90.3)	543 (91.0)

Body mass index was computed as weight (kg)/(height [cm]/100)^2.
One (1) subject was randomised but withdrew the consent, and never received study drug.

Table 14 Demographic Characteristics at Baseline, ITT Population – TP2

	PF-06410293/ PF-06410293 (N = 283)	Adalimumab-EU/ Adalimumab-EU (N = 135)	Adalimumab-EU/ PF-06410293 (N = 134)	Total (N=552)
Gender, n (%)				
Female	229 (80.9)	108 (80.0)	95 (70.9)	432 (78.3)
Male	54 (19.1)	27 (20.0)	39 (29.1)	120 (21.7)
Age (years)				
Mean (SD)	51.3 (13.7)	53.6 (12.1)	53.4 (13.4)	52.4 (13.3)
Median (range)	53.0 (19-80)	55.0 (24-78)	54.0 (18-79)	54.0 (18-80)
Weight (kg)				
Mean (SD)	74.6 (17.7)	76.2 (20.4)	75.7 (18.7)	75.3 (18.6)
Median (range)	72.0 (38.0-132.0)	74.0 (45.0-144.7)	74.1 (41.9-136.6)	73.0 (38.0-144.7)
Body Mass Index (kg/m^2)				
Mean (SD)	27.5 (6.2)	28.4 (7.4)	27.5 (6.4)	27.7 (6.6)
Median (range)	26.8 (16.0-52.9)	27.3 (16.3-56.4)	26.9 (17.8-48.7)	26.9 (16.0-56.4)
Race, n (%)				
White	250 (88.3)	113 (83.7)	116 (86.6)	479 (86.8)
Black	6 (2.1)	7 (5.2)	2 (1.5)	15 (2.7)
Asian	14 (4.9)	8 (5.9)	6 (4.5)	28 (5.1)
Other	13 (4.6)	7 (5.2)	10 (7.5)	30 (5.4)
Ethnicity, n (%)				
Hispanic/Latino	24 (8.5)	13 (9.6)	10 (7.5)	47 (8.5)
Not Hispanic/Latino	259 (91.5)	122 (90.4)	124 (92.5)	505 (91.5)

Baseline RA characteristics are summarised in Table 15 and Table 16.

Table 15 Baseline Rheumatoid Arthritis Characteristics, ITT Population – TP1

Study Day 1	PF-06410293 N=297	Adalimumab-EU N=300	Total N=597
RA duration[a] (years)			
Mean (SD)	6.8 (7.2)	6.8 (6.9)	6.8 (7.0)
Median (range)	4.1 (0.4 - 44.0)	4.9 (0.1 - 43.0)	4.7 (0.1 - 44.0)
Positive RF and/or anti-CCP positive, n (%)	242 (81.5)	245 (81.7)	487 (81.6)
Replaced and/or fused joint, n (%)	19 (6.4)	22 (7.3)	41 (6.9)
Swollen joint count			
Mean (SD)	15.4 (7.8)	17.0 (9.8)	16.2 (8.9)
Median (range)	13.0 (6 - 62)	14.0 (5 - 60)	14.0 (5 - 62)
Tender joint count			
Mean (SD)	24.3 (12.3)	26.7 (14.8)	25.5 (13.6)
Median (range)	22.0 (6 - 68)	22.5 (6 - 68)	22.0 (6 - 68)
hs-CRP (mg/L)			
Mean (SD)	21.3 (22.7)	22.8 (25.2)	22.1 (24.0)
Median (range)	14.7 (0.2 - 169)	16.0 (0.2 - 192)	15.3 (0.2 - 192)
DAS28-4 (CRP)			
Mean (SD)	5.9 (0.9)	6.1 (0.9)	6.0 (0.9)
Median (range)	5.9 (2.6 - 8.1)	6.1 (3.4 - 7.9)	6.0 (2.6 - 8.1)
HAQ-DI[c]			
Mean (SD)	1.5 (0.6)	1.7 (0.6)	1.6 (0.6)
Median (range)	1.5 (0 - 3)	1.8 (0 - 3)	1.6 (0 - 3)
PAAP			
Mean (SD)	63.7 (18.4)	65.9 (19.6)	NC
Median (range)	65.0 (0 - 99)	69.0 (3 - 100)	NC
PGA			
Mean (SD)	64.4 (19.3)	68.2 (19.5)	NC
Median (range)	67.0 (0 - 100)	72.0 (7 - 100)	NC
PGAA			
Mean (SD)	65.0 (15.2)	66.7 (15.8)	NC
Median (range)	66.0 (8 - 95)	68.0 (11 - 100)	NC
Prior use of 1 biologic drug[b], n (%)	8 (2.7)	5 (1.7)	13 (2.2)
Prior and current non-biologic DMARDs(including MTX)			
Mean (SD)	1.5 (0.9)	1.5 (0.9)	1.5 (0.9)
Median (range)	1.0 (1 - 8)	1.0 (1 - 5)	1.0 (1 - 8)
MTX dosage (mg/week)			
Mean (SD)	15.2 (4.4)	15.2 (4.5)	15.2 (4.4)
Median (range)	15.0 (5 - 25)	15.0 (5 - 25)	15.0 (5 - 25)
Duration of MTX use, n (%)			
<1 year	163 (54.9)	151 (50.3)	314 (52.6)
≥1 year to <3 years	72 (24.2)	77 (25.7)	149 (25.0)
≥3 years	62 (20.9)	71 (23.7)	133 (22.3)
Corticosteroid use, n (%)	164 (55.2)	170 (56.7)	334 (55.9)

a. One (1) subject had an incorrect RA diagnosis date recorded; the RA duration data is not corrected for this table and any corresponding text.
b. Use of no more than 2 doses of one non-adalimumab biologic drug. Five (5) of the 13 subjects exceeded this level of prior biologic use.

Table 16 Baseline Rheumatoid Arthritis Characteristics, ITT Population – TP2

Study Day 1	PF-06410293/ PF-06410293 (N = 283)	Adalimumab-EU/ Adalimumab-EU (N = 135)	Adalimumab-EU/ PF-06410293 (N = 134)	Total (N=552)
RA duration (years)				
Mean (SD)	6.9 (7.3)	7.1 (6.6)	6.6 (7.0)	6.9 (7.0)
Median (range)	4.1 (0.4 - 44.0)	5.1 (0.4 - 38.0)	4.5 (0.4 - 43.0)	4.8 (0.4 - 44.0)
Positive RF/ anti-CCP, n (%)	229 (80.9)	116 (85.9)	108 (80.6)	453 (82.1)
Replaced and/or fused joint, n (%)	18 (6.4)	10 (7.4)	8 (6.0)	36 (6.5)
Swollen joint count				
Mean (SD)	15.1 (7.7)	17.1 (9.6)	17.0 (10.3)	16.1 (8.9)
Median (range)	13.0 (6 - 62)	15.0 (5 - 55)	14.0 (6 - 60)	14.0 (5 - 62)
Tender joint count				
Mean (SD)	23.7 (11.9)	26.8 (14.7)	25.5 (15.0)	24.9 (13.5)
Median (range)	21.0 (6 - 68)	23.0 (6 - 68)	22.0 (6 - 68)	22.0 (6 - 68)
hs-CRP (mg/L)				
Mean (SD)	21.2 (22.5)	22.0 (24.5)	22.3 (25.9)	21.6 (23.8)
Median (range)	14.7 (0.2 - 169)	16.3 (0.2 - 179)	15.1 (0.2 - 192)	14.9 (0.2 - 192)
DAS28-4 (CRP)				
Mean (SD)	5.9 (0.9)	6.1 (0.8)	6.0 (1.0)	6.0 (0.9)
Median (range)	5.9 (2.6 - 8.1)	6.0 (3.5 - 7.8)	6.1 (3.4 - 7.8)	6.0 (2.6 - 8.1)
HAQ-DI				
Mean (SD)	1.5 (0.6)	1.6 (0.7)	1.7 (0.6)	1.6 (0.6)
Median (range)	1.5 (0 - 3)	1.8 (0 - 3)	1.8 (0 - 3)	1.6 (0 - 3)
PAAP				
Mean (SD)	63.5 (18.0)	65.6 (19.9)	64.4 (19.4)	64.2 (18.8)
Median (range)	64.0 (0 - 99)	68.0 (9 - 100)	67.0 (3 - 98)	67.0 (0 - 100)
PGA				
Mean (SD)	64.2 (19.1)	67.5 (21.0)	67.8 (17.6)	65.9 (19.3)
Median (range)	67.0 (0 - 100)	72.0 (7 - 100)	70.0 (18 - 98)	68.0 (0 - 100)
PGAA				
Mean (SD)	64.9 (15.2)	66.3 (15.3)	67.0 (15.6)	65.8 (15.3)
Median (range)	67.0 (8 - 95)	66.0 (18 - 95)	68.5 (17 - 100)	67.0 (8 - 100)
Prior use of 1 biologic drug[a], n (%)	8 (2.8)	4 (3.0)	1 (0.7)	13 (2.4)
Prior and current DMARDs (non-biologic) including MTX				
Mean (SD)	1.5 (0.9)	1.5 (0.9)	1.5 (0.8)	1.5 (0.9)
Median (range)	1.0 (1 - 8)	1.0 (1 - 5)	1.0 (1 - 5)	1.0 (1 - 8)
MTX dosage (mg/week)				
Mean (SD)	15.2 (4.4)	15.7 (4.7)	14.7 (4.0)	15.2 (4.4)
Median (range)	15.0 (5.0 - 25.0)	15.0 (6.0 - 25.0)	15.0 (5.0 - 25.0)	15.0 (5.0 - 25.0)
Duration of MTX use, n (%)				
<1 year	154 (54.4)	57 (42.2)	74 (55.2)	285 (51.6)
≥1 year to <3 years	69 (24.4)	36 (26.7)	36 (26.9)	141 (25.5)
≥3 years	60 (21.2)	42 (31.1)	24 (17.9)	126 (22.8)
Corticosteroid use, n (%)	155 (54.8)	77 (57.0)	80 (59.7)	312 (56.5)

a. Use of no more than 2 doses of 1 non-adalimumab biologic drug.

The baseline characteristics between compared treatment groups are highly similar at TP1 baseline as well as at TP2 baseline. The mean MTX dose 15.2 mg/week was the same between groups as well as the percentage of patients with prior corticosteroid use (appr. half of the patients).

The baseline rheumatoid arthritis characteristics were similar in RA duration, positive RF status, joint status, DAS-28 score, patient and professional global assessment and pain assessment as well as prior MTX, DMARD, and biologics use. Also, concomitant drug treatment and rescue therapy use was infrequent and the groups did not deviate significantly regarding it.

Numbers analysed

Altogether 1231 subjects were screened for the study, of whom 597 were randomized and 559 subjects completed TP1 (Table 11). A total of 584 subjects (291/297 vs. 293/300 in adalimumab-Pfizer and Humira-EU groups respectively) completed Week 12 (primary endpoint) and 551 subjects entered TP2 of whom 504 completed TP2 (Table 12).

Outcomes and estimation

Treatment period 1 (TP1)

Primary outcome

The **ACR20 response rate at week 12** in the Amsparity (PF-06410293) and adalimumab-EU groups are presented in Table 17. Therapeutic equivalence was demonstrated.

Table 17 Descriptive Summary of ACR20 Response at Week 12 – TP1

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

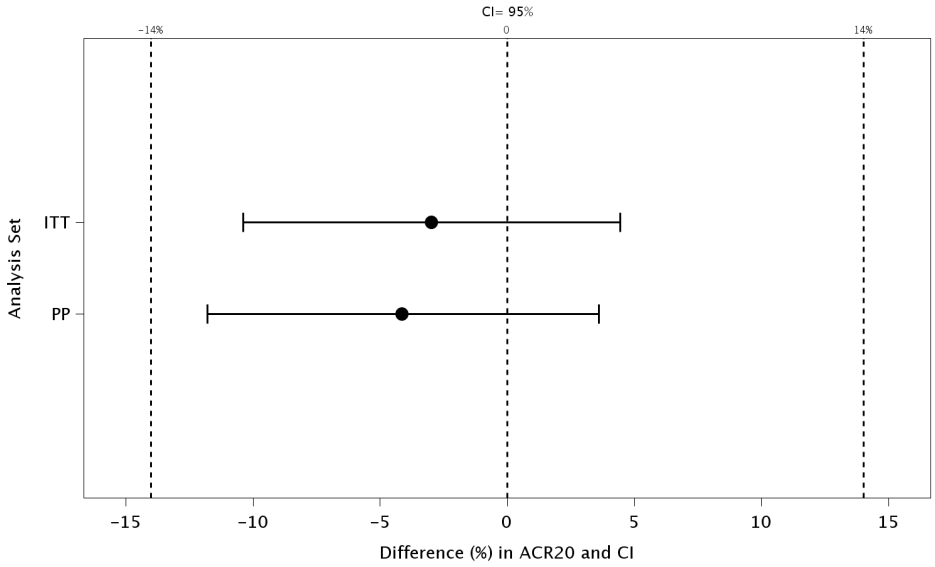
No imputation was applied for the PP population.
Per protocol 1 Subject had Week 12 ACR20 assessment on Day 71 (14 days before Day 85); however, the assessment fell outside of the Week 12 data analysis window (Day 72 - Day 106) by 1 day, resulting in a missing Week 12 ACR response. This subject was excluded from the PP analysis.

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). Treatment comparison for the ITT population using NRI is presented in Table 18. The 95% CI for the difference in ACR20 response rate point estimate of -2.98 at week 12 between the treatments [−10.38%, 4.44%] in ITT population was well within the pre-defined equivalence margin of ±14%. The robustness of the result was supported by the analysis in the PP population applying non-responder analysis. The 95% CI for the treatment difference was -4.14% [−11.79%, 3.61%] (Table 18, Figure 7, Figure 8).

Table 18 Exact Binomial Approach for ACR20 Response Rate at Week 12, Using Non–Responder Imputation for Missing Data, ITT and PP Populations – TP1 (95% and 90% CIs)

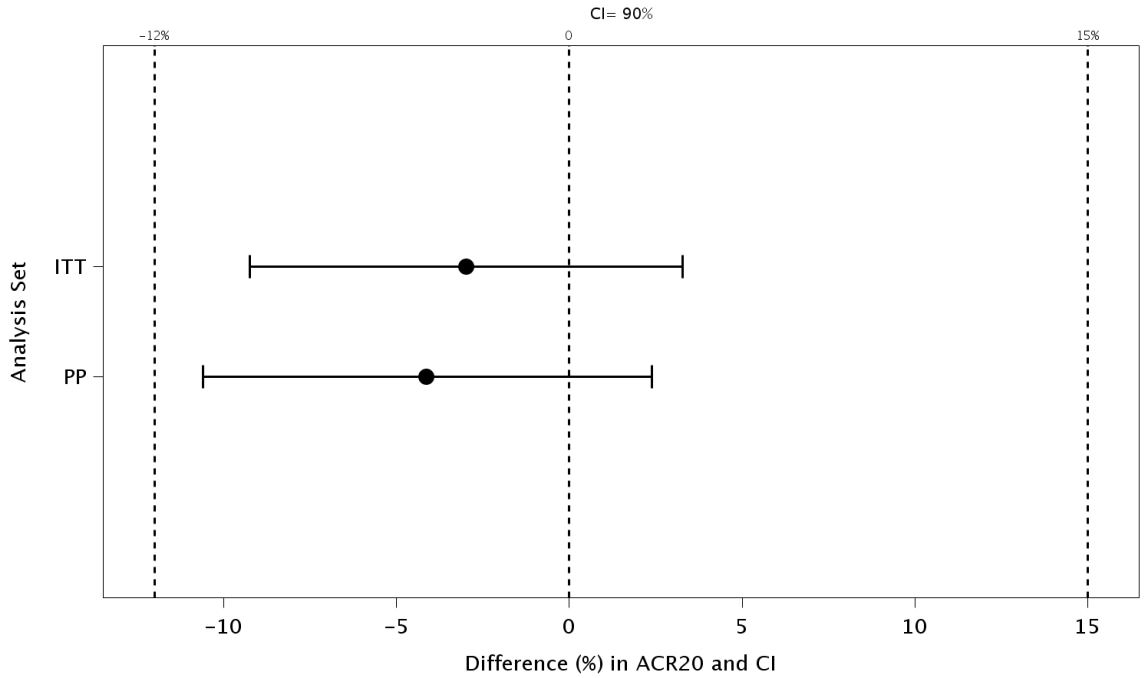
Visit	Exact Method	PF-06410293 n (%)	Adalimumab-EU n (%)	Difference in ACR20 Response Rate (PF-06410293 – Adalimumab-EU) (%) Point Estimate	95% CI	90% CI
ITT Population						
Week 12	N	297	300			
	Score statistic method[a]	203 (68.4)	214 (71.3)	-2.98	-10.38, 4.44	-9.25, 3.28
	Unconditional approach	203 (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

For subjects who discontinued treatment earlier (prior to Week 12) or had a missing Week 12 assessment for any reason, a non–responder was assigned to their Week 12 ACR20 assessment.
PP Subject had Week 12 ACR20 assessment on Day 71 (14 days before Day 85); however, the assessment fell outside of the Week 12 data analysis window (Day 72-Day 106) by 1 day, resulting in a missing Week 12 ACR response. This subject was excluded from the PP analysis.
No imputation was applied for the PP population
a. Score statistic method was the main primary analysis method used. If it did not converge then the unconditional approach was to be used.



This plot is based on exact score statistic method.
Comparisons between treatments are computed as PF-06410293 versus adalimumab-EU.

Figure 7 Therapeutic Equivalence of ACR20 Response Rate at Week 12 Established Between PF-06410293 and Adalimumab-EU, Using Non-Responder Imputation for Missing Data – TP1 (95% CI and Symmetric Margin)



Comparisons between treatments were computed as PF-06410293 versus adalimumab-EU.

Figure 8 Therapeutic Equivalence of ACR20 Response Rate at Week 12 Established Between PF-06410293 and Adalimumab-EU, Using Non-Responder Imputation for Missing Data – TP1 (90% CI and Asymmetric Margin)

The sensitivity analysis of ACR20 response rate at Week 12 (with observed data) adjusting for region was also within equivalence margin containing also value 0 (no difference) in both ITT and PP population. The analyses assuming all the missing observations in adalimumab-Pfizer arm as non-responders and all the missing observations in adalimumab-EU arm as responders and vice versa showed the 95% CI within acceptance margin, which included also value 0.

Secondary outcomes

A mixed-effect repeated measures model was used to estimate the difference in **DAS28-4 (CRP)** at visits up to Week 26. The differences between the treatment arms at each visit were all less than the minimal clinically important difference of 0.6 for DAS28-4 (CRP) in both ITT and PP populations. Mean changes from baseline in DAS28-4 (CRP) in the ITT population are presented in Figure 9.

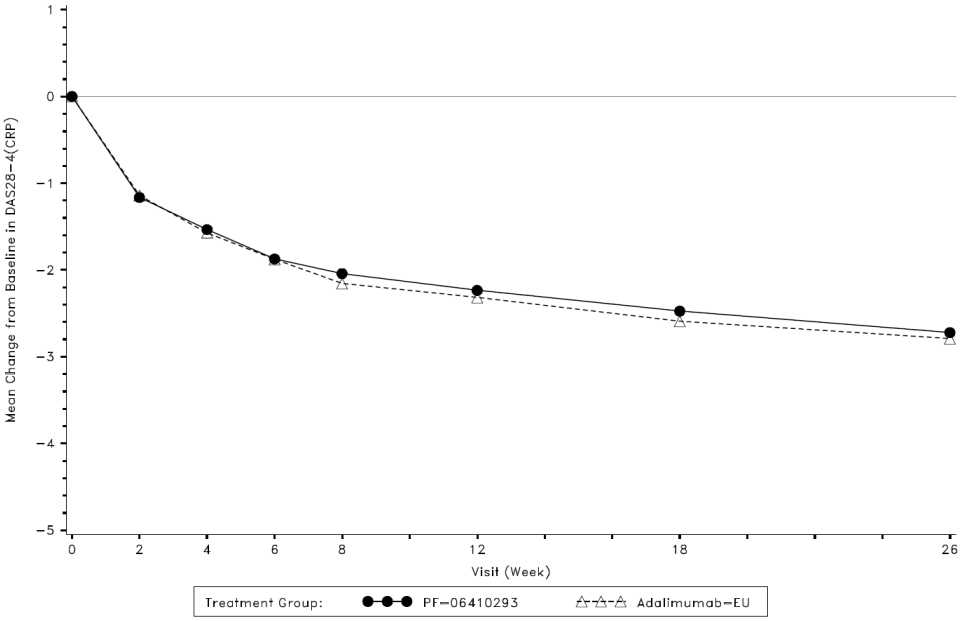


Figure 9 Mean change from baseline in DAS28-4 (CRP) by visit, ITT population – TP1

In addition, a tipping point analysis was conducted which showed the mean change from baseline across all visits in TP1 is within the range of (-1.1, -2.8) suggesting that the missing data do not substantially impact the conclusion for the **DAS28-4 (CRP)** change from baseline at Week 12 treatment comparison.

A total of 54.5% and 49.0% subjects had a good **EULAR response** in the adalimumab-Pfizer and Humira-EU arms, respectively, at Week 26.

The difference in ACR20 response rate between the treatment arms ranged from -4.17% to 2.26% across all study visits in the ITT population and ranged from -3.64% to 2.82% in the PP population, the 95% CI being, although not pre-specified, contained within equivalence margin set for Week 12 [-14%, 14%] (Figure 10).

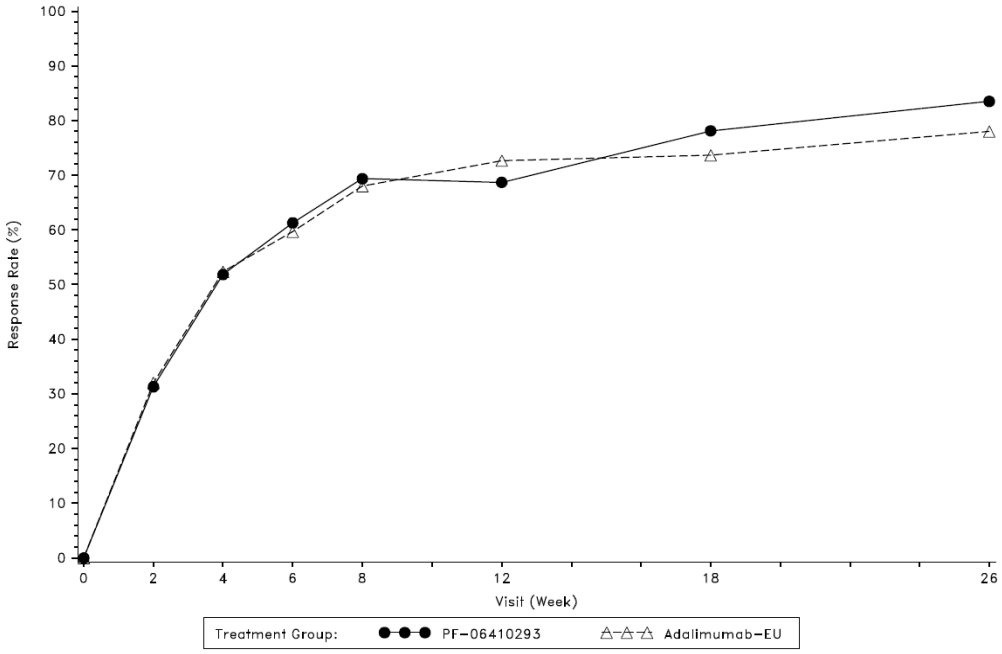


Figure 10 ACR20 response rate by visit, ITT population - TP1

Similarly **ACR50 and ACR70 response rates** were very similar between compared groups with the treatment differences in response rates ranging from -1.88% to 4.93% and 2.50% to 0.79%, respectively, across all study visits in the ITT population up to Week 26.

Mean baseline **PAAP score** was 63.7 for the adalimumab-Pfizer arm and 65.9 for the Humira-EU arm. The mean score decreased over time by 35.1 in the adalimumab-Pfizer arm, and by 33.5 in the Humira-EU arm at Week 26 as compared to the baseline values. Mean baseline **PGA score** was 64.4 for the adalimumab-Pfizer arm and 68.1 for the Humira-EU arm. The mean score decreased over time by 36.2 in the adalimumab-Pfizer arm, and by 36.3 in the Humira-EU arm at Week 26 as compared to the baseline values.

Mean baseline **hs-CRP concentration** was 21.3 mg/L for the adalimumab-Pfizer arm and 22.8 mg/L for the Humira-EU arm. Mean (SD) hs-CRP level decreased by 9.5 (22.81) mg/L and 12.2 (25.59) in the adalimumab-Pfizer and Humira-EU arm, respectively, at Week 12, while the respective decrease was 11.1 (21.92) and 13.6 (26.47) mg/L at Week 26 as compared to the baseline values Figure 11.

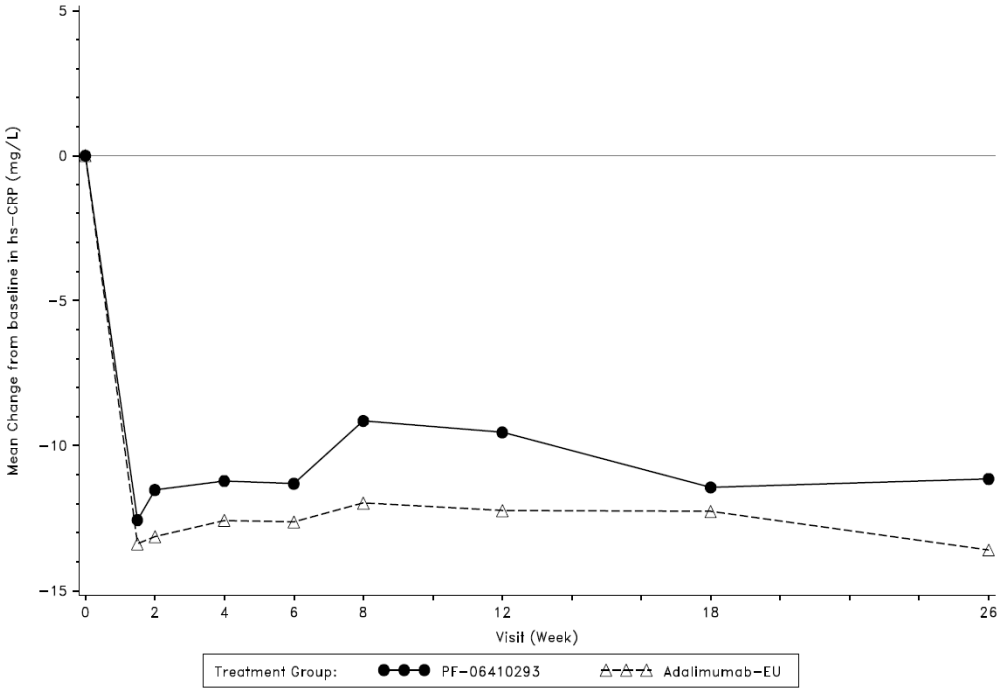


Figure 11 Mean change from baseline in hs-CRP by visit, ITT population – TP1

Subgroup Analysis (TP1)

The subgroups were analysed in their ACR20 response rate at Week 12 and 2-sided 95% CI was calculated. Small number of subjects in each subgroup does not allow reliable comparison, but no clear evidence of marked differences at study Week 12 was seen.

Geographic region

The main differences were seen in the Latin American (including Mexico) subgroup in which high rates of Week 12 ACR20 response overall were seen (see Figure 12).

ADA and NAb development

In both arms, ACR20 response rate at Week 12 trended higher in the ADA negative and in the neutralising antibody (NAb) non-positive subjects, as compared to the ADA positive and NAb positive subjects, respectively. Week 12 ACR20 response rates were 63.7% and 65.7% for the adalimumab-Pfizer and Humira-EU ADA-positive subgroups, respectively, and 70.9% and 77.2% for the adalimumab-Pfizer and Humira-EU ADA-negative subgroups, respectively. Week 12 ACR20 response rates were 50.0% and 64.0% for the adalimumab-Pfizer and Humira-EU NAb-positive subgroups, respectively, and 70.9% and 74.0% for the adalimumab-Pfizer and Humira-EU NAb-non-positive subgroups, respectively.

ACR20 week 26 results also trended higher in the ADA-negative and particularly in the NAb-non-positive subjects. The response rates were similar between the 2 treatment arms for each ADA and NAb status group. The ACR20 response rates at Week 26 were 81.82% and 77.48% for the adalimumab-Pfizer and Humira-EU ADA-positive subgroups, respectively, and 84.85% and 79.59% for the adalimumab-Pfizer and Humira-EU ADA-negative subgroups, respectively. Week 26 ACR20 response rates were 65.8% and 66.7% for the adalimumab-Pfizer and Humira-EU NAb-positive subgroups, respectively, and 86.3% and 80.5% for the adalimumab-Pfizer and Humira-EU NAb-non-positive subgroups, respectively. The CIs for the Week 26 ACR20 risk differences (test minus

reference) in each of the ADA positive/negative subgroups all included 0 with the exception of the NAb non-positive subgroup with 90% CI.

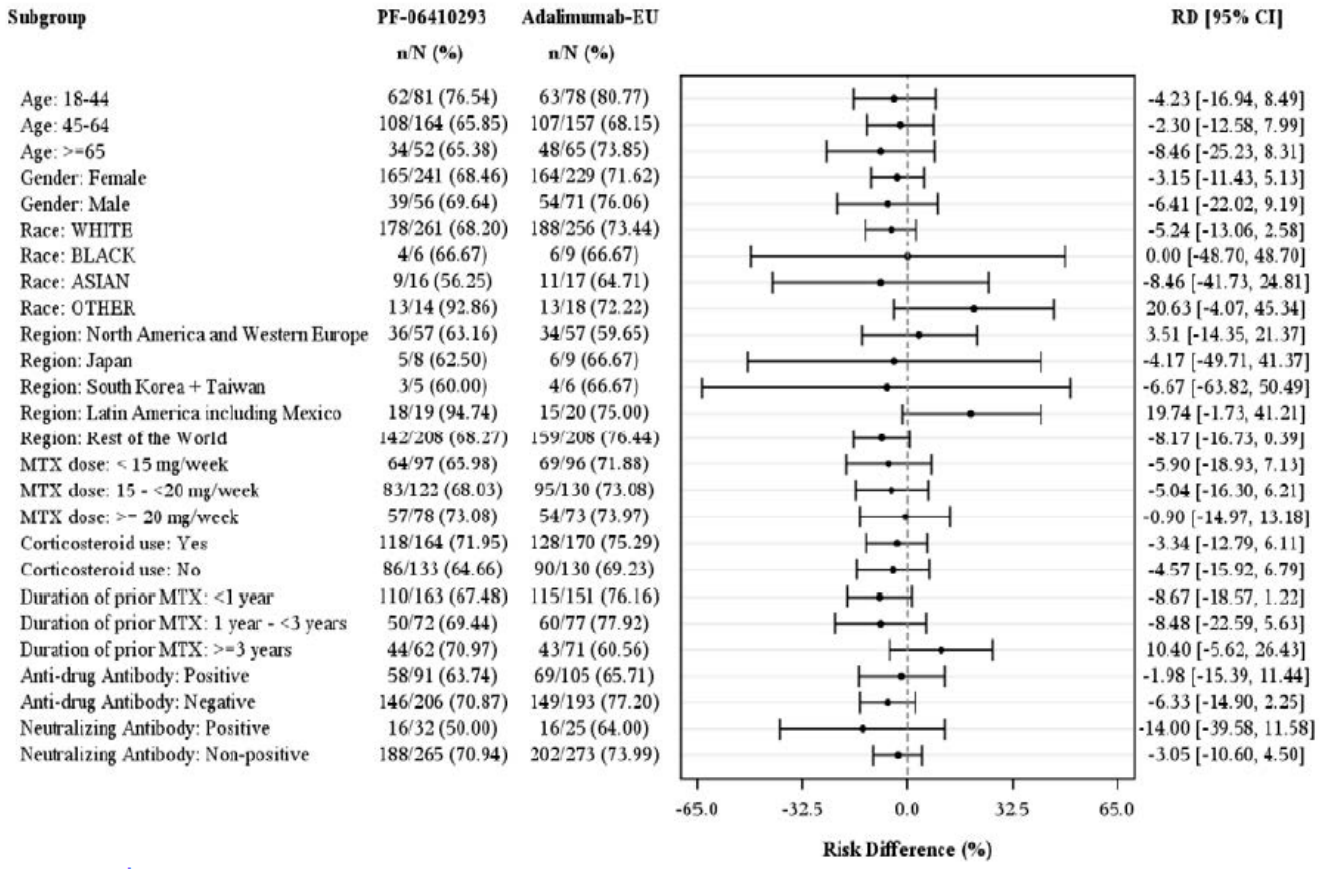


Figure 12 Risk Difference for ACR20 Response at Week 12, by Subgroups, ITT Population (95% CI; Symmetric Margin)

Treatment period 2 (TP2)

Mean **DAS28-4 (CRP)** value at Week 26 pre-dose was 3.2, 3.4, and 3.0 in the Amsparity/Amsparity, Humira-EU/Humira-EU, and Humira-EU/Amsparity groups, respectively, and decreased over TP2 in all study groups to 3.0, 3.2 and 2.8 at Week 52, respectively. The decreases from Week 26 pre-dose to Week 52 were comparable among the 3 treatment groups, and the differences between the treatment groups at each visit were all less than the minimal clinically important difference of 0.6 for DAS28-4 (CRP).

At Week 26 pre-dose, 56.9%, 49.6% and 59.7% of subjects had reached good **EULAR response** in the Amsparity/Amsparity, Humira-EU/Humira-EU, and Humira-EU/Amsparity groups, respectively; the response rates were 59.7%, 45.2% and 63.4% at Week 52, respectively.

The **ACR20** response rates at Week 26 pre-dose for the re-randomised TP2 subjects (ITT population), prior to the first injection of study drug in TP2, were 86.6%, 84.4% and 86.6% for the Amsparity/Amsparity, Humira-EU/Humira-EU, and Humira-EU/Amsparity groups, respectively. The corresponding ACR20 response rates at Week 52 were 82.7%, 79.3% and 84.3%. The ACR20 response rate was maintained in all 3 treatment groups during TP2.

Overall, also the **ACR50** and **ACR70** response rates were comparable among the 3 treatment groups over TP2.

No clinically meaningful differences were observed in the other secondary endpoints although the Amsparity/Amsparity group had marginally worse outcome compared to Humira-EU/Humira-EU group at TP2.

Summary of main study

Table 19 summarises the efficacy results from the main efficacy and safety study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy (section 2.6.3.) as well as section 3 Biosimilarity assessment.

Table 19 Summary of Efficacy for trial B5381002

Title: A Phase 3 Randomized, Double-blind Study Assessing the Efficacy and Safety of PF-06410293 and Adalimumab in Combination with Methotrexate in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Methotrexate		
Study identifier	Pfizer Study B5381002 (ISRCTN number / NCT number NCT02480153) EudraCT number:2014-000352-29	
Design	A multi-national, 2-armed, randomized, double blind, parallel group, comparative clinical study designed to evaluate the safety, efficacy, population PK, and immunogenicity of adalimumab-Pfizer versus adalimumab-EU in combination with methotrexate to treat subjects with moderately to severely active RA	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks 21 days Blinded Period 2: 26 weeks Open-label extension Period 3: 26 weeks Safety follow-up: 16 weeks after the final dose of study drug
Hypothesis	PF-06410293 will be biosimilar to Adalimumab-EU (Equivalence)	
Treatment groups	PF-06410293	PF-06410293 40 mg SC every 2 weeks Duration 76 weeks Number randomized on Day 1= 297
	Adalimumab-EU then: Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU 40 mg SC every 2 weeks Duration 52 weeks (Followed by Open-label extension Period 3, continuing to receive PF-06410293) Number randomized on Day 1= 300 [includes the subjects in the Adalimumab-EU/PF-06410293 box below] [50% of the Adalimumab-EU subjects completing to Week 26 were blindly re-randomized to remain on Adalimumab-EU: Number re-randomized at Week 26 = 135]
	Adalimumab-EU then: Adalimumab-EU/ PF-06410293	Adalimumab-EU 40 mg SC every 2 weeks Duration 26 weeks, then changed to PF-06410293 (Followed by Open-label extension Period 3, continuing to receive PF-06410293) [50% of the Adalimumab-EU subjects completing to Week 26 were blindly re-randomized to change to PF-06410293: Number re-randomized at Week 26 = 134]

Endpoints and definitions	Primary endpoint (also Secondary endpoint at time points other than Week 12)	ACR20 Response	20% improvement in both the tender joint (N=68) (TJC) + swollen joint (N=66) (SJC) counts, and in 3 of 5 additional parameters: Patient's Assessment of Arthritis Pain (PAAP), Patient's Global Assessment of Arthritis (PGA), Physician's Global Assessment of Arthritis, Health Assessment Questionnaire – Disability Index (HAQ-DI), and high sensitivity C-reactive protein (hs-CRP)
	Secondary endpoint	ACR50 Response	50% improvement in both the tender joint (N=68) (TJC) + swollen joint (N=66) (SJC) counts, and in 3 of 5 additional ACR parameters
	Secondary endpoint	ACR70 Response	70% improvement in both the tender joint (N=68) (TJC) + swollen joint (N=66) (SJC) counts, and in 3 of 5 additional ACR parameters
	Secondary endpoint	Change in DAS28-4 (CRP)	DAS28-4 (CRP) calculated by: DAS28-4 (CRP) = 0.56*sqrt (tender joint (N=28) count) + 0.28*sqrt (swollen joint (N=28) count) + 0.36*ln(CRP [mg/L] +1) + 0.014 (PGA [mm]) + 0.96
	Secondary endpoint	EULAR good Response	Subjects had Good EULAR response when: present DAS28-4 (CRP) is ≤3.2 and change from baseline in DAS28-4 (CRP) is >1.2
	Secondary endpoint	DAS Remission (≤2.6)	DAS Remission is present when DAS28-4 (CRP) is ≤2.6
	Secondary endpoint	ACR/EULAR Remission	Subjects were in ACR/EULAR remission when either: Boolean definition: Scores on the TJC (N=28), SJC (N=28), hs-CRP (mg/dL), and PGA (0-10 cm scale) are all ≤1 OR, SDAI is ≤3.3 where SDAI is calculated using the following formula: TJC (N=28), SJC (N=28), PGA (0–10 cm scale), PGAA (0-10 cm scale), and hs-CRP (mg/dL) are summed
	Secondary endpoint	Change in individual ACR components	Change from baseline in the individual ACR parameters listed for the Primary endpoint
Database lock	Week 52 database lock: 26May2017; Final database lock: 05Jan2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population & time point description	Intent to treat Week 12		
Effect estimate per comparison	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	297	300
	Primary endpoint [ITT, NRI] **ACR20 response rate at Week 12**	68.35%	71.33%

		Point estimate of ACR20 response rate treatment difference (PF-06410293 – Adalimumab-EU) at Week 12 = -2.98 [95% CI = (-10.38%, 4.44%)]	
		Non-responder imputation (NRI) 95% confidence interval for treatment difference fell within the pre-specified equivalence margin [-14%, 14%]	
	statistic variability statistic P value	Point estimate Not calculated Not calculated	
Analysis description	**Secondary Endpoints: Treatment Period 1 (Day 1 - Week 26 pre-dose)**		
Analysis population & time point description	Intent to treat Day 1 over time to Week 26 pre-dose (Weeks 2, 4, 6, 8, 12, 18, 26)		
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	297	300
	ACR20 response rate at Week 26	83.5%	78.0%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	297	300
	ACR50 response rate at Week 26	59.6%	54.7%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	297	300
	ACR70 response rate at Week 26	29.6%	31.0%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	288	276
	Change from Baseline in DAS28-4 (CRP) at Week 26	-2.7 (1.18)	-2.8 (1.31)
	Statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	297	300
	EULAR Good Response at Week 26	54.5%	49.0%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	297	300
	DAS Remission (≤2.6) at Week 26	29.3%	33.0%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	297	300
	ACR/EULAR Remission at Week 26	12.8%	14.7%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated

Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	289	278
	Change from baseline in Tender Joint Count at Week 26	-18.4 (11.41)	-19.2 (12.52)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	289	278
	Change from baseline in Swollen Joint Count at Week 26	-12.2 (7.18)	-13.6 (9.12)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	289	278
	Change from baseline in Patient's Assessment of Arthritis Pain at Week 26	-35.1 (24.62)	-33.5 (26.09)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	289	278
	Change from baseline in Patient's Global Assessment of Arthritis at Week 26	-36.2 (25.16)	-36.3 (26.21)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	287	278
	Change from baseline in Physician's Global Assessment of Arthritis at Week 26	-47.2 (18.68)	-46.5 (19.96)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	289	278
	Change from baseline in Health Assessment Questionnaire at Week 26	-0.654 (0.6262)	-0.674 (0.6618)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293	Adalimumab-EU
	Number of subjects	288	276
	Change from baseline in high sensitivity (hs) CRP at Week 26 (mg/L)	-11.1 (21.92)	-13.6 (26.47)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation

Analysis description	**Secondary analysis: Treatment Period 2 (Week 26 - Week 52 pre-dose)**			
Analysis population & time point description	Treatment Period 2 ITT (all subjects re-randomized at Week 26) Week 26 over time to Week 52 pre-dose (Weeks 30, 36, 44, 52)			
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	283	135	134
	ACR20 response rate at Week 52	82.7%	79.3%	84.3%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	283	135	134
	ACR50 response rate at Week 52	62.9%	55.6%	72.4%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	283	135	134
	ACR70 response rate at Week 52	36.4%	31.9%	44.0%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	267	123	127
	Change from Baseline in DAS28-4 (CRP) at Week 52	-2.9 (1.23)	-2.9 (1.33)	-3.3 (1.26)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	283	135	134
	EULAR Good Response at Week 52	59.7%	45.2%	63.4%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	283	135	134
	DAS Remission (≤2.6) at Week 52	37.8%	29.6%	44.0%
	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	283	135	134
	ACR/EULAR Remission at Week 52	18.7%	20.7%	26.1%

variability	statistic variability statistic	Point estimate Not calculated	Point estimate Not calculated	Point estimate Not calculated
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	268	123	129
	Change from baseline in Tender Joint Count at Week 52	-18.9 (11.49)	-21.0 (14.14)	-21.2 (12.95)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	268	123	129
	Change from baseline in Swollen Joint Count at Week 52	-12.6 (6.92)	-14.2 (8.29)	-15.2 (9.82)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	268	123	129
	Change from baseline in Patient's Assessment of Arthritis Pain at Week 52	-37.4 (25.09)	-36.8 (24.05)	-40.6 (24.16)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	268	123	129
	Change from baseline in Patient's Global Assessment of Arthritis at Week 52	-37.5 (25.88)	-38.6 (24.97)	-44.0 (22.94)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	267	122	129
	Change from baseline in Physician's Global Assessment of Arthritis at Week 52	-47.9 (18.89)	-48.4 (17.75)	-52.1 (20.01)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	267	123	129

estimate variability	**Change from baseline in Health Assessment Questionnaire at Week 52**	-0.70 (0.678)	-0.73 (0.636)	-0.84 (0.686)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation	Mean Standard Deviation
Secondary Endpoint Descriptive statistics and estimate variability	Treatment group	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ Adalimumab-EU/ PF-06410293
	Number of subjects	267	123	127
	Change from baseline in high sensitivity (hs) CRP at Week 52 (mg/L)	-10.6 (20.84)	-11.8 (23.85)	-12.8 (28.49)
	statistic variability statistic	Mean Standard Deviation	Mean Standard Deviation	Mean Standard Deviation
Notes	Secondary endpoints presented for the final visit of Treatment Period 1 (Week 26) and for the final visit of Treatment Period 2 (Week 52). Additional data are available for the additional visits during each Treatment Period, as listed above for each Treatment Period.			

2.6.2. Supportive study – Study B5381002b

This study was an open-label, multi-national, single arm, pre-filled pen (PFP) sub-study in a subset of subjects (n=50) from the main study with rheumatoid arthritis on concomitant methotrexate participating in protocol B5381002.

The primary endpoint was a delivery system success rate (DSSR) based on participant (actual PFP User) and investigator/designated observer observations of the success of adalimumab-Pfizer administration by PFP.

Substudy subjects received 6 consecutive bi-weekly adalimumab-Pfizer doses over a period of 10 weeks using the PFP device (Figure 13). The 1st, 3rd, and 6th doses were injected under the supervision of the investigator or a designated observer. The rest of the injections were administered at home by subjects or their caregiver.

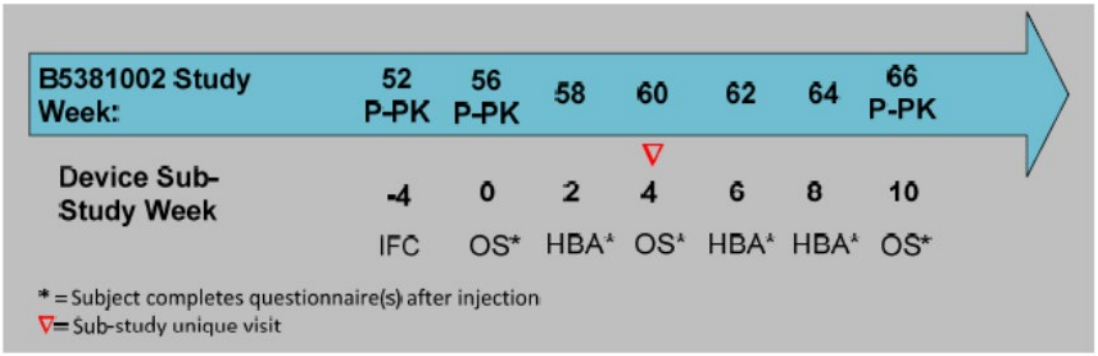


Figure 13 Substudy Design Schematic

Methods

Study participants

The substudy (B5381002b) was conducted in 19 centres in 4 countries.

The participants were between 18 to 65 years old (mean (54.9 years old) representing both genders (26% males and 74% females).

Participant flow

Only one subject out of 50 withdrew from the substudy and two subjects chose to continue with PFS device once they had completed the substudy with the PFP.

Baseline data

At baseline (week 52) the mean swollen joint count and number of tender joints was 1.9 (SD=4.7) and 5.4 (SD=8.7), respectively. The mean DAS28-CRP was 2.87 (SD=1.14) at baseline. The mean length of prior RA history was 8 years (SD=10.4 years) and six subjects had additional medical history in upper arm (2 subjects had carpal tunnel syndrome, 1 finger joint contracture, 3 hand or wrist tendon rupture, 1 hand or wrist tendon rupture). None of the subjects had prior experience on the use of auto injector or injection pen.

Numbers analysed

The Intent-to-Treat (ITT) Population was defined as all subjects who are randomised to study treatment. The ITT population was used as the primary analysis population.

The safety population was defined as all substudy subjects who received at least a portion of 1 dose of adalimumab-Pfizer using the PFP device.

If the subject engaged in multiple PFP injection attempts at a visit, only the first attempt (i.e, the first PFP) was to be included in the calculation of the DSSR at the visit.

Results

Outcomes and estimation

Primary outcome

The DSSR at each visit was 100.0% with the lower bound of the 2-sided 95% CI exceeding 92% and the upper bound being 100.0%.

The Observer Assessment Tool (OAT) observers recorded all injections as successful. Specific non-physical help was reported by the observer for 3 (6.0%) subjects at Week 56 and 1 (2.3%) subject at Week 60.

A total of 3 PFP users entered open text information in the Patient Assessment Tool (PAT) Question 7 'Other' field, of whom 2 subjects received verbal help with 1 or more of the instruction steps during the substudy. One (1) subject answered 'NA (not applicable)' for the PAT Question 7 'Yes – I could not get the cap off'.

Secondary outcomes

Characterization of unsuccessful PFP injections

The DSSR at each visit and overall DSSR were 100.0%. A high proportion of completed substudy subjects (95.9%) selected to continue PFP injections for the remainder of the B5381002 study treatment. The 2 substudy subjects who selected the PFS device injections for the remainder of the

main B5381002 study were one with PAT comments including difficulty 'hearing the first click' and difficulty 'making sure it's in' and other who had no PAT comment.

A determination, by inspection, of the correct mechanical function of returned PFP devices

The inspection of 292 used PFPs confirmed successful injection of the full drug volume for all returned used PFPs. There were no medical device complaints presented. CT scans documented a bent needle after use in 5 (1.7%) of the returned used PFPs.

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal phase 3 study B5381002

The design and conduct of the clinical equivalence study are generally considered as adequate. The study design was in accordance with the principles and expectations outlined in the EMA guidelines, following an equivalence design with symmetric inferiority and superiority margins. The overall design was also agreed by the CHMP in Scientific Advice. The primary efficacy endpoint was ACR20 response rate at week 12. The pre-defined equivalence margin ±14% is based on meta-analysis of four representative studies and preserves ≥50% of the treatment effect based on the lower bound of the 2-sided 95% CI for week 12 ACR20 response rate.

The version of adalimumab-Pfizer used in the clinical studies was identical to the to-be-marketed product. The dose regimen was according to the posology and labelling of the reference product in RA and the one-year duration of treatment was adequate to evaluate the comparability in the preservation of the treatment effect, safety and long-term immunogenicity. The switching of the treatment from the reference product to adalimumab-Pfizer and the demonstration of interchangeability was not a requirement for biosimilars within EU (EMEA/CHMP/BMWP/42832/2005 Rev1), but it supported the global development programme. This is acceptable since the adequate number of patients were included for one-year comparison between adalimumab-Pfizer and Humira-EU groups.

The patients included in the trial were diagnosed with RA for at least 4-month fulfilling Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA, with moderately to severely active disease and who were on MTX for at least 12 weeks and been on a stable dose for at least 4 weeks prior to first dose of study drug and on a stable dose of oral folic acid or oral folinic acid supplementation for at least 21 days prior to the first dose of study drug. The patient population chosen was an adequate sensitive population to detect differences between adalimumab-Pfizer and Humira-EU.

Based on the demographic features and baseline characteristics of the study subjects the compared groups were balanced including the RA disease status [e.g prior duration of RA, the number of swollen and tender joints, DAS28-4 (CRP) level], prior treatments as well as the previous medical history in general. There were no notable differences at baseline after re-randomisation. The inclusion and exclusion criteria were appropriate.

Several protocol amendments (6) were implemented and some of them after the first subject visit. The proportion of protocol violations was very similar between the treatment arms, but more protocol deviations leading to exclusion of subjects from PP population were reported for adalimumab-EU arm compared to adalimumab-Pfizer arm. The protocol amendments and exclusion of subjects did not have a significant impact on the study outcome. The patients excluded from the PP population and the sensitivity analysis in this population supported the result obtained in the ITT population and

biosimilarity in efficacy. The number of informed dropouts was relatively low and balanced in all treatment arms. There were more discontinuations in Humira-EU group as compared to the adalimumab-Pfizer during TP 1. During TP 2, there were more discontinuations in adalimumab-Pfizer/adalimumab-Pfizer group as compared to other two treatment arms. However, it is considered that the frequency of discontinuation is too low to cause interference to the study outcome. The applicant has provided the region/country/centre specific data on dropouts and although the data in Latin American region seem exceeding the normal response rate expected in adalimumab-Pfizer its impact on the overall study outcome is limited.

The objectives of the study were appropriately set. The chosen primary endpoint and equivalence margin are acceptable, justified and sensitive while the primary endpoint time point was selected from the still ascending part of the time-response curve although the steepest phase had already been passed at week 12. The chosen secondary endpoints comprising also continuous endpoint DAS28-4 (CRP) and ACR20, ACR50, and ACR70 measured in eleven time points up to one year are appropriate.

The study was adequately powered (87%) and the sample size measurements were appropriate for equivalence design with symmetric inferiority and superiority margins for EU of [-14%, 14%] with a total sample size of 596 subjects in a 1:1 ratio. The selected study populations and their definitions with sensitivity analysis performed in PP population were acceptable although both ITT and PP populations should have been kept equally important in primary analysis. Sensitivity analyses for ACR20 and DAS28-4 (CRP) at week 12 were performed using various imputation methods for missing data to explore the potential impact of assumptions regarding missing data, which is agreed. The randomisation procedure and stratification conditions of study sample were set appropriately.

<u>The B5381002b substudy</u>

The study design and the endpoints are acceptable as well as the duration of the study and the posology, which is according to the labelling. In addition, the sample size of 50 subjects is adequate. The baseline demographic characteristics are appropriate with a wide age range (also elderly) and both genders presented. The applicant has explained how the subjects were selected to the screening from the TP2 population and the criteria how the eventual study population was enrolled (50 subjects entered the substudy of 63 subjects screened). The compliance of the study was high with only one subject discontinuing the study.

Human factor (HF) validation studies were performed in parallel to the preparation for and conduct of the B5381002b substudy. Multiple iterations of the IFU were tested on both trained and untrained participants with a variety of previous experience of using autoinjectors in seven (7) formative studies and one (1) summative human factors test (data not shown). It was determined from the formative studies that prior training of users was not required in order to ensure safe and effective use of the PFP. The Summative HF study was, therefore, conducted with untrained participants only.

In the B5381002 substudy training was provided for the study subjects or their caregivers on proper use of the device with the available product instructional material, and the first injection was administered at the clinic under the supervision of the investigator. The investigator or designated observer determined whether the subject or their caregiver was able to correctly administer the injection with PFP.

In principle the population indicated would represent the population possessing problems in self-administration. Thus, a statement has been added to the PFP and PFS product labelling stating "After proper training in injection technique, patients may self-inject with Amsparity if their physician determines that it is appropriate and with medical follow-up as necessary". The healthcare provider can determine if the patients are suitable for using an injector device and provide suitable training using the instructions for use provided with the product before first use of the product. Based on the

validation data the PFP presentation is easy to hold and safe to use, but the subjects with more severe hand disability need further evaluation by the physician on their ability to use the injector device.

Efficacy data and additional analyses

The pivotal Phase 3 study B5381002

The primary endpoint, ACR20 response rate at week 12, in ITT population was 68.4% (203/297) and 71.3% (214/300) in adalimumab-Pfizer and Humira-EU treatment groups, respectively, the point estimate for the difference being -2.98% (-10.38%, 4.44%). The 95% CI for the difference in response rate was well within the pre-determined equivalence margin of ±14% including also zero. The corresponding figures in PP population were 71.1% (189/266) and 75.2% (191/254), the point estimate for the difference in efficacy being –4.14% (-11.79%, 3.61%). Thus, the equivalence was contained within the equivalence margin also in PP population and the response rates consistent using both the observed data and non-responder imputation. Similarly, the equivalence was reached also in geographic area covariate-adjusted analysis.

The secondary endpoint, mean DAS28-4 (CRP) value at week 12, in ITT population was -2.2 (n=290; SD=1.20) and -2.3 (293; 1.26) in adalimumab-Pfizer and Humira-EU groups, respectively, the difference between treatments being less than the minimally clinically important difference of 0.6. This was demonstrated also with tipping point analysis of the missing values. Similarly, in the other time points measured up to week 26 the difference between treatments was minimal and not clinically important indicating low disease activity. The curves of the mean change from baseline in DAS28-CRP over time were superimposable in ITT population, with slightly higher improvement in Humira-EU group. The results in the other secondary variables ACR20, ACR50 and ACR70 response rates by visits supported also the similarity with highly similar time-response curves throughout the period up to week 26. Slightly higher response rate was seen in adalimumab-Pfizer group at the later time points up to week 26, but the opposite was seen in the number of tender and swollen joints. The difference and treatment effect in ACR and DAS28-4 (CRP) remained the same during the TP2 up to week 52 without any signs of the withering effect. The difference between treatments was seen in the mean change from baseline in hs-CRP by visit in ITT population, the change being larger in Humira-EU group after week 1 visit. However, also the baseline level was higher in Humira-EU group explaining larger decrease in this group. The absolute CRP level reached did not differ meaningfully between the treatments. Similarity was seen also in global patient and professional assessment and EULAR/ACR components. Altogether, the secondary outcomes were in line with the primary outcome supporting the biosimilarity claim.

The subgroup analysis by ADA status showed similar ACR20 response in ADA-positive subjects between treatment groups at week 12 (63.7% vs. 65.7% in adalimumab-Pfizer and Humira-EU groups, respectively), the response rate overall being slightly lower comparing to the ADA-negative subjects. The respective response rate in ADA-negative patients was 70.9% and 77.2%. Instead, the difference in ACR20 response at week 12 was significantly higher in Humira-EU group (64.0%) compared to adalimumab-Pfizer group (50.0%) in NAb-positive subjects. Based on descriptive data the point estimate for ACR20 difference in ADA-positive patients was -1.98 (95% CI -15.4; 11.4) and in the more sensitive antibody negative patients -6.33 (95% CI -14.9; 2.25). In NAb-positive patients the difference was -14% (95% CI -39.6; 11.6) and in NAb-negative patients -3.05 (95% CI -10.6; 4.5). Although, this difference in efficacy in NAb-positive patients might be related to the low number of patients in this NAb-positive subgroup leading to the low precision and wide CI, the applicant was requested to demonstrate the temporal impact of the ADA- and NAb positivity in efficacy and whether withering effect is present in ADA- or NAb-positive patients in clinical efficacy. At week 12, the number of subjects with Nab was higher (n= 32) in the adalimumab-Pfizer group than in the Humira-EU group

(n=25). At week 26, however, the number of NAb positive subjects was similar (41 vs. 42 in adalimumab-Pfizer and Humira–EU, respectively). The difference in ACR20 response rate had decreased from the 14% at week 12 and was small (-0.813%), though still in favour of Humira-EU, at Week 26. The differences between groups were statistically non-significant at both time points.

Analyses performed with the more sensitive DAS28-4(CRP) endpoint showed a significant overlap in the mean (+/- SD) for both NAb and ADA status with no withering effect or trending down overtime in Nab positive subjects. A small and statistically non-significant difference was seen in the change of DAS28-1 (CRP) value from baseline to week 12 (appr. -1.6 vs. -2; difference -0.4) increasing slightly at week 26 (appr. -1.8 vs. -2.6; difference -0.8). The DAS28-4 (CRP) values were closely similar overtime in ADA positive subgroups of the adalimumab-Pfizer and Humira-EU arms of the study. Hence, the observed slight differences in treatment response between adalimumab-Pfizer and Humira-EU groups are considered clinically non-relevant regardless of Nab and ADA status. The small differences are deemed not to exclude biosimilarity.

Since geographic area variation in ACR20 response between treatments was seen the possible centre effect was inspected by the applicant by comparing the data from the centres with at least 10 study subjects (ranging from 10 to 19 by centre). Based on the data, heterogeneous results were obtained, the treatment response difference ranging from the positive difference of 42.9% on benefit of biosimilar candidate to negative difference of 33.33%. Although the numbers of subjects per compared treatment group per centre were not provided the data did not imply some of the centres to drive the efficacy outcome and bias the study.

Extrapolation from RA to other indications where neutralising the soluble TNF-α is the primary mechanism involved, e.g. psoriasis and ankylosing spondylitis, is acceptable. The applicant has provided supportive documentation and justification for the extrapolation to all indications registered for the originator with the discussion on the impact of slightly higher exposure on safety in various indications. Based on the provided supportive data the extrapolation to all Humira-EU indications is acceptable from the clinical point of view.

The B5381002b substudy

The data showed good usability of the PFP device in the selected population in self injection with the delivery system success rate being 100% in all study participants and good functionality of the device. However, the data from patients with extreme manual disability is missing. The training and evaluation of patients for self-injection is required and is included in the instructions in the labelling of the product.

2.6.4. Conclusions on the clinical efficacy

The main efficacy and safety study B5381002 showed therapeutic equivalence between Amsparity and Humira-EU in the sensitive RA study population supporting the similarity claim in efficacy. These findings are supported by the secondary endpoints results in TP1 and TP2 that were similar for Amsparity and Humira-EU as well as the data on the sustained treatment effect seen in TP3. Extrapolation to all Humira-EU indications is also acceptable from the clinical point of view. Furthermore, the data showed good usability of the PFP device in the selected population with self-injection. Based on the clinical data the claim for the biosimilarity between Amsparity and Humira-EU is supported.

2.7. Clinical safety

The safety profile of Amsparity was investigated in 4 clinical studies: 2 single subcutaneous (SC) dose PK studies in healthy volunteers, 1 single SC dose study using a pre-filled syringe (PFS) and a pre-filled pen (PFP) in healthy volunteers, and 1 multi-dose safety and efficacy study in subjects with moderately to severely active RA which included an optional device substudy using a PFP.

Patient exposure

A total of 1,329 subjects received at least 1 dose of study medication, 950 of them Amsparity. The number of subjects in each treatment group is also provided in Table 2.

Healthy volunteers

In study B5381001, a total of 210 subjects were randomised and treated in 1 of the of 3 study treatment groups: 69 subjects received Amsparity, 71 subjects received Humira-US, and 70 subjects received Humira-EU.

In study B5381007, a total of 359 subjects were randomised and treated in 1 of 3 study treatment groups: 121 subjects received Amsparity, 119 subjects received Humira-US, and 119 subjects received Humira-EU.

In study B5381005, a total of 164 subjects were randomised and treated in 1 of 2 study treatment arms: 81 subjects received Amsparity treatment dosed with the PFS device, and 83 subjects received Amsparity treatment dosed with the PFP device.

The safety follow-up in the PK studies ranged from 6 to 10 weeks.

Rheumatoid arthritis patients *(Study B5381002)*

Treatment Period 1 (week 26)

A total of 597 subjects were randomised and 596 subjects received treatment in the safety population of TP1: 297 subjects in the Amsparity arm, and 299 subjects in the Humira-EU arm. The median duration of both Amsparity and Humira-EU treatments in TP1 was 24.1 weeks for each of the treatment arms. The subjects received Amsparity or Humira-EU during TP1, injected SC by PFS in either the thigh or the abdomen.

Treatment Period 2 (week 52)

Prior to Week 26 dosing, 552 subjects were blindly re-randomised at entry into TP2: 283 and 135 subjects originally assigned to Amsparity and Humira-EU in TP1 remained on their original study drug, respectively, and 134 subjects originally assigned to Humira-EU blindly switched to Amsparity. One subject in the Humira-EU/Amsparity group was re-randomised but not treated in TP2; therefore, the safety population included 283 subjects in the Amsparity/Amsparity, 135 subjects in the Humira-EU/Humira-EU, and 133 subjects in the Humira-EU/Amsparity treatment groups.

Treatment Period 3 (week 52 – week 78; and follow-up study week 79 – week 92)

The median duration of treatment was 24.1 weeks during TP3 for all 3 treatment groups. Drug exposure was generally balanced across the 3 treatment groups, the median total dose of study drug received in TP3 being 520.0 mg in all 3 treatment groups.

Safety Analysis of One-Year Safety Data

The overall safety data over a 52-week period were summarised for subjects who received either Amsparity only (351 days median duration) or Humira-EU only (170 days median duration) for the one-year (TP1 Safety Population) of Study B5381002. The patient year of exposure was 287.5 and 216.1 for Amsparity only and Humira-EU only.

B5381002 Sub-study

Subcutaneous injections (N=294) were administered by the subject or their non-healthcare professional caregiver using the Amsparity PFP device for up to 12 weeks. Altogether, 49 subjects completed the sub-study (6 PFP injections). These PFP users successfully administered the full volume of Amsparity in 100% of the injection attempts. Of these subjects 47 were elected to continue PFP injections for the remainder of TP3.

In conclusion, the follow-up time of the comparative safety and efficacy study is considered long enough for a biosimilar development programme, and the dosing of Amsparity / Humira-EU corresponds with the recommended dosing of Humira in clinical practise.

Adverse events

All subjects randomised and treated with at least 1 dose of study drug were included in the safety analysis. No integrated analyses of adverse events (AEs) across the 4 studies were planned or performed due to the different study designs, including different treated populations and duration of treatments.

Single dose PK studies in Healthy volunteers

Study B5381001

All-causality Treatment-Emergent Adverse Events (TEAEs) in the PK studies are presented in Table 20, Table 21, Table 22.

Table 20 Summary of Treatment-Emergent Adverse Events, All-Causality - Safety Population in Study B5381001

	Adalimumab			Total
Number (%) of Subjects	**PF-06410293 (N=69)**	**US (N=71)**	**EU (N=70)**	**(N=210)**
Number of AEs	49	77	93	219
Subjects with AEs	32 (46.4%)	38 (53.5%)	44 (62.9%)	114 (54.3%)
Subjects with SAEs	0	0	1 (1.4%)	1 (0.5%)
Subjects with Grade 3 or 4 AEs[a]	0	1 (1.4%)	2 (2.9%)	3 (1.4%)
Subjects with Grade 5 AEs	0	0	0	0
Subjects discontinued from study due to AEs	0	0	0	0
Subjects with dose reduced due to AEs	0	0	0	0
Subjects with temporary d/c due to AEs	0	0	0	0

a. 2 subjects had 2 laboratory abnormalities that were reported as Grade 2 AEs, however, the abnormalities were actually Grade 3, numbers and percentages affected by these 2 subjects are not corrected in this table and relevant text.

Table 21 Summary of Treatment-Emergent Adverse Events, All-Causality – Safety Population in Study B5381007

Number (%) of Subjects	PF-06410293 (N = 121)	Adalimumab-US (N = 119)	Adalimumab-EU (N = 119)	Total (N = 359)
Number of AEs	159	128	97	384
Subjects with AEs	69 (57.0)	56 (47.1)	48 (40.3)	173 (48.2)
Subjects with SAEs	0	0	0	0
Subjects with Grade 3 or 4 AEs	8 (6.6)	5 (4.2)	3 (2.5)	16 (4.5)
Subjects with Grade 5 AEs	0	0	0	0
Subjects discontinued from study due to AEs	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	0	0

Table 22 Summary of Treatment-Emergent Adverse Events, All-Causality - Safety Population in Study B5381005

Number (%) of Subjects	Arm A: PFS (PF-06410293) n (%)	Arm B: PFP (PF-06410293) n (%)	Total n (%)
Subjects evaluable for AEs	81	83	164
Number of AEs	50	51	101
Subjects with AEs	31 (38.3)	29 (34.9)	60 (36.6)
Subjects with SAEs	1 (1.2)	0	1 (0.6)
Subjects with Grade 3 or 4 AEs	4 (4.9)	2 (2.4)	6 (3.7)
Subjects with Grade 5 AEs	0	0	0
Subjects discontinued from study due to AEs	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	0

The most frequently reported AEs in the MedDRA SOCs for the PK studies are presented in Table 23, Table 24, Table 25.

Table 23 Incidence of Treatment-Emergent Adverse Events in ≥5% of Subjects, All-Causality, Safety Population in Study B5381001

Number (%) of Subjects With AEs by SOC MedDRA version 16.1 Preferred Term	Adalimumab			Total
	PF-06410293 N=69	US N=71	EU N=70	N=210
Gastrointestinal Disorders	**1 (1.4%)**	**2 (2.8%)**	**4 (5.7%)**	**7 (3.3%)**
Nausea	1 (1.4%)	2 (2.8%)	4 (5.7%)	7 (3.3%)
Infections and Infestations	**9 (13.0%)**	**8 (11.3%)**	**11 (15.7%)**	**28 (13.3%)**
Nasopharyngitis	4 (5.8%)	4 (5.6%)	9 (12.9%)	17 (8.1%)
Influenza	1 (1.4%)	5 (7.0%)	1 (1.4%)	7 (3.3%)
Oral herpes	4 (5.8%)	0	2 (2.9%)	6 (2.9%)
Musculoskeletal and Connective Tissue Disorders	**1 (1.4%)**	**4 (5.6%)**	**2 (2.9%)**	**7 (3.3%)**
Back pain	1 (1.4%)	4 (5.6%)	2 (2.9%)	7 (3.3%)
Nervous System Disorders	**5 (7.2%)**	**6 (8.5%)**	**12 (17.1%)**	**23 (11.0%)**
Headache	5 (7.2%)	6 (8.5%)	12 (17.1%)	23 (11.0%)

Table 24 Incidence of Treatment-Emergent Adverse Events in ≥5% of Subjects, All-Causality, Safety Population in Study B5381007

Number (%) of Subjects by SOC and MedDRA Preferred Term	PF-06410293 N = 121	Adalimumab-US N = 119	Adalimumab-EU N = 119	Total N = 359
With any AEs	**42 (34.7)**	**27 (22.7)**	**30 (25.2)**	**99 (27.6)**
Investigations	**14 (11.6)**	**8 (6.7)**	**9 (7.6)**	**31 (8.6)**
Blood creatine phosphokinase increased	7 (5.8)	3 (2.5)	3 (2.5)	13 (3.6)
Neutrophil count decreased	7 (5.8)	5 (4.2)	6 (5.0)	18 (5.0)
Musculoskeletal and connective tissue disorders	**7 (5.8)**	**1 (0.8)**	**4 (3.4)**	**12 (3.3)**
Back pain	7 (5.8)	1 (0.8)	4 (3.4)	12 (3.3)
Nervous system disorders	**14 (11.6)**	**13 (10.9)**	**12 (10.1)**	**39 (10.9)**
Headache	14 (11.6)	13 (10.9)	12 (10.1)	39 (10.9)
Respiratory, thoracic and mediastinal disorders	**18 (14.9)**	**14 (11.8)**	**13 (10.9)**	**45 (12.5)**
Cough	11 (9.1)	9 (7.6)	2 (1.7)	22 (6.1)
Oropharyngeal pain	7 (5.8)	6 (5.0)	4 (3.4)	17 (4.7)
Nasal congestion	9 (7.4)	3 (2.5)	8 (6.7)	20 (5.6)

Table 25 Incidence of Treatment-Emergent Adverse Events in ≥5% of Subjects, All-Causality, Safety Population in Study B5381005

Number (%) of Subjects With AEs by SOC	Arm A: PFS (PF-06410293) n (%)	Arm B: PFP (PF-06410293) n (%)	Total n (%)
Any AEs	31 (38.3)	29 (34.9)	60 (36.6)
Gastrointestinal Disorders	7 (8.6)	6 (7.2)	13 (7.9)
General Disorders and Administration Site Conditions	8 (9.9)	7 (8.4)	15 (9.1)
Investigations	4 (4.9)	5 (6.0)	9 (5.5)
Nervous System Disorders	12 (14.8)	12 (14.5)	24 (14.6)
Headache	11 (13.6)	10 (12.0)	21 (12.8)
Respiratory, Thoracic and Mediastinal Disorders	2 (2.5)	5 (6.0)	7 (4.3)

Subjects with AEs were fewer in the adalimumab-Pfizer group than that in the Humira-EU group: 32 (46.4%) vs. 44 (62.9%) in PK study B5381001. One SAE occurred in the study, in the Humira-EU group (discussed more in detail in the next section). Treatment–related TEAEs were half as common in the adalimumab-Pfizer group (49) than in the Humira-EU group (93). Of the most common AEs (SOCs ≥5% presented) oral herpes (PT) was the only AE that appeared more often in the adalimumab-Pfizer group than in the either of the Humira groups. The incidence in this case was, however, low with 4 subjects in the adalimumab-Pfizer group and 2 subjects in the Humira EU-group, thus no concern is raised about this.

In the PK study B5381007, 69 subjects (57.0%) experienced a TEAE in the adalimumab-Pfizer group, which is more than compared to Humira-EU group: 48 subjects (40.3%). No SAEs were reported. Treatment-related TEAEs were reported in 90 subjects, including 55 TEAEs in the adalimumab-Pfizer group which is more often than the 35 TEAEs reported in the Humira-EU group. Respiratory, thoracic and mediastinal disorders were the most common AEs in this PK study and cough was notably more commonly seen in the adalimumab-Pfizer group than in the Humira-EU group: 11 (9.1%) vs. 2 (1.7%). The coughs were, however, reported not to be severe in nature, and this slight numerical difference was not seen in the RA-study, hence the difference is considered a chance finding. The second most common AE was headache, but these were more equally present across the study groups. AEs related to laboratory parameters are discussed in a separate section.

Proportion of subjects with AEs and receiving adalimumab-Pfizer was smaller in study B5381005 (36.6%) than it was in study B5381001 (46.4%) or in study B5381007 (57.0%). One SAE was seen in this study (see next section). The most common AE in this study was headache, which occurred in 12.8% of the subjects.

Study in rheumatoid arthritis patients

All-causality TEAEs in the clinical study in RA patients in treatment periods (TP) 1 and 2, as well as in TP1 safety population one-year data, are presented Table 26, Table 27, Table 28.

Table 26 All-causality TEAEs, safety population – TP1, study B5381002

Number (%) of Subjects	PF-06410293 n (%)	Adalimumab-EU n (%)
Subjects evaluable for AEs	297	299
Number of AEs	343	379
Subjects with AEs	143 (48.1)	143 (47.8)
Subjects with SAEs	12 (4.0)	13 (4.3)
Subjects with Grade 3 AEs	15 (5.1)	16 (5.4)[a]
Subjects with Grade 4 AEs	2 (0.7)	4 (1.3)
Subjects with Grade 5 AEs	0	1 (0.3)
Subjects with temporary discontinuation[c] due to AEs	17 (5.7)	29 (9.7)
Subjects discontinued from treatment due to AEs	11 (3.7)[b]	14 (4.7)
Subjects discontinued from study due to AEs	8 (2.7)	9 (3.0)

a. One (1) subject in the adalimumab-EU arm had an AE of neutropenia incorrectly recorded as Grade 2; the correct severity was Grade 3. Numbers and percentages affected by this subject were not corrected in this table.
b. One (1) subject in the PF-06410293 arm was incorrectly recorded as discontinuation from treatment due to an AE; the correct reason was insufficient clinical response. Numbers and percentages affected by this subject were not corrected in this table.
c. PF-06410293 or adalimumab-EU could be temporarily discontinued at the discretion of the investigator in case of AE and resumed.

Table 27 All-causality TEAEs, safety population – TP2, study B5381002

Number (%) of Subjects:	PF-06410293/ PF-06410293	Adalimumab-EU/ Adalimumab-EU	Adalimumab-EU/ PF-06410293
Subjects evaluable for AEs	283	135	133
Number of AEs	243	112	100
Subjects with AEs	123 (43.5)	60 (44.4)	51 (38.3)
Subjects with SAEs	4 (1.4)	6 (4.4)	3 (2.3)
Subjects with Grade 3 AEs	7 (2.5)	5 (3.7)	4 (3.0)
Subjects with Grade 4 AEs	0	2 (1.5)	0
Subjects with Grade 5 AEs	0	0	0
Subjects with temporary[a] discontinuation due to AEs	16 (5.7)	8 (5.9)	5 (3.8)
Subjects discontinued from treatment due to AEs	6 (2.1)	8 (5.9)	2 (1.5)
Subjects discontinued from study due to AEs	5 (1.8)	8 (5.9)	1 (0.8)

a. PF-06410293 or adalimumab-EU could be temporarily discontinued at the discretion of the investigator in case of AE and resumed as described in Section 5.6.3 in the protocol.

Table 28 All-causality TEAEs, one-year, TP1 safety population study B5381002

Number of Subjects	PF-06410293 (PY = 287.521) n (n/PY*100)	Adalimumab-EU (PY = 216.077) n (n/PY*100)
Subjects evaluable for AEs	297	299
Number of AEs	565	481
Subjects with AEs	184 (64.0)	162 (75.0)
Subjects with SAEs	16 (5.6)	20 (9.3)
Subjects with Grade 3 AEs	21 (7.3)	20 (9.3)
Subjects with Grade 4 AEs	2 (0.7)	6 (2.8)
Subjects with Grade 5 AEs	0	1 (0.5)
Subjects with temporary discontinuation due to AEs	29 (10.1)	36 (16.7)
Subjects discontinued from treatment due to AEs	17 (5.9)	23 (10.6)
Subjects discontinued from study due to AEs	14 (4.9)	18 (8.3)

The most frequently reported AEs for TP1 and TP2 are presented in the MedDRA SOCs in Table 29 and Table 30, respectively.

Table 29 All-causality TEAEs (≥2% Subjects in Any Treatment Arm by Preferred Term), Safety Population – TP1, Study B5381002

SOC PT (MedDRA version 20.0)	PF-06410293 N=297 n (%)	Adalimumab-EU N=299 n (%)
Any AEs	**143 (48.1)**	**143 (47.8)**
Blood and lymphatic system disorders	**19 (6.4)**	**13 (4.3)**
Anaemia	9 (3.0)	2 (0.7)
General disorders and administration site conditions	**9 (3.0)**	**22 (7.4)**
Injection site reaction	5 (1.7)	6 (2.0)
Infections and infestations	**74 (24.9)**	**75 (25.1)**
Bronchitis	2 (0.7)	6 (2.0)
Upper respiratory tract infection	6 (2.0)	12 (4.0)
Viral upper respiratory tract infection	21 (7.1)	18 (6.0)
Investigations	**26 (8.8)**	**23 (7.7)**
Alanine aminotransferase increased	8 (2.7)	13 (4.3)
Aspartate aminotransferase increased	7 (2.4)	7 (2.3)
Musculoskeletal and connective tissue disorders	**31 (10.4)**	**26 (8.7)**
Arthralgia	6 (2.0)	1 (0.3)
Back pain	5 (1.7)	7 (2.3)
Nervous system disorders	**13 (4.4)**	**19 (6.4)**
Headache	10 (3.4)	8 (2.7)
Vascular disorders	**12 (4.0)**	**16 (5.4)**
Hypertension	8 (2.7)	13 (4.3)

Table 30 All-causality TEAEs (≥2% Subjects in Any Treatment Group by Preferred Term), Safety Population – TP2, Study B5381002

SOC and PT (MedDRA version 20.0)	PF-06410293/ PF-06410293 N=283 n (%)	Adalimumab-EU/ Adalimumab-EU N=135 n (%)	Adalimumab-EU/ PF-06410293 N=133 n (%)
Any AEs	**123 (43.5)**	**60 (44.4)**	**51 (38.3)**
Blood and lymphatic system disorders	**9 (3.2)**	**7 (5.2)**	**2 (1.5)**
Neutropenia	2 (0.7)	4 (3.0)	2 (1.5)
Infections and infestations	**49 (17.3)**	**23 (17.0)**	**28 (21.1)**
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)
Injury, poisoning and procedural complications	**12 (4.2)**	**3 (2.2)**	**5 (3.8)**
Fall	4 (1.4)	1 (0.7)	4 (3.0)
Investigations	**22 (7.8)**	**13 (9.6)**	**10 (7.5)**
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)
Musculoskeletal and connective tissue	**21 (7.4)**	**13 (9.6)**	**10 (7.5)**
Rheumatoid arthritis	4 (1.4)	2 (1.5)	3 (2.3)
Nervous system disorders	**14 (4.9)**	**1 (0.7)**	**5 (3.8)**
Headache	9 (3.2)	1 (0.7)	2 (1.5)
Vascular disorders	**12 (4.2)**	**5 (3.7)**	**3 (2.3)**
Hypertension	8 (2.8)	3 (2.2)	3 (2.3)

In TP3 and follow-up, no significant differences between the groups were seen in AEs (Table 31, Table 32).

Table 31 All-Causality TEAEs, TP3 Safety Population - TP3 and Follow-up

	PF-06410293/ PF-06410293/ PF-06410293 (N = 258) n (%)	Adalimumab-EU/ Adalimumab-EU/ PF-06410293 (N = 120) n (%)	Adalimumab-EU/ PF-06410293/ PF-06410293 (N = 127) n (%)	Total (N = 505) n (%)
Number of AEs	206	146	94	446
Subjects with AEs	110 (42.6)	61 (50.8)	47 (37.0)	218 (43.2)
Subjects with SAEs	9 (3.5)	9 (7.5)	3 (2.4)	21 (4.2)
Subjects with Grade 3 AEs	14 (5.4)	7 (5.8)	3 (2.4)	24 (4.8)
Subjects with Grade 4 AEs	0	3 (2.5)	0	3 (0.6)
Subjects with Grade 5 AEs	0	1 (0.8)	0	1 (0.2)
Subjects with temporary discontinuation[a] due to AEs	14 (5.4)	9 (7.5)	2 (1.6)	25 (5.0)
Subjects discontinued from treatment due to AEs	6 (2.3)	3 (2.5)	2 (1.6)	11 (2.2)
Subjects discontinued from study due to AEs	4 (1.6)	3 (2.5)	1 (0.8)	8 (1.6)

a. PF-06410293 could have been temporarily discontinued due to safety reasons and resumed

Table 32 All-Causality TEAEs (≥1% by PT in Any Treatment Group), TP3 Safety Population – TP3 and Follow-up Source

SOC and PT (MedDRA Version 20.1)	PF-06410293/ PF-06410293/ PF-06410293 (N = 258) n (%)	Adalimumab-EU/ Adalimumab-EU/ PF-06410293 (N = 120) n (%)	Adalimumab-EU/ PF-06410293/ PF-06410293 (N = 127) n (%)	Total (N = 505) n (%)
Any AEs	**110 (42.6)**	**61 (50.8)**	**47 (37.0)**	**218 (43.2)**
Blood and Lymphatic System Disorders	**7 (2.7)**	**6 (5.0)**	**5 (3.9)**	**18 (3.6)**
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)
Gastrointestinal Disorders	**10 (3.9)**	**11 (9.2)**	**8 (6.3)**	**29 (5.7)**
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)
Infections and Infestations	**52 (20.2)**	**23 (19.2)**	**26 (20.5)**	**101 (20.0)**
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)
Injury, Poisoning and Procedural Complications	**13 (5.0)**	**6 (5.0)**	**1 (0.8)**	**20 (4.0)**
Fall	3 (1.2)	2 (1.7)	0	5 (1.0)
Investigations	**13 (5.0)**	**11 (9.2)**	**7 (5.5)**	**31 (6.1)**
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 increased	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)
Musculoskeletal and Connective Tissue Disorders	**28 (10.9)**	**21 (17.5)**	**13 (10.2)**	**62 (12.3)**
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)
Nervous System Disorders	**8 (3.1)**	**5 (4.2)**	**2 (1.6)**	**15 (3.0)**
Headache	6 (2.3)	3 (2.5)	0	9 (1.8)
Respiratory, Thoracic and Mediastinal Disorders	**7 (2.7)**	**7 (5.8)**	**1 (0.8)**	**15 (3.0)**
Cough	3 (1.2)	0	0	3 (0.6)
Oropharyngeal pain	0	2 (1.7)	0	2 (0.4)
Skin and Subcutaneous Tissue Disorders	**6 (2.3)**	**3 (2.5)**	**2 (1.6)**	**11 (2.2)**
Urticaria	0	0	2 (1.6)	2 (0.4)
Vascular Disorders	**4 (1.6)**	**5 (4.2)**	**5 (3.9)**	**14 (2.8)**
Hypertension	4 (1.6)	2 (1.7)	5 (3.9)	11 (2.2)

Table 33 All-causality TEAEs with the highest rates per 100 patient-years occurring in ≥5% of subjects in any treatment arm

	Adalimumab-Pfizer		Humira-EU	
	subjects	rate per 100 patient-years	subjects	rate per 100 patient-years
Viral upper respiratory tract infection	29	10.1	21	9.7
Upper respiratory tract infection	9	3.1	15	6.9
Headache	19	6.6	9	4.2
Hypertension	15	5.2	15	6.9
ALT increased	13	4.5	16	7.4

All-causality TEAEs with the highest rates per 100 patient-years are shown in Table 33. The AE incidences were similar in study B5381002 TP1 and TP2 in study patients receiving adalimumab-Pfizer and Humira-EU. The five most common AE types (PTs) in TP1 were: Viral upper respiratory tract infection, Headache, Anaemia, ALT increased, and Hypertension. Anaemia was more often seen in adalimumab-Pfizer than in Humira-EU group: 3.0% vs. 0.7%. In TP2, the most common AE types were: Viral upper respiratory tract infection, Upper respiratory tract infection, Hypertension, ALT increased, Aspartate aminotransferase (AST) increased, Neutropenia, Headache, and Urinary tract infection. Of these, headache was more often (3.2% vs 0.7%), and viral upper respiratory tract infection and hypertension slightly more often seen in the adalimumab-Pfizer/adalimumab-Pfizer arm than in the Humira-EU/Humira-EU arm. Only one of the headache cases was severe (Grade 3), but considered unrelated to study drug, adalimumab-Pfizer. No concerns were raised about this event type, though headache was more common also in any adalimumab-Pfizer than in the Humira-EU-treated study patients in the one-year follow-up. In general, subjects with AEs were fewer in adalimumab-Pfizer arms than in Humira-EU arms (64% vs. 75%) in this one-year safety analysis.

There were 8 (2.7%) AEs of Grade 3 or higher related to the treatment in the adalimumab-Pfizer arm and 9 (3.0%) in Humira-EU arm in TP1. In TP2, these numbers were: 3 (1.1%) subjects in the adalimumab-Pfizer/adalimumab-Pfizer group and 2 (1.5%) subjects in the Humira-EU/Humira-EU group (no subjects in the Humira-EU/adalimumab-Pfizer group). In TP3 and the follow-up period, 28 (5.5%) subjects reported Grade 3 or higher all-causality TEAEs (Table 31).

Serious adverse event/deaths/other significant events

Serious adverse events

In the PK studies, one serious adverse event (SAE) was reported requiring hospitalisation in the Humira-EU arm (study B5381001) and one SAE was requiring hospitalisation in the adalimumab-Pfizer arm (study B5381005). No SAEs were reported in study B5381007.

In the clinical study in RA patients, SAEs occurred as often in both treatment arms during TP1 (rate being 4.0% for adalimumab-Pfizer vs. 4.3% for Humira-EU). There were no major differences in rates in treatment relation either: 1.7% and 1.3%, respectively. Two suspected unexpected serious adverse reactions (SUSARs) were reported for adalimumab-Pfizer during TP1 in two subjects. Subsequently,

these were downgraded, and they were no longer meeting SUSAR criteria. In TP2, the study patients in the adalimumab-Pfizer/adalimumab-Pfizer arm experienced SAEs less often than the study patients in the Humira-EU/Humira-EU arm: 1.4% vs. 4.4%. SAEs were less often treatment-related too: 0.7% vs. 1.5%, respectively. No subjects, who had changed from adalimumab-Pfizer to Humira-EU experienced SAEs. Two SUSARs were reported during TP2 in two subjects, one in the adalimumab-Pfizer/adalimumab-Pfizer arm and one in the Humira-EU/Humira-EU arm. Both events were reported as resolved.

In TP1, related to laboratory there were 2 SAEs in the adalimumab-Pfizer arm (1 pancytopenia, 1 anemia) and 1 SAE in the Humira-EU (hypokalemia). The grades of these SAEs were as follows: pancytopenia Grade 3, anemia Grade 4, and hypokalemia Grade 3. There were no SAEs related to laboratory findings in TP2.

No significant differences between-group were seen in SAEs in TP3 and Follow-up (Table 31).

Death

In total, two deaths were reported in the adalimumab-Pfizer clinical development programme. These occurred during the comparative safety and efficacy study B5381002. The first case occurred in the Humira-EU arm during TP1, and according to the investigator, the case was related to underlying medical history. The other death was due to SAEs of anaemia, upper gastrointestinal haemorrhage, shock, pneumonia aspiration and respiratory failure during TP3. This patient received adalimumab-Pfizer (in Humira-EU/Humira-EU/adalimumab-Pfizer group), but the death was reported to be related to a concomitant medication (meloxicam).

Adverse Events of Special Interest

Injection site reaction (ISR) occurred more often with the US product than with the EU products in PK studies in healthy volunteers. In the PK study comparing two devices, the ISRs occurred equally as often in both groups, and no remarkable differences were observed in the injection site pain assessment in relation to two different devices or two injection sites. In the clinical study in RA patients, ISRs did not differ between the treatment groups (1.7% vs 2%). Hypersensitivity AEs were less often seen in the adalimumab-Pfizer arm than in the Humira-EU arm in B5381002 TP1; in TP2, the trend was similar. No cases of anaphylaxis were reported in clinical trials.

The incidence of latent tuberculosis (TB) was greater in the adalimumab-Pfizer arm than in the Humira-EU arm (5 vs. 1 cases) in B5381002 TP1. (These led to study discontinuation.) In TP2, the latent TB cases were more equally divided between the study arms. On the other hand, in the one-year safety set the incidence of latent TB was again greater in the adalimumab-Pfizer group 7 (2.4 per 100 patient-years) than in the Humira-EU group 3 (1.4 per 100 patient-years). However, the difference between treatments was statistically non-significant being on the same level with the other adalimumab biosimilars in adalimumab-Pfizer. Furthermore, the specificity of the QuantiFERON-TB test for TB latency is limited and false positives might occur in the follow up examinations. One case of latent tuberculosis was seen in the group receiving adalimumab-Pfizer only during TP3.

After infections and infestations (that were equally distributed between study groups), blood and lymphatic system events were the most commonly reported targeted medical events (TMEs), and anaemia, neutropenia and leukopenia the most common AE types among them in TP1. Serious anaemia and pancytopenia were each reported by 1 (0.3%) subject in the adalimumab-Pfizer arm. In TP 2, these AE types were more equally divided between the study arms. No SAEs were reported under the TME category of Blood and Lymphatic System in TP2.

In general, it seems that the adverse events of special interest / TMEs occurred in the beginning of the safety follow-up, i.e. in TP1. Neoplasms were seen also in TP2, which is natural in relation to the

nature of the AE. Switching the product did not seem to increase the risk of adverse events of special interest / TMEs, although the incidence of the most common event type, infections and infestations, was somewhat higher in Humira-EU/adalimumab-Pfizer arm (21.1%) than in other arms in TP2 (17% and 17.3% in Humira-EU/Humira-EU and adalimumab-Pfizer/adalimumab-Pfizer arms).

Laboratory findings

In Study B5381001, across all treatment arms, the most frequent haematological abnormality was decreased white blood cells, while the most frequent chemistry abnormality was increased creatinine. No subjects in the adalimumab-Pfizer group experienced laboratory abnormalities of Grade 3 or greater.

In Study B5381007, the most frequent haematological abnormality was neutrophil count decreased, while the most frequent chemistry abnormality reported was increased creatinine. By severity, the most prominent chemistry abnormality was increased creatine phosphokinase (CPK), across all treatment arms.

In Study B5381005, both in pre-filled syringe (PFS) and pre-filled pen (PFP) treatment arms, the most frequent haematological abnormalities reported were neutrophil count decreased and white blood cells decreased, while the most frequent chemistry abnormality was creatinine increased.

No significant differences between-group were reported in laboratory parameters in the clinical study in RA patients (B5381002). The numbers of subjects who had abnormalities in total bilirubin, ALT and AST were comparable between the adalimumab-Pfizer and Humira-EU treatment arms in TP1. In TP2, the incidence rates of the abnormalities were low in all 3 treatment groups.

In TP1, the majority of chemistry abnormalities were Grade 1-2. There were no events of chemistry laboratory values of Grade 5. Grade 3 results were reported as ALT, AST increased, hypercalcemia, hyperglycaemia, and hyponatremia. Grade 4 creatinine increased and hyperkalaemia were each experienced by 1 (0.3%) subject from the adalimumab-Pfizer arm and none was reported for the Humira-EU arm. Overall, for chemistry laboratory parameters, the numbers of subjects with abnormalities and severity of abnormalities were comparable between the adalimumab-Pfizer and Humira-EU treatment arms.

In TP2, the majority of abnormalities were of Grade 1-2; none were Grade 4. Grade 3 chemistry results were reported for ALT increased, hyponatremia, and hyperglycaemia. Overall, for chemistry parameters, the numbers of subjects with abnormalities and severity of abnormalities were comparable between the 3 treatment groups.

In haematology parameters, most abnormalities were of Grade 1 or 2; none were Grade 4. Grade 3 haematology results were reported for anaemia, lymphocyte count decreased, and neutrophil count decreased in TP1. The majority of the events of anaemia (7 of the 9 TEAEs) in the adalimumab-Pfizer arm were mild and Grade 1-2 severity. None of the 9 events of anaemia reported for subjects in the adalimumab-Pfizer arm was assessed as related to the study drug.

In TP2, the majority of haematology abnormalities were Grade 1-2. Grade 4 haematology results were reported for lymphocyte count decreased. Grade 3 haematology results were reported for lymphocyte count decreased, neutrophil count decreased, and anaemia. Overall, for haematology parameters, the numbers of subjects with abnormalities were small and the severity of the abnormalities was comparable between the 3 treatment groups.

In total, no more than two Grade 4 AEs related to laboratory findings in Study B5381002. One of them was an anaemia case in the adalimumab-Pfizer treatment arm in TP1 that was classified as a SAE. The

other one was a lymphopenia case in the Humira-EU/Humira-EU treatment arm in TP2. The latter was alleviated to Grade 2 and thus assessed as a non-serious AE by the investigator.

Immunological events

The immunogenicity of Amsparity was compared to the reference product Humira in the 4 same previously mentioned studies (B5381001, B5381007, B5381005, B5381002). Blood samples for the detection of anti-drug antibodies (ADA) and neutralising antibody (Nab) were collected at pre specified times before and during treatment, and at extended follow-up based on study duration. Serum samples collected for ADA assessment were tested for ADA, and samples that were confirmed positive for ADA were further tested for NAb. See Section 2.5.2. Pharmacokinetics for assessment of analytical methods.

In this section, impact of immunogenicity on PK and safety is discussed. See Section 2.6. Clinical efficacy for results regarding impact of immunogenicity on efficacy.

Table 34 summarises the results of these studies in terms of percentage of ADA and NAb.

Table 34 Percentage of patients with ADA and Nab by studies

	Number of Patients/Subjects (%)								
	B5381001			B5381007			B5381005	B5381002 (TP1)[a]	
	PF-06410293 (N=69)	Adalimumab-US (N=71)	Adalimumab-EU (N=70)	PF-06410293 (N = 121)	Adalimumab-US (N = 119)	Adalimumab-EU (N = 119)	PF-06410293 PFS/PFP (N = 164)[b]	PF-06410293 (N=297)	Adalimumab-EU (N=299)
Anti-Drug Antibody (ADA)[c]									
ADA positive at Baseline	3/69 (4.3%)	2/71 (2.8%)	2/70 (2.9%)	1/121 (0.8%)	0	6/119 (5.0%)	0/30	10/297 (3.4)	11/299 (3.7)
≥1 occurrence of positive ADA post-dose overall	59/69 (85.5%)	67/71 (94.4%)	63/70 (90.0%)	91/119 (76.5%)	94/118 (79.7%)	83/118 (70.3%)	18/30 (60.0%)	132/297 (44.4)	151/299 (50.5)
Neutralizing Antibody (NAb)[d]									
NAb positive at Baseline	2/69 (2.9%)	1/71 (1.4%)	1/70 (1.4%)	0	0	3/118 (2.5%)	0/30	8/297 (2.7)	5/299 (1.7)
≥1 occurrence of positive NAb post-dose overall	37/69 (53.6%)	47/71 (66.2%)	43/70 (61.4%)	77/119 (64.7%)	74/118 (62.7%)	71/118 (60.2%)	12/30 (40.0%)	41/297 (13.8)	42/299 (14.0)

a. The summary is for TP1. Overall, a positive subject was defined as one having at least 1 post-dose sample that tested positive during TP1, regardless of the pre-dose ADA status.
b. ADA testing was performed for a subset of subjects with AEs of ISR and/or rash (n=15) and for a subset of matched control subjects (n=15).
c. ADA positive and negative test results were defined as ADA titer ≥1.88 and <1.88 for all studies, respectively.
d. NAb positive and negative results were defined as NAb titer ≥0.70 and <0.70 for all studies, respectively.

Immunogenicity in healthy subjects

The overall percentage of ADA was very high in healthy subjects after administration of a single 40mg SC dose of adalimumab in both single-dose PK studies. A majority of ADA-positive subjects also tested positive for NAb. Percentage of ADA was numerically lower in the adalimumab-Pfizer group in comparison with the Humira-EU group in one of the PK-studies (B5381001: 85.5% vs 90%) and higher in the other PK-study (B5381007; 76.5 vs 70.3%). The same trend can be seen in the percentage of NAb.

The development of ADA/NAb affected the PK of adalimumab in all three study arms in studies B5381001 and B5381007, especially the elimination phase (AUC_t and AUC_{inf}) and had less impact on

the PK parameters that reflect the absorption phase (C_{max}, $AUC_{0\text{-}2wk}$). It is expectable that the impact of ADA on PK increases as the time from injection increases, as more subjects turn ADA-positive.

In study B5381005 (comparison of PFS and PFP), ADA and NAb were tested only on the samples from subjects where there was a need for the data to help interpret the PK or safety results. No immunogenicity testing was needed for interpretation of PK. Therefore, immunogenicity testing was only performed on subjects with an injection site reaction (ISR) and/or rash AE and randomly selected control subjects from the same study arm, who did not experience ISR or rash AEs, matched to the test subjects (by age, gender, weight and device). The test subjects included 8 PFS and 7 PFP subjects with AEs of injection site reaction (ISR) and/or rash, and respective control subjects. A majority (12) of the 18 subjects with who tested positive for ADA also tested positive for NAb; 7/11 of ISR and/or rash AE subjects and 5/7 of matched control subjects were NAb-positive. The overall percentage NAb were comparable among patients with ISR and/or Rash AE (63.6%) and without ISR and/or Rash AE (71.4%).

Immunogenicity in patients with rheumatoid arthritis

Immunogenicity of adalimumab-Pfizer was compared with Humira-EU in patients with RA in study B5381002 as a secondary endpoint during the two blinded treatment periods (TP1 up to week 26 and TP2 up to week 52). The percentage of ADA-positive subjects was lower in RA patients than in the studies conducted in healthy volunteers. This is in line with published literature on RA patients and may be due to the concomitant methotrexate medication and/or the treated condition, RA.

During TP1 (26 weeks, 297 patients in the adalimumab-Pfizer arm and 299 in the Humira-EU arm), the evolution of ADA was overall similar in the two study arms. Numerically, there were more ADA-positive subjects in the Humira-EU arm (50.5%) than in the adalimumab-Pfizer arm (44.4%). However, the percentage of NAb-positive subjects of the total study cohort was similar: 13.8% of subjects administered adalimumab-Pfizer and 14.0% of subjects administered Humira-EU.

During TP2, comparable percentage of ADA and titres were observed in the groups switching or continuing in TP2 the treatment received in TP1. The overall TP1 + TP2 (1 year) percentage of a positive ADA test result in the TP2 safety population was 52.3%, 59.3% and 49.6% for the Adalimumab-Pfizer/ Adalimumab-Pfizer, Humira-EU/Humira-EU, and Humira-EU/Adalimumab-Pfizer groups, respectively. Specifically, for the switching group (Humira-EU/Adalimumab-Pfizer) as compared to the Humira-EU group that did not switch, the increase in ADA percentage over TP2 for subjects with an ADA test sample was not higher: 0.8% (from 45.1% to 45.9%) versus 6.7% (from 47.4% to 54.1%), respectively.

The NAb percentage in ADA-positive subjects with RA was comparable among the treatment groups, with the majority of ADA-positive subjects testing negative for NAb. Comparable NAb titres were observed in all groups; however, there was high inter-subject variability.

Impact of immunogenicity on safety, pharmacokinetics and efficacy

Safety

Immunogenicity did not affect safety in the clinical study in RA patients or in either of the single-dose PK studies. Only in the device comparison study B5381005 it could be seen that injection-site reactions and rash were somewhat more frequent in patients with ADA. On the other hand, the frequency of hypersensitivity reactions was low in all clinical studies, even though a majority of study subjects turned ADA-positive. There were no significant differences seen in immunogenic safety events between the adalimumab-Pfizer and Humira-EU-groups.

Pharmacokinetics

Overall, in the first PK-study B5381001 that did not meet the formal bioequivalence criteria (with higher exposure to adalimumab-Pfizer compared to Humira-EU), the percentage of ADAs was slightly lower (85,5% versus 90%) for adalimumab-Pfizer compared to Humira-EU, which would be in line with the faster elimination in ADA-positive patients and could have played a role in the failed bioequivalence result. Opposite to that, in the other PK-study B5381007, the percentage of ADAs was slightly higher in the adalimumab-Pfizer group compared to Humira-EU group (76.5% versus 70.3%), which could have also played some role. Further, in study B5381002 in RA-patients, patients treated with adalimumab-Pfizer had slightly lower percentage of ADAs (44.4% versus 50.5% in the Humira-EU group), which finding could corroborate with the higher serum trough concentrations seen in the adalimumab-Pfizer group. It is noteworthy that the difference in median serum concentrations between the two treatment arms was markedly higher in ADA-positive than ADA-negative patients, the difference of which explanation though remains unclear.

As a conclusion, the percentage of ADA was not concordantly different between adalimumab-Pfizer and Humira EU across the clinical trials; in studies B5381001 and B5381002 the percentage of ADA was slightly higher in the Humira-EU group, but the opposite was true in study B5381007. The differences in trough concentrations seemed to be partially in line with the differences in the percentage of ADA-positive subjects, although the difference cannot be solely accounted by immunogenicity, as the percentage of ADA and NAb in the adalimumab-Pfizer arms was not consistently lower than in originator arms. Furthermore, the sampling period for the PK studies did not cover the entire PK profile. Hence, the impact of ADA on elimination phase was not fully covered.

Finally, for better understanding of the impact of ADA and NAb on adalimumab exposure after the initial 2 week phase after administration in each study group, the applicant was requested to calculate the $AUC_{2wk-inf}$ for ADA/Nab-negative and positive subjects and for the combined group, separately for all three study groups (adalimumab-Pfizer, Humira-EU and Humira-US) in studies B5381001 and B5381007. In addition, a sensitivity and statistical analysis on all PK parameters (including elimination half-life) in the ADA-negative subgroup to be able to evaluate more clearly the comparability of adalimumab pharmacokinetics was requested. The applicant provided the results of descriptive statistics and statistical analyses for studies B5381001 and B5381007 for $AUC_{2wk-inf}$, C_{max}, AUC_{0-2wk}, AUC_t, AUC_{inf} and $t_{½}$ for all subjects combined, anti-drug antibody (ADA) negative subjects, and ADA positive subjects for all three study groups (adalimumab-Pfizer, Humira-EU and Humira-US) in both studies.

In the study B5381001, it was observed that the 90%CIs in almost all PK parameters were wide regardless of treatment comparison or ADA status. In the ADA-positive subjects, although most of the GMRs were >100 %, most of the 90% CIs were been between 0.80−1.25 for all treatment comparisons. In the ADA-negative subjects, the adalimumab-Pfizer concentrations were higher than Humira-EU and Humira-US concentrations and all GMRs in exposure PK parameters were >100 %. The percentage of ADA-negative subjects was too small for drawing definitive conclusions in this subgroup.

In the study B5381007, all 90% CIs in the studied PK parameters of the ADA-positive subjects and combined subjects were within 0.80-1.25 (although the range not always included 1.00). In the ADA-negative group, the 90% CIs were wider in the studied PK parameters (most upper limits >1.25 and the most ranges did not include 1.00) than in the combined /ADA-positive subjects. The amount of ADA-negative subjects compared to the ADA-positive subjects was relatively small, therefore, no definitive conclusions in this subgroup of subjects can be drawn.

The PK results provided support the earlier PK conclusions that adalimumab-Pfizer concentrations are higher (especially in ADA-negative subjects); however, the difference in the concentrations can be considered not to be clinically relevant.

Efficacy

The subgroup analysis by ADA status showed similar ACR20 responses within ADA-positive and ADA-negative and NAb-negative patients between treatment groups at Week 12. Instead, in NAb -positive patients the ACR20 response at week 12 was significantly higher in Humira-EU group (64.0%) compared to adalimumab-Pfizer group (50.0%); the difference was −14% (95% CI −39.6; 11.6). Although this difference in efficacy in NAb-positive patients might be related to low number of patients in this subgroup leading to the low precision and wide CI, the Applicant was requested to demonstrate the temporal impact of the ADA- and NAb positivity on efficacy in RA patients and whether withering effect is present in ADA- or NAb-positive patients. The additional analyses showed marked decrease in the (non-significant) difference in ACR20 response rate from week 12 to week 26, to a clinically non-relevant level. Analyses performed with the more sensitive DAS28-4(CRP) endpoint showed no withering effect or trending down overtime in Nab positive subjects. The observed slight differences in treatment response between adalimumab-Pfizer and adalimumab-EU groups are deemed clinically non-relevant and not to preclude biosimilarity (see 2.6.3.).

Discontinuation due to adverse events

There were no discontinuations due to AEs in the PK studies (Table 20, Table 21, Table 22).

In the comparative safety and efficacy study (B5381002) in general, all discontinuation types (i.e. Subjects with temporary discontinuation due to AEs; Subjects discontinued from treatment due to AEs; Subjects discontinued from study due to AEs) were slightly fewer in the adalimumab-Pfizer arm than in the Humira-EU arm in TP 1 (Table 26). The same applies also to one-year safety data of TP1. In TP2, these end-points were seen the most often in those who received Humira-EU/Humira-EU and the less often in those who switched from Humira-EU to adalimumab-Pfizer (Table 27). These differences were, however, small. In TP3, the greatest numbers were in the Humira-EU/Humira/EU-adalimumab-Pfizer group, but again the between-group differences were small (Table 31). Permanent treatment discontinuation in TP1 due to SAEs was seen in 10 subjects: in 3 receiving adalimumab-Pfizer and in 7 receiving Humira-EU.

On the other hand, even if the discontinuation due to AEs in TP1 was less common in the adalimumab-Pfizer group, the incidences due to the most common reasons were more common in this group compared to the Humira-EU group: Infections and infestations 2.7% vs. 1.0% among which latent TB 1.7% vs. 0.3%, respectively, for permanent discontinuation from the study.

2.7.1. Discussion on clinical safety

The safety profile of adalimumab-Pfizer was investigated in four clinical studies (B5381001, B5381007, B5381005, B5381002).

The number of subjects (altogether 773 healthy volunteers out of which 354 were administered adalimumab-Pfizer; and 596 RA patients out of which 430 were administered adalimumab-Pfizer, and among which the compliance was high) is sufficient for comparing the safety profile of the biosimilar candidate and reference medicinal product (Humira-EU), and studying the safety of a biosimilar product for up to one year. This is in line with the EMA guideline to establish immunogenicity of biosimilar product, as well as with the given scientific advice.

A pooled safety analysis was not performed due to the heterogeneity of study populations (RA patients versus healthy subjects) and the difference in duration of treatment/exposure (multiple doses versus single-dose), which is acceptable.

In the PK study B5381001, subjects with AEs were fewer in the adalimumab-Pfizer group than in the Humira-EU group (46.4% and 62.9%), whereas in the PK study B5381007 the corresponding figures were 57% and 43%, these differences hence reflecting possibly chance findings. Treatment-related TEAEs were reported more often in the adalimumab-Pfizer group than in the Humira-EU group (55 and 35 subjects), with no clear clustering of TEAEs; however, a slight imbalance was seen in coughs (9.1% and 1.7%) but considered of no clinical relevance here. Proportion of subjects with AEs and receiving adalimumab-Pfizer was smaller in study B5381005 than it was in study B5381001 or in study B5381007.

In RA patients, the AE incidences were similar in patients receiving adalimumab-Pfizer and Humira-EU in TP1 and TP2. The most frequently reported AEs were viral upper respiratory tract infection, headache, anaemia, ALT increased, and hypertension. All these are in line with the known safety profile of Humira. There were 8 (2.7%) AEs of Grade 3 or higher related to the treatment in the adalimumab-Pfizer arm and 9 (3.0%) in Humira-EU arm in TP1. In TP2, there were only single AEs of Grade 3 or higher related to the treatment.

Injection site reactions occurred more often with the US product than with the EU products in PK studies in healthy volunteers; in RA-patients the incidence of ISR was very similar (1.7% and 2.0%) in adalimumab-Pfizer and Humira-EU groups (in TP1). In the PK study comparing two devices, the ISRs occurred equally as often in both groups, and no notable differences were observed in the injection site pain assessment in relation to two different devices or two injection sites.

There was slight imbalance in the incidence of latent TB between the adalimumab-Pfizer and the Humira-EU arm (5 vs. 1 cases) in B5381002 TP1. In TP2, the latent TB cases were more equally divided between the study arms. On the other hand, in the one-year safety set the incidence of latent TB was again greater in the adalimumab-Pfizer group than in the Humira-EU group (7 cases, 2.4/100 patient years vs 3 cases, 1.3/100 patient years). In TP3, one case of latent TB was seen in a patient receiving adalimumab-Pfizer only. TB is an identified risk in the risk management plan (RMP) and will be followed in post-marketing.

In general, it seems that the adverse events of special interest / target medical events (TMEs) occurred in the beginning of the safety follow-up, i.e. in TP1. Neoplasms were seen also in TP2, which is natural in relation to the nature of the AE. During TP3 and follow-up period, a total of 4 cases (including 2 SAEs) of neoplasms were reported: 2 cases each in the adalimumab-Pfizer/ adalimumab-Pfizer/ adalimumab-Pfizer and Humira-EU/Humira-EU/ adalimumab-Pfizer groups. Switching the product did not seem to increase the risk of adverse events of special interest / TMEs, although the incidence of the most common event type, infections and infestations, was slightly higher in Humira-EU/adalimumab-Pfizer arm than in other arms in TP2.

In PK studies, there was one SAE in the Humira-EU arm (study B5381001) and one SAE in the adalimumab-Pfizer arm (study B5381005). No SAEs were reported in study B5381007.

In the clinical study in RA patients, one death was reported in the Humira-EU arm during TP1. Another death was due to SAEs of anaemia, upper gastrointestinal haemorrhage, shock, pneumonia aspiration and respiratory failure during TP3. This patient received adalimumab-Pfizer (in Humira-EU/Humira-EU/adalimumab-Pfizer group) but the death was reported to be related to the concomitant medication meloxicam. SAEs occurred as often in both treatment arms during TP1. In TP2, the study patients in the adalimumab-Pfizer/adalimumab-Pfizer arm experienced SAEs less often than the study patients in the Humira-EU/Humira-EU arm. No subjects, who had changed from adalimumab-Pfizer to Humira-EU suffered from SAEs. No significant between-group differences were seen in SAEs in TP3 and Follow-up.

In the PK studies, there were alterations in laboratory data and chemistry laboratory data in parameters such as platelet count decreased, white blood cell decreased, anaemia, neutrophil count

decreased, haemoglobin increased, ALT increased, AST increased, CPK increased, creatinine increased, hyperglycaemia, hypernatremia, but these were not more highlighted in the adalimumab-Pfizer groups than in the Humira-EU groups. In addition, there were cases of Hypernatremia and Hypocalcaemia in B5381005.

No TEAEs of Blood and Lymphatic, Investigations, or Metabolism and Nutrition were reported for adalimumab-Pfizer in Study B5381001. Only single cases of these TEAEs in relation to adalimumab-Pfizer were seen in studies B5381007 and B5381005.

No significant differences between-group were reported in laboratory parameters in the clinical study in RA patients. The numbers of subjects who had abnormalities in total bilirubin, ALT and AST were comparable between the adalimumab-Pfizer and Humira-EU treatment arms in TP1. In TP2, the incidence rates of the abnormalities were low in all 3 treatment groups. In TP1 and TP2, the majority of chemistry as well as haematology abnormalities were of Grade 1-2. In total, no more than two Grade 4 AEs related to laboratory findings in Study B5381002.

In PK study B5381007 five pregnancy cases (3 female subjects, and 2 male subjects as exposed partners of pregnant women) were reported, but none of these subjects received adalimumab-Pfizer. No pregnancies were reported in studies B5381001, B5381005, or B5381002. The application concerns also indications in children, but as far as similar biological medicinal products are concerned, there is no requirement for special paediatric development.

A great majority of patients developed ADA. Nevertheless, no anaphylaxis or other serious hypersensitivity reactions were seen; and allergic and hypersensitivity reactions were not frequent. In most of the clinical studies, no difference was seen in rash or ISR. Only in the device-comparison study, the 15 subjects with rash or ISR had somewhat higher prevalence of ADA in comparison with matched controls. As a conclusion on immunogenicity, the percentage of ADA was not concordantly different between adalimumab-Pfizer and Humira EU across the clinical trials; in studies B5381001 and B5381002 the percentage of ADA was slightly higher in the Humira-EU group, but the opposite was true in study B5381007.

Although discontinuation due to AEs in TP1 was less common in the adalimumab-Pfizer group, the incidences due to the most common reasons (infections and infestations, among which latent TB) were more common in this group compared to the Humira-EU group.

2.7.2. Conclusions on the clinical safety

The number of subjects was sufficient for comparing the safety profile of the biosimilar candidate adalimumab-Pfizer and the reference medicinal product Humira-EU and studying the safety of a biosimilar product for up to one year, including comparative period of 52 weeks. The number, severity and type of SAEs, AEs of special interest, treatment discontinuations due to AEs, and laboratory findings were broadly comparable between adalimumab-Pfizer and Humira-EU, and in line with the known safety profile of Humira. The frequency of related AEs, severity of AEs and AEs of special interest remained relatively similar for the group who transitioned from Humira-EU to adalimumab-Pfizer at week 26. There were no new or unexpected safety findings in TP3. With regard to immunogenicity, the percentage of ADAs was lower in the adalimumab-Pfizer group compared to the Humira-EU group (52.3% vs 59.3% at one year).

In general, Amsparity seemed to be well-tolerated and the AE incidence was either at the same or lower level than that of the Humira-EU. Hypersensitivity reactions, injection site reactions and injection site pain were minor.

The safety profiles of the original and biosimilar candidate appear to be similar.

2.8. Risk Management Plan

Safety concerns

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious infections	Routine risk minimisation measures: Proposed SmPC Section 4.3 Contraindications Proposed SmPC 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: There are none.
Tuberculosis (TB)	Routine risk minimisation measures: Proposed SmPC Section 4.4, Special warnings and precautions for use Prescription only medicine. Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none Additional pharmacovigilance activities: There are none.
Malignancies	Routine risk minimisation measures: Proposed SmPC 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: There are none.
Demyelinating disorders (including MS, GBS and ON)	Routine risk minimisation measures: Proposed SmPC 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: There are none.
Bacillus Calmette-Guérin (BCG) disease following live BCG vaccination in infants with in utero exposure to adalimumab	Routine risk minimisation measures: SmPC Section 4.6 Fertility, pregnancy, and lactation Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none Additional pharmacovigilance activities: There are none.
Progressive multifocal leukoencephalopathy (PML)	Routine risk minimisation measures: Text in SmPC: None Additional risk minimisation measures: There are none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		There are none.
Reversible posterior leukoencephalopathy syndrome (RPLS)	Routine risk minimisation measures: Text in SmPC: None Additional risk minimisation measures: There are none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none Additional pharmacovigilance activities: There are none.
Adenocarcinoma of colon in ulcerative colitis (UC) patients	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use Additional risk minimisation measures: There are none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none Additional pharmacovigilance activities: There are none.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.9. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, AMSPARITY (adalimumab) is included in the additional monitoring list as a biological product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Amsparity was developed as a biosimilar to the reference medicinal product Humira. The route of administration (subcutaneous), posology, and indications are according to the reference product as described in the Humira SmPC.

The applicant applied for the same therapeutic indications as approved for the reference product Humira: rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA), active enthesitis-related arthritis, axial spondyloarthritis (ankylosing spondylitis [AS], and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis (PsA), adult and paediatric plaque psoriasis (PsO), adult and paediatric Crohn's disease (CD), ulcerative colitis (UC), adult and adolescent hidradenitis suppurativa (HS), adult and paediatric non-infectious uveitis (UV).

The following presentations are proposed: solution for injection in pre-filled syringe (20 mg and 40 mg), solution for injection (40 mg/0.8 ml) and solution for injection in pre-filled pen (40 mg).

Summary of analytical comparability (quality data)

The applicant performed a comprehensive similarity exercise which followed the general principles outlined in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues" (EMA/CHMP/BWP/247713/2012).

Sufficient Humira-EU and Humira-US products lots were compared to adalimumab-Pfizer and included in the similarity analyses.

All methods and assays used are reported to be sensitive and suitable for evaluating biosimilarity, validation data is provided for the methods used also for routine release testing. In addition, qualification reports for biological activity assays have been provided.

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 Fab and Fc related functions, and comparative stability studies.

Summary of non-clinical data

The applicant conducted comprehensive *in vitro* studies to address the similarity of key functional activities of adalimumab-Pfizer and Humira-EU (and Humira-US). The shortened nonclinical similarity exercise followed the guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) and was in accordance with the overarching guideline on similar biological medicinal products (CHMP/437/04 Rev 1).

In addition to *in vitro* functional studies, a 1-month GLP compliant comparative toxicity and toxicokinetic study was conducted in cynomolgus monkeys who received weekly subcutaneous dosing of 157 mg/kg of adalimumab-Pfizer of Humira-EU (study 12GR307).

The analytical method employed for determination of adalimumab in cynomolgus monkey serum was reported to be sensitive and suitable for assessment of similarity of exposure levels in cynomolgus monkey. The analytical method employed for determination of ADA positivity in cynomolgus monkey serum could have underestimated the ADA positivity due to the lack of drug tolerance testing.

Summary of clinical comparability data

Two PK studies (B5381001 and B5381007) were conducted: single-dose (40 mg SC) randomised, double-blind (Sponsor open), 3-arm parallel PK studies in healthy subjects comparing adalimumab-Pfizer, Humira-EU and Humira-US (B5381001: N = 70 subjects randomised/arm, B5381007: N ~120 subjects randomised/arm). Supportive PK data in patients with RA in the clinical efficacy and safety study B5381002 were also collected.

A clinical efficacy and safety study (B5381002) was carried out: a 52-week (TP1 and TP2) randomised double-blind equivalence study comparing adalimumab-Pfizer and Humira-EU (40 mg SC every 2 weeks) in combination with MTX in subjects with moderately to severely active RA with inadequate response to MTX therapy (N=297 in adalimumab-Pfizer arm and N=299 in Humira-EU arm). Patients on Humira-EU arm in treatment period 1 (TP1) were re-randomised 1:1 at week 26 to continuation or switching to adalimumab-Pfizer (TP2). The primary outcome was ACR20 at Week 12, with an equivalence margin of +/- 14%. Secondary endpoints were safety, immunogenicity, PK, PD, and additional clinical response measures including ACR20 at visits other than Week 12, ACR50, ACR70, individual ACR components including HAQ-DI, DAS28-4 (CRP), EULAR response, DAS remission and ACR/EULAR remission.

3.2. Results supporting biosimilarity

Quality data

High similarity between adalimumab-Pfizer and Humira-EU was demonstrated for the following quality attributes:

- Primary structure
- Higher order structure
- Dimers, aggregations, and fragments
- Glycosylation, with the exception of total afucosylation and high mannose variants where differences are seen
- Charge variant profile
- Binding to sTNFα and mTNFα
- C1q binding and CDC activity

The differences identified are further discussed in section 3.3.

Nonclinical data

Regarding Fab-related activities similar binding to sTNFα and mTNFα, similar inhibition of TNFα -induced apoptosis activity (caspase 3/7 activity), similar reverse signalling activity on Jurkat cells and similar inhibition of ELAM-1 expression was demonstrated.

Comparable Fc-related effector functions *in vitro* were demonstrated; similar ADCC activity using PBMNCs as effector cells, similar activity in FcγRIIIa RGA assay, similar inhibition of T-cell proliferation in a mixed lymphocyte reaction, similar CDC activity and C1q binding, and similar binding to FcγRI, FcγRIIa, FcγRIIIb and FcRn.

Similar uptake to the mannose receptor expressing rat alveolar macrophages was demonstrated.

Similar safety and TK profile was demonstrated in the cynomolgus monkeys.

Clinical data

Pharmacokinetics

The PK biosimilarity of adalimumab-Pfizer to Humira-EU is supported by the PK data from studies B5381007 (although the point estimates were above 100%) and B5381002 (although the means of trough concentrations were slightly higher for adalimumab-Pfizer compared to Humira-EU). Also, the C_{max} and $AUC_{0\text{-}2wk}$ when ANOVA was used in statistical analysis and PK data (i.e. C_{max}, $AUC_{0\text{-}2wk}$, AUC_t and AUC_{inf}) when ANCOVA (the weight as a covariate) was used in statistical analysis in the PK-study B5381001 support the biosimilarity of adalimumab-Pfizer to Humira-EU.

Furthermore, in the phase 3 study in RA patients at weeks 6, 12, 26 the differences in median serum concentrations between adalimumab-Pfizer and Humira-EU were 24%, 32%, 23% in ADA-positive patients, but only 2%, 2% and 10% in ADA-negative patients. The explanation of these differences remains unclear. Thus, when analysing only the ADA-negative patients, in the absence of interfering ADAs, the differences in the trough serum concentrations were very small; this supports biosimilarity from the PK point of view.

Efficacy

The data from the main efficacy and safety study of both primary and secondary endpoints support biosimilarity and equivalence between adalimumab-Pfizer and Humira-EU in subjects with moderately to severely active RA with inadequate response to MTX therapy. The proportion of subjects reaching ACR20 response at week 12 was similar being 68.4% (203/297) and 71.3% (214/2003) in the adalimumab-Pfizer and Humira-EU groups, respectively. The point estimate for the ACR20 treatment difference at week 12 in ITT population was -2.98% and the 95% CI of the adjusted treatment difference was within the pre-defined equivalence margin of +/- 14% including 0 [-10.38%, 4.44%]. Similarly, the equivalence criteria were met also in PP population at week 12 with 71.1% (189/266) and 75.2% (191/254) of subjects reaching ACR20 in the adalimumab-Pfizer and Humira-EU groups, respectively. The point estimate for the difference was -4.14% and the 95% CI of the adjusted treatment difference was within the equivalence margin including 0 [-11.79%, 3.61%].

Also, in the continuous DAS-28 (CRP) parameter, although this data was only descriptive, the difference between the compared groups was smaller than the minimally clinically meaningful difference of 0.6 in each visit up to week 26. Furthermore, the secondary endpoints in ACR20, ACR50, and ACR70 showed similar largely overlapping response curves throughout the treatment period 1 and 2, without significant difference in response rate after switching the treatments. No withering effect of the treatment response was present in any of the treatment arms. Finally, other secondary endpoints showed comparable results in all treatment groups in both treatment periods, TP1 and TP2. In TP3, efficacy was sustained and comparable clinical responses were observed among the subjects who

continued to receive adalimumab-Pfizer in TP3, and for the subjects who switched from Humira-EU to adalimumab-Pfizer at Week 52.

Safety

In the healthy volunteer PK-study B5381001 the frequency of the TEAEs was lower in the adalimumab-Pfizer group compared to the Humira-EU group (46.4% vs. 62.9%), while in PK-study B5381007 the TEAEs were reported more often in adalimumab-Pfizer group compared to the Humira-EU group (57% vs. 40.3%). One SAE was reported in PK studies B5381001 (in Humira-EU group) and B5381005 (in adalimumab-Pfizer group). In the PK studies the number of injection site reactions (ISR) was equal in each group.

In the pivotal Phase 3 study the adalimumab-Pfizer and Humira-EU groups showed similar frequency of the AEs (TP1: 48.1% vs. 47.8% of the subjects experienced TEAEs; TP2: 43.5% vs. 44.4%) in each treatment period. The same was true also in the reported SAEs (TP1: 2.7% vs. 3.0% of the subjects experienced TEAEs of Grade 3 or higher, respectively; TP2: 1.4% vs. 4.4%, respectively). Additional data provided from TP3 and further follow-up period did not change the conclusions made based on TP1 and TP2 data.

Latent TB were seen in TP1 with 5 observed cases in adalimumab-Pfizer group and 1 case in Humira-EU group, but the numbers of affected were small and the difference between treatments statistically non-significant. In TP3, one case of latent TB was seen in a patient receiving adalimumab-Pfizer only. Of the AEs of special interest neoplasms occurred in similar incidence in both groups (5 in each) and similar frequency of the infections and infestations was observed (approximately 25% of subjects in each group) during the TP1. During TP3 and follow-up period, a total of 4 cases (including 2 SAEs) of neoplasms were reported: 2 cases each in the adalimumab-Pfizer/ adalimumab-Pfizer/ adalimumab-Pfizer and Humira-EU/Humira-EU/ adalimumab-Pfizer groups. The equal incidence was also seen during the TP2.

The number of ISRs was in general equal during the TP1 (1.7% and 2.0% in adalimumab-Pfizer and Humira-EU groups, respectively). Only one case of ISR was seen in patients continuing with adalimumab-Pfizer during the TP2 and none in Humira-EU/Humira-EU group.

The frequency of subjects developing ADAs was 85.5% vs. 90.0% (B5381001), 76.5% vs. 70.3% (B5381007) and 44.4% vs. 50.5% (B5381002, TP1) in adalimumab-Pfizer and Humira-EU groups, respectively. The corresponding figures in NAb development were 53.6% vs. 61.4% (B5381001), 64.7% vs. 60.2% (B5381007) and 13.8% vs 14.0% (B5381002, TP1). The 1-year immunogenicity data (ADAs) in RA-patients showed similar results (52.3 vs 59.3%). No anaphylaxis or systemic allergic reactions were observed in any of these studies and the differences in the immunogenicity profiles were small in general.

3.3. Uncertainties and limitations about biosimilarity

Quality data and in vitro pharmacology data

Uncertainties and limitations were identified for the following quality attributes and *in vitro* properties. They were subsequently addressed during the review with supporting clinical and non-clinical data.

- The levels of high mannose variants differ. In the response to LoQ, the applicant has provided a literature-based discussion on the impact of high mannose variants on pharmacokinetics. Based on previous knowledge on literature and other anti-TNF products, the applicant's conclusion can be agreed. The difference observed in high mannose content is minor and the impact on the PK of adalimumab is not expected to be significant. No uncertainties remain.

- Lower level of ADCC function correlating with lower levels of mannosylation/afucosylation. The applicant provided new data and discussion on the clinical relevance of the differences observed in ADCC activity. In conclusion, even though a difference in ADCC activity is observed between adalimumab-Pfizer and Humira-EU using the most sensitive assays based on NK or PBMC V/V effector cells, the ADCC assays believed to be more physiologically relevant show similar or lower but overlapping activity for adalimumab-Pfizer and Humira-EU. Furthermore, the data from IBD donor cells supports the conclusion that clinical relevance of the observed differences in ADCC activity is not expected to be significant.

- In the response to the list of outstanding issues, the applicant provided new data to demonstrate the correlation between afucosylated levels with FcγRIIIa binding.

Non-clinical data

For uncertainties related to the comparative *in vitro* studies, please refer to the Uncertainties and limitations about biosimilarity Quality data.

The TK profiles were comparable, but there was a tendency for higher exposures (AUC_{168} and C_{max}) in animals treated with adalimumab-Pfizer in comparison to Humira-EU on day 22. The exposures were approximately 1.2 –fold higher in adalimumab-Pfizer treated animals. However, the study included only 3 cynomolgus monkeys/gender/treatment which limits the value of the study.

The ADA formation in adalimumab-Pfizer and Humira-EU treated cynomolgus monkeys was similar, but the ADA positivity could have been underestimated due to drug interference.

Clinical data

Pharmacokinetics

Although there are supportive PK data for biosimilarity of adalimumab-Pfizer to Humira-EU, the first PK study B5381001 when ANOVA was used in statistical analysis failed to demonstrate the PK biosimilarity of adalimumab-Pfizer in AUC_t and AUC_{inf} to Humira-EU and another PK study (B5381007) with improved study design was performed. The biosimilarity was formally met in all primary PK parameters (i.e. the 90%CIs were within the 0.80-1.25% range); however, the 90%CIs in the C_{max} and $AUC_{0\text{-}2wk}$ in comparison of adalimumab-Pfizer and Humira-EU were above 100% and consequently not including the 100%.

In addition, in both PK studies the sampling time for PK was too short to optimally characterisation of the whole PK profiles. However, in the study B5381007, the biosimilarity in PK can be considered formally met between adalimumab-Pfizer and Humira-EU and the PK results in this study can be considered to support biosimilarity.

The mean concentrations of adalimumab-Pfizer were numerically slightly higher than the reference/comparator products in all clinical studies included in the dossier. However, these were not seen to have an impact on clinical efficacy or safety.

Efficacy

The number of involved centres/ countries/ regions was high in the main study. Furthermore, clear difference in ACR responses were seen depending on the geographic region. Nevertheless, based on the provided data from the single centres, no clear indication was seen that the overall efficacy outcome results would be driven by results from certain individual centres; the single centres being also small in the number of subjects recruited.

Higher ACR20 response rate was seen in Humira-EU group compared to adalimumab-Pfizer group in NAb- positive subjects. The applicant submitted additional analyses demonstrating no clinically

relevant difference in efficacy as measured by the more sensitive DAS28-4(CRP) over time between adalimumab-Pfizer and Humira-EU, up to week 26, regardless of NAb/ADA status.

Safety

None

Immunogenicity

The percentage of ADA positivity was not concordantly different between adalimumab-Pfizer and Humira EU across the clinical trials; in studies B5381001 and B5381002 the percentage of ADA was slightly lower in the adalimumab-Pfizer group, but the opposite was true in study B5381007. Hence, the effect of immunogenicity on small differences in exposure between adalimumab-Pfizer and Humira-EU (higher levels with the biosimilar candidate) is not fully clear. Furthermore, sampling times were too short for characterisation of the whole PK in studies B5381001, B5381005 and B5381007; and formation of ADA naturally affected most the elimination phase, as the percentage of ADA increased by time. Hence, the impact of immunogenicity on entire PK profile was not covered. Since the results on ADA percentage in the clinical studies in total did not indicate a constant difference in immunogenicity of adalimumab-Pfizer vs. Humira-EU and the slightly higher exposures of the biosimilar did not affect efficacy and safety, the lack of entire coverage of PK profile was not considered as crucial.

3.4. Discussion on biosimilarity

On the quality level, a comprehensive biosimilarity exercise was performed following the general principles outlined in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues" (EMA/CHMP/BWP/247713/2012). The comparability exercise is mostly based on comparison of analytical characterisation data collected during the years of drug development.

A lower level of afucosylated glycans, including high mannose glycans, was observed in adalimumab-Pfizer batches. In general, therapeutic IgG containing high mannose glycans can be cleared more rapidly. According to the applicant, the differences in high mannose levels are not expected to have a clinical impact but may impact binding to mannose receptor and associated clearance. Mannose receptor binding was analysed as part of the non-clinical studies, and the results indicated that the mannose receptor in the test system used was not the major receptor mediating the adalimumab cellular uptake. Furthermore, no significant difference in mannose receptor uptake between the reference product (Humira-US was used in this assay) and adalimumab-Pfizer was observed. However, the sensitivity of this assay is questionable, thus the assay results were not considered reliable. Therefore, the relevance of the results generated using this assay is considered low. In responses to the list of question, the applicant provided literature-based discussion on the impact of high mannose variants on pharmacokinetics. Based on previous knowledge on literature and other anti-TNF products, the applicant's conclusion can be agreed upon. The difference observed in high mannose content is minor and the impact on the PK of adalimumab is not expected to be significant.

Adalimumab-Pfizer was less potent in triggering ADCC activity in the ADCC NK assay(FcyRIIIa 158 V/V genotype). Afucosylation levels were plotted against ADCC NK assay data demonstrating a correlation between low ADCC activities in batches with lower afucosylation. The applicant performed an additional assay with new NK donor cells. Based on this assay, it was argued by the applicant that the apparent sensitivity to total afucosylation observed in the primary NK ADCC assay is a characteristic of the individual donor cells used in that assay, as it is not reproduced with either of the other NK cell donors tested.

Even though ADCC activity effector functions are thought not to be involved in the primary mode of action and functionality of adalimumab, Fc functions could be important in certain indications. The applicant provided discussion and new data in their response with regards to differences observed in ADCC activity. It is concluded, that even though difference in the ADCC activity is observed between adalimumab-Pfizer and Humira-EU using the most sensitive assays based on NK or PBMC V/V effector cells, the ADCC assays, believed to be more physiologically relevant, show similar or lower, but overlapping activity for adalimumab-Pfizer and Humira-EU. Furthermore, the data from IBD donor cells supports the conclusion that clinical relevance of the observed differences in ADCC activity is not expected to be significant.

Biosimilarity in the pivotal PK study B5381007 including healthy subjects has been formally demonstrated between adalimumab-Pfizer and Humira-EU as the primary parameters C_{max}, AUC_t and AUC_{inf}, the 90% CI for the ratio of test-to-reference products fell within the acceptance range of 80.00-125.00%. Also in the first PK study B5381001, the PK parameters C_{max} and AUC_{0-2wk} , the 90% CI for the ratio of test-to-reference products fell within the bioequivalence range, and in the exploratory analysis when weight was used as a covariate, all primary PK parameters were within 80.00-125.00% (including 100%). Additional support for similarity between adalimumab-Pfizer and Humira-EU was obtained in the study in RA patients (clinical study B5381002). The mean C_{trough} concentrations were slightly higher with adalimumab-Pfizer than with Humira-EU; however, when taking into account the overlap in concentrations and high inter-patient variability (CVs ranging from 48-75% in TP1 and 65-81% in TP2), the concentrations can be considered to be at comparable levels. The steady state mean trough concentrations were about 5-8 µg/ml as reported in RA patients with MTX in the Humira SmPC.

The clinical efficacy and safety study was adequately designed and the primary and secondary outcome parameters and equivalence criteria correctly set. The clinical efficacy data was highly supportive for the similarity between adalimumab-Pfizer and Humira-EU in both primary and secondary endpoints. The percentage of ADA was overall high in all studies, as expected for adalimumab. Differences in the percentage of ADA (85.5% versus 90% for adalimumab-Pfizer compared to Humira-EU), together with timing of ADA formation, were thought by the applicant to contribute to the failure of the AUC_t to meet the PK similarity criteria in the first PK study B5381001. However, in the other PK-study B5381007 that formally met the bioequivalence criteria, the percentage of ADAs was slightly higher in the adalimumab-Pfizer group compared to Humira-EU group (76.5% versus 70.3%). It is agreed that ADA might have played some role in both PK studies; but to different directions.

In RA-patients (B5381002), patients treated with adalimumab-Pfizer had slightly lower percentage of ADAs: 44.4% versus 50.5% in the Humira-EU group (TP1; at 1-year 52.3% vs 59.3%); though the percentage of NAb was comparable (13.8 vs. 14%). However, there was considerable overlap in serum drug concentrations between the treatment arms, with very high variability (CV% ranging from 49 to 67%). Notably, the difference in median serum concentrations between the two RA patient groups was markedly higher in ADA-positive vs. ADA-negative patients (in the absence of interfering ADAs), the difference of which explanation remains unclear. Nevertheless, taking into account the discrepant results on ADA percentage in the clinical studies in total, current data do not indicate a constant difference in immunogenicity of adalimumab-Pfizer vs. Humira-EU, although somewhat lower ADA percentage (~6%) with the biosimilar candidate possibly could have played some role in two of the submitted studies in relation to the slightly higher exposures.

The safety data from the pivotal Phase 3 trial indicated similar incidence of AEs, SAEs and the AEs of special interest (neoplasms, infections and infestations, ISRs) between the adalimumab-Pfizer and Humira-EU groups. No clear safety differences or issues were either detected in the 3 PK studies in the healthy volunteers. Furthermore, the developed ADAs and NAbs did not correlate with the hypersensitivity events, the frequency of which was low or non-existent in the clinical studies submitted and the differences between the immunogenicity profiles between the compared treatments

were small. Based on these results the safety data support biosimilarity. The applicant performed additional analyses on efficacy results in Nab and ADA positive and negative subgroups, comparing adalimumab Pfizer and adalimumab EU arm of study B5381002 to clarify the temporal relationship between the NAb development and potential lack of efficacy and whether differences between treatment groups are present. At week 12, there was a difference of 14% in ACR20 results in favour of adalimumab-EU. Nevertheless, the difference largely disappeared by time, and at 26 weeks there was a small, clinically and statistically non-significant difference (-0.813) in favour of adalimumab-EU. The evolution of DAS28-4 (CRP) values was closely similar in study B5381002 regardless of ADA status.

3.5. Extrapolation of safety and efficacy

Regarding the quality characterisation and biofunctional assays the adequate parameters have been studied and appropriate methods used. These have included receptor binding assays, ADCC and CDC effector functions, reverse signalling, sTNFα apoptosis inhibition and regulatory macrophage activity assay. Furthermore, Vectra-DA descriptive comparison in 12 biomarkers (VCAM-1, TNFR-I, IL-6, EGF, VEGF, YKL-40, MMP-1, MMP-3, resistin, leptin, SAA, and CRP) showed comparability between adalimumab-Pfizer and Humira-EU. Sufficient justification and discussion were provided on the pathomechanistical aspects (e.g. cytokine profile) related to adult and adolescent hidradenitis suppurativa (HS), adult and paediatric non-infectious uveitis (UV) indications and the impact of the slightly higher exposure in adalimumab-Pfizer to adalimumab-EU. Based on these data the extrapolation to all EU-Humira indications is acceptable. In quality, the difference in ADCC response between the products was seen by using sensitive method, but in more physiological assays no difference was recognised. The difference in ADCC is not considered to be clinically relevant and is not expected to have impact on extrapolation.

Slight differences in PK were seen with the first PK study (B5381001) in healthy volunteers formally not meeting the equivalence criteria in AUC_t and AUC_{inf}. Also, the mean PK parameters (i.e. AUCs and C_{max}) were numerically higher in adalimumab-Pfizer treatment group than in Humira-EU. In the second PK trial in healthy subjects (B5381007) the biosimilarity in PK was considered formally met between adalimumab-Pfizer and Humira-EU; however, the point estimates in exposure indicating PK parameters are all above 100% and lower boundary of 90% CI over 100% in C_{max} and $AUC_{0\text{-}2\ wk}$. However, the slight numerically higher concentrations of adalimumab-Pfizer compared to the Humira-EU was not seen to have an impact on clinical efficacy or safety possibly indicating the dose level approved for the clinical use exceeding the maximal efficacy level reachable due to the saturation of the biological target for the treatment.

The chosen model disease for the pivotal clinical Phase 3 study, i.e. the subjects with moderately to severely active RA with inadequate response to MTX therapy, is considered adequately sensitive and homogeneous population to support biosimilarity in all of the sought indications. Based on the efficacy trial data the similarity was shown in both primary and secondary outcomes. It was also shown that the treatment effect did not decline up to 76 weeks and the response rate profile was highly similar between treatment arms. Furthermore, the supportive sensitivity analyses showed similar outcome.

Overall, comprehensive set of models have been presented on the quality, non-clinical and clinical level to support extrapolation to all indication of Humira.

3.6. Additional considerations

Not applicable

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Amsparity is considered biosimilar to Humira. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Amsparity is favourable in the following indications:

Rheumatoid arthritis

Amsparity in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Amsparity can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Amsparity in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Amsparity can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Amsparity is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Amsparity is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Amsparity is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Amsparity is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

Amsparity is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Amsparity is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Amsparity is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn's disease

Amsparity is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Amsparity is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Amsparity is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Adolescent hidradenitis suppurativa

Amsparity is indicated for the treatment of active moderate to severe hidradenitis suppurativa (HS) (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Uveitis

Amsparity is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric uveitis

Amsparity is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Amsparity in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The educational program consists of a Patient Reminder Card.

The Patient Reminder Cards (adult and paediatric) contain the following key elements:

- infections, including tuberculosis
- cancer
- nervous system problems
- vaccinations