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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hulio

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/004429/0000

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Transaminase
AS	Ankylosing Spondylitis
AUC_{0-t}	Area under the concentration time curve from time 0 to the time of the last serum drug concentration sample taken
$AUC_{0-\infty}$	Area under the concentration time curve from time 0 to infinity
AUC_{0-360h}	Area under the concentration time curve from time 0 to 360 hours
axSpA	Axial Spondyloarthritis
C_{max}	Maximum observed concentration
CD	Crohn's Disease
CHF	Congestive Heart Failure
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CRP	C-reactive Protein
CSR	Clinical Study Report
CVA	Cerebrovascular Accident
DAS	Disease Activity Score
DBT	Double Blind Trial
DMARD	Disease-modifying Anti-rheumatic Drugs
eCRF	electronic Case Report Form
EM	Erythema Multiforme
EMA	European Medicines Agency
eow	Every other week
ERA	Enthesitis-related Arthritis
ESR	Erythrocyte Sedimentation Rate
EU	European
FAS	The Full Analysis Set
FKB	FUJIFILM KYOWA KIRIN BIOLOGICS Co., Ltd.
GBS	Guillain-Barre Syndrome
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
HAQ-DI	Health Assessment Questionnaire Disability Index
HBV/HCV	Hepatitis B virus/Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Hazard Risk
HS	Hidradenitis Suppurativa
HSTCL	Hepatosplenic T-cell Lymphoma

HTLV-1	Human T-cell Leukaemia Virus type 1
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Disease
IMP	Investigational medicinal product
JIA	Juvenile Idiopathic Arthritis
LOCF	Last observation carried forward
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
mAb	Monoclonal Antibody
MCC	Merkel Cell Carcinoma
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTX	Methotrexate
NMSC	Non-Melanoma Skin Cancer
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OLE	Open Labelled Extension
PE	Pulmonary Embolism
PFP	Pre-filled Pen
PFS	Pre-filled Syringe
pJIA	Paediatric Juvenile Idiopathic Arthritis
PK	Pharmacokinetics
PPAS	Per-protocol Analysis Set
Ps	Plaque Psoriasis
PsA	Psoriatic Arthritis
PT	Preferred Term
PY	Patient-Years
RA	Rheumatoid Arthritis
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
sc	Subcutaneous
SCC	Squamous Cell Carcinoma
SD	Standard deviation
SJC	Swollen joint count
SJS	Stevens Johnson Syndrome
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SpA	Spondyloarthritis
$t_{½}$	Elimination half life
TJC	Tender joint count

t_{max}	The time to maximum observed concentration (Cmax)
TB	Tuberculosis
Th	T-helper
TNF	Tumour Necrosis Factor
TSE	Transmissible Spongiform Encephalopathy
UC	Ulcerative Colitis
UK	United Kingdom
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infection
US	United States
UV	Ultra Violet
VAS	Visual analogue scale
WCB	Working Cell Bank
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Kyowa Kirin Limited submitted on 25 April 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Hulio, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The application was transferred from Kyowa Kirin Limited to Mylan S.A.S. during the submission of responses to the CHMP consolidated List of Outstanding Issues on 25 June 2018. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 1 April 2016

The applicant applied for the following indication:

Rheumatoid arthritis

Hulio 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.

Hulio 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

Hulio 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). Hulio 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

Hulio 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)

Hulio 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

Hulio 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

Hulio 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

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

Paediatric plaque psoriasis

Hulio 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)

Hulio 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

Hulio 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

Hulio 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

Hulio 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.

Uveitis

Hulio 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

Hulio 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 a 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, solution for injection
- Marketing authorisation holder: AbbVie Ltd.
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/256/001

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, solution for injection
- Marketing authorisation holder: AbbVie Ltd.
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/256/001

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability 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 Ltd.
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union
- 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 from the CHMP on 19 September 2013, 22 May 2014 and 26 March 2015. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bart Van der Schueren Co-Rapporteur: Greg Markey

The application was received by the EMA on	25 April 2017
The procedure started on	18 May 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 August 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	4 August 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 August 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 February 2018
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at two sites: one responsible for active substance manufacture and second for finished product prefilled syringe and prefilled pen manufacture; both located in Japan between 16 April 2018 and 20 April 2018. The outcome of the inspection carried out	29 June 2018 and 02 July 2018

was issued on.	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	03 April 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 April 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 April 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	06 July 2018
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 Hulio on	26 July 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Hulio (FKB327) is being developed as a biosimilar candidate to Humira (INN: adalimumab; ATC code L04AB04).

The reference product Humira is authorised for the treatment of Rheumatoid Arthritis (RA), Juvenile idiopathic arthritis (JIA) (polyarticular JIA and enthesitis-related arthritis), Axial spondyloarthritis (ankylosing spondylitis [AS], and axial spondyloarthritis without radiographic evidence of AS), Psoriatic arthritis (PsA), Psoriasis (PsO), paediatric plaque Psoriasis, Crohn´s Disease (CD), paediatric Crohn´s Disease, Ulcerative colitis (UC), Hidradenitis suppurativa (HS) including adolescent HS and Non-infectious Uveitis (UV) including paediatric uveitis in the European Union.

The applicant is seeking all of the indications and dosing regimens for which Humira is registered in the EU.

The dosage form and route of administration is identical to Humira.

About the product

Adalimumab, the active ingredient of Hulio (development code “FKB327”) belongs to the pharmacotherapeutic group “immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors” (ATC code: L04AB04). Adalimumab is a recombinant human immunoglobulin IgG1 type monoclonal antibody specific for TNF-α. Adalimumab binds to soluble and membrane associated TNF-α, thereby

inhibiting the interaction of TNF-α with the TNF-α receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events, which is considered the primary mechanism of action in all indications approved for Hulio.

Three presentations are being developed:

- 40 mg/0.8 ml vial
- 40 mg pre-filled syringe
- 40 mg pre-filled pen

Each product presentation contains 0.8 mL deliverable volume of FKB327 (40 mg) at a concentration of 50 mg/mL.

Type of Application and aspects on development

During the development of FKB327, the Applicant has received scientific advice from EMA.

The scientific advice procedures covered questions on the pharmaceutical quality, the non-clinical and clinical program.

In general, the Applicant´s development program to demonstrate the similarity between Hulio and Humira is considered adequate and was performed according to the CHMP guidance on similar biological products and the recommendations given in the Scientific Advices except for some non-clinical aspects (see Section 2.3).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as sterile, single-use, ready-to-use, solution for injection containing 40 mg of adalimumab as active substance in 0.8 mL deliverable volume at a concentration of 50 mg/mL.

Other ingredients are: Monosodium glutamate, sorbitol, methionine, polysorbate 80, hydrochloric acid (for pH adjustment) and water for injections.

The product is available in three presentations: single-use pre-filled syringe (plastic) with safety device, in single-use pre-filled pen, and, for paediatric use, in single-use pre-filled vial (type I glass), fitted with rubber stoppers, aluminium crimps and flip-off seals.

Hulio is developed as a biosimilar to Humira (adalimumab, AbbVie Ltd.).

2.2.2. Active Substance

General Information

The active substance (INN: adalimumab, manufacturer's code: FKB327) is a recombinant, human monoclonal antibody (IgG1 kappa) expressed in Chinese Hamster Ovary (CHO) cells. FKB327 has a molecular weight of approximately 148 kDa. Adalimumab is comprised of two identical heavy chains (HCs) and two identical light chains (LCs). One N-linked glycosylation site is located at asparagine-301 on

each HC. The main N-linked oligosaccharide structures of FKB327 are asialo, biantennary and fucosylated complex type structures containing 0 and 1 galactose residues.

The mechanism of action of adalimumab is known to be its selective binding to human soluble and membrane bound tumour necrosis factor alpha (TNFα). This neutralises the biological function of TNF by blocking its interaction with the cell surface membrane receptors TNFR1 (p55) and TNFR2 (p75). 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

Description of the manufacturing process and process controls

The active substance manufacturing process has been adequately described. Manufacturing flow charts are provided for each step of the manufacturing process, including critical/key process parameters, in-process controls, and hold times for process intermediates. 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. Further detail on the manufacturing process description was initially requested and has been provided to a sufficient extent. The active substance manufacturing process is considered acceptable.

The manufacturing process for the active substance includes steps for cell culture, harvest, purification with a series of chromatography, viral inactivation/filtration and ultra-/diafiltration steps. Excipients are added and the formulated active substance is stored and transported under appropriate conditions. The process has been sufficiently described and in-process controls are adequately set to control the process.

Reprocessing conditions at the viral removal step and the bulk filling step are appropriately described. In addition, a protocol for validation of future reprocessing during commercial manufacturing is provided. The tests proposed to evaluate the active substance quality following reprocessing are considered appropriate.

A detailed description of the container closure system is provided. The container meets the USP requirements for bacterial endotoxins, cytotoxicity testing Class VI, particulate matter, physicochemical test for plastics, food contact, and the Ph. Eur. 3.2.2.1 requirements for plastic containers for aqueous solutions for parenteral infusion and the requirements of the “Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products” (EMEA/410/01 Rev.3).

Extractable and toxicological assessment studies are 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 submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

Recombinant CHO cells expressing the monoclonal antibody adalimumab were established by co-transfection of the expression vectors followed by genetic selection. Generation and testing of the

expression vectors was described. A two tiered cell banking system is used and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs. Also end of production (EOP) cells and cells at the limit of *in vitro* cell age (LIVCA) were generated and tested. Genotypic and phenotypic stability of the recombinant cell line at and beyond the limit of cell age are adequately addressed. Foetal bovine serum was used to establish the host cell line and appropriate TSE Certificates are provided. No other animal-derived compounds are used during production of FKB327.

Control of critical steps and intermediates

An overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Information has been provided on the control strategy in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. 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 Applicant has taken a comprehensive, three-stage approach towards process validation. The first stage relates to the process development/design and characterisation studies. Information is provided on aspects of process establishment in a stepwise approach. CQAs were identified and linked to performance attributes. The second stage relates to process verification, with the conduction of formal process performance qualification (PPQ) studies. The active substance manufacturing process has been satisfactorily validated, 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, uniformity of bulk filling, reprocessing, and shipping qualification. The third stage relates to the ongoing process verification and the maintenance of the commercial production. The overall control strategy is acceptable. Consistency in production has been shown on a suitable number of full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are 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 active substance manufacturing process was directly developed at the intended commercial scale. No substantial changes have been made to the process during development. Consequently, all active substance lots produced are considered representative of the commercial manufacturing process and some of these lots were used in clinical studies. Comparability studies are thus not needed.

Characterisation

The active substance has been thoroughly characterised by using several active substance lots. Characterisation studies encompass N- and C-terminal sequencing, peptide mapping, disulfide bonds, analysis of glycosylation, molecular weight, isoform pattern, extinction coefficient, electrophoretic patterns, post translational modifications, liquid chromatographic patterns, spectroscopic profiles, thermal unfolding properties, biological activity, functional activity and characterisation of product-related variants in forced degradation studies. The characterisation studies employed physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG1-type antibody.

In general, the studies included in the characterisation are considered relevant, comprehensive and in line with the requirements of Ph. Eur. monograph no. 2031 “Monoclonal antibodies for human use” and guideline on development, production, characterisation and specification for monoclonal antibodies and related products (EMA/CHMP/BWP/532517/2008). Further characterisation data have been presented in the biosimilarity assessment.

Product-related variants are classified as product-related impurities or product-related substances based on characterisation and criticality assessment for potential impact on potency, pharmacokinetics (PK) and clinical safety.

As process-related impurities, the Applicant has considered host cell protein (HCP), host cell DNA, other specified contaminants and media/buffer components. All process-related impurities were observed at consistently low levels. Impurity clearance has been discussed during PPQ validation studies and process characterisation studies. Additionally, a summary of safety assessment of process-related impurities was provided.

Specification

Control of the active substance has been established as part of the overall control strategy based on criticality assignment of the quality attributes, process development and validation, PPQ lot results, historical data from commercial manufacturing, and stability data. The main aspects comprising quality control testing for monoclonal antibodies are covered in line with the relevant guidelines.

The specification is in line with ICH Q6B and includes tests and limits for general attributes, identity, purity/impurities, potency and microbiological attributes. Apart from the routine release testing, the CHMP recommends consideration of specified additional characterisation tests in case of relevant changes of the active substance manufacturing process.

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 for batches which were manufactured with the intended commercial process and at commercial scale for the active substance were provided. The results are within the specifications and demonstrate manufacturing process consistency.

Reference materials

The Applicant provided detailed information on the Reference Standards used to date. Each lot of Reference Standard was extensively qualified according to release tests as well as additional characterisation tests. Future Primary and Working Reference Standards will be qualified according to the same set of release and characterisation tests. The management of Reference Standards is considered adequately described.

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.

Stability data on an appropriate number of batches of active substance from the commercial manufacturing process stored in the intended container under real time, under intermediate and under accelerated conditions according to the ICH guidelines were provided.

Appropriate photostability and stress-condition studies have also been conducted.

No decrease or trends were observed for potency or purity under normal storage conditions. From the data currently available, it appears that the active substance is stable at long-term storage conditions and does not show any signs of degradation or loss of potency. In addition, the forced degradation studies demonstrated that the analytical procedures used for active substance release and stability testing are stability-indicating.

The Applicant commits to continue the ongoing primary long-term stability studies. In addition, the Applicant commits to post-approval long-term stability studies. In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product Hulio is presented as a sterile, single-use, ready-to-use, solution for injection. The solution contains adalimumab, monosodium glutamate (buffering agent), sorbitol (tonicity agent), methionine (stabiliser), polysorbate 80 (stabiliser), hydrochloric acid (pH modifier), and Water for Injections (WFI) (solvent). All excipients are well known pharmaceutical ingredients and their quality is compliant with European Pharmacopoeia (Ph. Eur.) standards; compliance with National Formulary (NF) for monosodium glutamate is accepted as there is no monograph for this excipient in the Ph.Eur. The excipients used are compendial grade and acceptable There are no novel excipients used in the finished product formulation and none of them are of animal or human origin.

Each product presentation contains 0.8 mL deliverable volume of FKB327 (40 mg) at a concentration of 50 mg/mL. Syringes are filled to ensure that there is sufficient deliverable volume provided from each syringe. Three product presentations are planned to be commercialised: Vial (glass vial), pre-filled syringe (PFS) and pre-filled pen (PFP), also referred to as auto-injector (AI).

The materials of the primary packaging comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The devices (i.e. PFS and AI) are considered as integral part of the medicinal product and are for single use only. Hence, CE markings are not required. The medical devices are adequately described. Appropriate, biocompatible materials are used to manufacture the devices. Sufficient design verification testing, human factors and risk assessment were performed to ensure proper functioning of the devices.

The presentations fulfil the needs of adult and paediatric patients alike.

The function and characterisation of each excipient is provided and is satisfactory. The stability and compatibility with the active substance has been adequately discussed.

It should be noted that the composition differs from that of the reference product which contains mannitol, polysorbate 80 and water for injections. However, characteristics of the formulation and the rationale for the selected excipients have been adequately discussed; development studies supporting the formulation rationale have been adequately discussed.

The finished product formulation is the same as the one used during the clinical development.

Comparability of products used during clinical development and intended for commercialisation is accepted.

The Quality Target Product Profile (QTPP) has been defined for each presentation. This is followed by a summary of the CQAs identified based on the QTPP. For the vial product format an evaluation of the criticality of manufacturing process steps and process parameters by risk analysis is summarised. Process parameters associated with each identified critical control point have been summarised and linked to particular relevant CQAs according to a clear rationale. Process characterisation is described for which a risk assessment was conducted to identify, prioritize and mitigate risks associated with process parameters to be characterised. Each of the manufacturing stages were characterised either by off line studies or from historical manufacturing data. Adequate details of the studies and their results have been provided. The process development supports the proposed manufacturing process description and its controls. For the PFS/AI product formats the methodology and approach in evaluating criticality for manufacturing process parameters is similar to that already seen for the active substance.

It can be concluded that the pharmaceutical development is described in sufficient detail and is generally acceptable.

Manufacture of the product and process controls

The manufacturing process in each case is a non-standard aseptic process normally associated with biological product manufacture. Manufacture includes formulation and fill finish activities, and an adequate control strategy is defined. The material is sterile filtered, filled and sealed. For the PFS/AI the PFS is assembled with the safety device or the pen administration device. The manufacturing process has been validated by manufacture of an appropriate number of full scale commercial batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate. Data from shipping validation studies has been provided.

Product specification

The specifications for Hulio 40 mg vials, PFS and AI for commercial batch release and throughout the specified shelf-life include identity, purity, potency and other general tests.

Control of the finished product has been established similarly as for the active substance.

Analytical methods

The validation data for analytical methods is acceptable. Appropriate validation of device specific functionality testing has been provided.

Batch analysis

Batch analysis data of an appropriate number of lots of the finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Please refer to the active substance section. The same reference standards are used for control of the active substance and finished product.

Stability of the product

Based on available stability data, the proposed shelf-life of 24 months for all product presentations when packaged in the proposed container closure system, protected from light, and stored at 5 ± 3°C as stated in the SmPC is acceptable.

For the vial, finished product real time/real condition stability data and data for product stored under accelerated conditions were provided on a suitable number of lots. In addition, data from batches exposed to stress conditions, including photostability studies and forced degradation studies as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, were provided. The batches of the vial finished product used for the stability studies are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

For the syringe presentations (PFS and AI) real time/real condition stability data, and accelerated condition data on an appropriate number of lots were provided. In addition, accelerated and stress condition data, including photostability and forced degradation studies as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, were provided. The batches of the PFS finished product used for the stability studies are representative of those proposed for marketing as both container closure systems have the same primary packaging and the same stability profile.

From the data available, the finished product appears stable at long-term storage conditions and does not show any signs of degradation or loss of potency.

The results from the photostability study indicate that the product is sensitive to light and consequently the SmPC states that the product should be kept in its outer carton in order to protect from light.

The pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. This is supported by the accelerated stability data provided.

The Applicant commits to continue the ongoing long-term stability studies. In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Biosimilarity

The general approach for evaluating biosimilarity is acceptable and in line with the current guidelines on biosimilarity. This includes justification of the number, age and disposition of batches used, the kind of tests performed, and justification of the use of active substance versus finished product of Hulio in the comparative analysis.

The evaluation of similarity required a bridging study between EU approved Humira (Humira (EU) and US licenced Humira (Humira (US)) to demonstrate that Humira (US) is representative of the reference product (Humira (EU)). Humira (US) was used as comparator throughout the Phase III clinical development program.

An overview of the tests included in the comparability studies and the key findings is provided in **Table 1**.

Multiple batches of FKB327, Humira (EU) and Humira (US) were tested where the parameters were expected to show variability between the products. A subset of the reference product lots were tested for the measurement of visible and sub-visible particles, conducted in accordance with the compendial test methods. Limited number of lots each of FKB327, Humira (EU) and Humira (US) were tested for primary

structure and higher order structure which are expected to have little variability. The choice of number of lots for each test was adequately justified.

The regulatory assessment of comparability was made primarily on the basis that measured quality attribute ranges of Hulio should reside within the range of variability observed for the reference medicinal product batches.

For the biosimilarity analysis, the company performed three exercises: i) Hulio versus Humira (EU), ii) Hulio versus Humira (US), and iii) Humira (EU) versus Humira (US). In addition, Hulio active substance was compared to Hulio finished product.

The three exercises performed revealed that most of the quality attributes are similar between Hulio and Humira (EU). However, differences at the level of the glycosylation profile, charge variants (basic and acidic peaks), size heterogeneity (HMWS, MMWS, LMWS), and hydrophobic heterogeneity have been identified between Hulio and Humira. The Applicant claimed that these differences are minor and do not impact the biological functionality based on the comparability data from the *in vitro* assays: binding to soluble TNF-α (ELISA and SPR), binding to transmembrane TNF-α, cytotoxicity neutralising and apoptosis assays, ADCC, CDC, binding to C1q complement. This conclusion was initially not endorsed and evidence of the sensitivity of these assays to detect meaningful differences in biological activity was requested as a major objection. Moreover, additional *in vitro* testing/data was also requested as part of the major objection in order to further substantiate the claim of biosimilarity between Hulio and Humira, i.e. to address residual concerns associated with the non-comparability of the analytical data for certain quality attributes.

In response to the major objections, the Applicant provided a comprehensive review of literature data justifying the difference in glycosylation between Hulio and Humira (EU). In line with this review, the differences were confirmed to have no impact on the primary biological activities through the functional characterization. This was supported by further evidence that the sensitivity of the biological assays is sufficient to detect any meaningful differences in the function of Hulio as compared to Humira (i.e. qualification/validation results of the biological assay methods indicated that all assay methods have high precision, accuracy, linearity and specificity) and by additional *in vitro* bioassay testing through the mixed lymphocyte reaction (MLR). This additional assay evaluates the anti-proliferative effect of adalimumab on T-cells (via the induction of regulatory macrophages; a potential mechanism of action of adalimumab in inflammatory bowel disease (IBD) patients) as well as the Fab and Fc function. The Applicant showed that Hulio, Humira (EU) and Humira (US) inhibited cell proliferation in a concentration-dependent manner and that the level of the inhibitory effect on T-cells was similar for Hulio, Humira (EU) and Humira (US) at three different concentrations. These results further support the similarity of Hulio to its reference product.

Hence, it is acknowledged that Hulio is highly similar to Humira (EU) in physicochemical and biological properties. No clinically meaningful differences are expected between Hulio and the reference product, as further supported by the results of the functional characterization and the clinical studies. In addition, the Applicant has successfully demonstrated that Humira (US) is representative of the EU reference product, justifying its use as comparator throughout the Phase III clinical development program.

Table 1 Biosimilarity assessment used to characterize and compare Hulio and Humira

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Physicochemical methods			
Primary structure	Amino acid sequence	N-terminal amino acid sequencing	Consistent with Humira
		Peptide mapping (LC/MS)	Consistent with Humira
		C-terminal amino acid	Consistent with Humira
	Disulfide bond	Reduced/Non-reduced peptide mapping (LC/MS)	Consistent with Humira
	N-glycosylation site	N-glycosydase F-digested/Non-digested peptide mapping	Consistent with Humira
	Molecular weight	Intact MS	Consistent with Humira
	pI	IEF	Consistent with Humira
	Extinction coefficient	AAA and UV spectroscopy	Consistent with Humira
High order structure	Secondary structure	Far-UV CD	Visually identical to Humira
		FT-IR	Visually identical to Humira
	Tertiary structure	Near-UV CD	Visually identical to Humira
		IF	Similar maximum wavelength.
		DSC	Similar profile, with a minor difference in T_m due to the formulation buffers. Difference not clinically meaningful.
Glycosylation	Mannosylation (M5), Galactosylation, Fucosylation and Sialylation	N-linked glycan profiling	Minor quantitative differences in non-fucosylated variants and sialic acid. Differences not clinically meaningful.
	Galactose, Fucose, Mannose, GlcNAc and Sialic acid contents	Monosaccharide analysis	Minor quantitative differences in galactose and sialic acid. Differences not clinically meaningful.
	Glycosylation site occupancy	CE-SDS (R)	Comparable amounts of glycosylation site occupancy
	Non-consensus glycosylation content	CE-SDS (R)	Comparable amounts of non-consensus glycosylation content
Size heterogeneity	HMWS (aggregates), Main species (HC+LC or monomer), MMWS and LMWS (fragments)	CE-SDS (R), CE-SDS (NR)	Minor quantitative differences in MMWS and LMWS. Differences not clinically meaningful.
	HMWS (aggregates), Monomer, LMWS (fragments)	SE-HPLC	Levels of HMWS are quantitatively comparable. Minor difference in profile is not clinically meaningful.

Molecular parameter	Attribute	Methods for control and characterization	Key findings
	HMWS (aggregates), Monomer, LMWS (fragments)	FFF	Levels of HMWS are quantitatively comparable. Minor difference in prolife is not clinically meaningful.
Charge heterogeneity	Acidic variants, main species, basic variants	CEX-HPLC	Quantitative differences in acidic and basic peaks. Differences not clinically meaningful
Hydrophobic heterogeneity	Hydrophilic variant of Fc	HI-HPLC	Quantitative differences in the hydrophobic heterogeneity of the Fc fragment. Difference not clinically meaningful
Amino acid modifications	C-terminal variants (Lys variants, amidated proline)	Reduced Peptide mapping (LC/MS)	Quantitative differences in C-terminal variants. Difference not clinically meaningful
	N-terminal variants	Reduced Peptide mapping (LC/MS)	Comparable amounts of N-terminal variants
	Deamidation/Isomerization	Reduced Peptide mapping (LC/MS)	Comparable amounts of deamidated/isomerized variants
	Glycation	BAC	Comparable amounts of glycated variants
	Oxidation	Reduced Peptide mapping (LC/MS)	Comparable amounts of oxidized variants
	Sulfhydryl content	Ellman's assay	Comparable amounts of sulfhydryl content
	Trisulfide	Non-reduced Peptide mapping (LC/MS)	Quantitative differences in the trisulfide variants. Difference not clinically meaningful
	Thioether	CE-SDS (R)	Comparable amounts of thioether
	Cysteinylation	CE-SDS (NR)	Comparable amounts of cysteinylated variants
Process related impurities	Residual DNA	Threshold assay	Comparable amounts of residual DNA
	HCP	ELISA	Lower HCP content in Hulio
Visible and sub-visible particles	Visible particles	Visual inspection	Practically free from particles
	Sub-visible particles	Light obscuration	Lower amounts of sub-visible particles in Hulio
		MFI	Common features to Humira
Strength	Protein concentration	UV absorbance at 280 nm	Comparable concentration
Binding assays and *in-vitro* bioassays			
Binding assays	Soluble rhTNF-α binding	ELISA assay	Comparable binding
	Soluble rhTNF-α binding	Surface plasmon resonance (SPR) assay	Comparable K_D
	tmTNF-α binding	Flow cytometry assay	Comparable binding

Molecular parameter	Attribute	Methods for control and characterization	Key findings
	FcγRI binding	SPR assay	Comparable K_D
	FcγRIIa binding	SPR assay	Comparable K_D
	FcγRIIb binding	SPR assay	Comparable K_D
	FcγRIIIa(V) binding	SPR assay	Comparable K_D
	FcγRIIIa(F) binding	SPR assay	Comparable K_D
	FcγRIIIbNA1 binding	SPR assay	Comparable K_D
	FcγRIIIbNA2 binding	SPR assay	Comparable K_D
	FcRn binding	SPR assay	Comparable K_D
	C1q binding	ELISA assay	Comparable binding
In-vitro bioassays	Cytotoxicity neutralization	Cell-based assay	Comparable activity
	Apoptosis inhibition	Cell-based assay	Comparable activity
	ADCC	Cell-based assay	Comparable activity
	CDC	Cell-based assay	Comparable activity
	Regulatory macrophage induction in MLR assay	Cell-based assay	Comparable activity

Adventitious agents

Raw materials are sufficiently controlled for possible contaminating viruses. In-process testing is performed on the active substance harvest to screen for possible virus, mycoplasma or microbial contamination. The MCB and WCB were adequately qualified and tested for possible viral contamination. The active substance manufacturing process contains various steps that were shown to contribute to virus removal/inactivation. Virus removal/inactivation was properly validated

The information provided regarding transmissible spongiform encephalopathies (TSE) risk and materials of animal or human origin is sufficient and in line with relevant guidelines.

In conclusion, viral safety and safety concerning other adventitious agents including TSE has been sufficiently assured.

2.2.4. Discussion and conclusions 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 satisfactory 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 the clinic.

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.

A number of incidences of non-comparability versus Humira (EU) were identified in the physico-chemical quality data. In addition a lack of data demonstrating sensitivity of the biological assays was identified. These issues gave rise to a major objection. In response, the Applicant provided further data and justifications to show that the minor differences observed do not impact the biological functionality based on the comparability data from the *in vitro* assays: binding to soluble TNF-α (ELISA and SPR), binding to transmembrane TNF-α, cytotoxicity neutralising and apoptosis assays, ADCC, CDC, binding to C1q complement, and the additional *in vitro* bioassay testing through the mixed lymphocyte reaction (MLR). Further evidence that the sensitivity of the biological assays is sufficient to detect any meaningful differences was also provided. Hence, it was acknowledged that Hulio is highly similar to the reference medicinal product in physicochemical and biological properties and the major objection was considered satisfactorily resolved.

In addition, a major objection was raised during the procedure relating to EU GMP compliance of the active substance and finished product manufacturing sites. This major objection was also satisfactorily resolved as the Applicant provided the requested documentation.

2.2.5. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends a point for investigation: consideration of specified characterisation tests in addition to routine release testing, in case of relevant changes of the active substance manufacturing process.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical development of FKB327 (Hulio) was performed in accordance with the “Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues” (EMEA/CHMP/BMWP/403543/2010); with 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) and with ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998).

2.3.2. Pharmacology

Primary pharmacodynamic studies

A series of side-by-side studies related to the modes of action of adalimumab were conducted to demonstrate the similarity between FKB327 and the reference medicinal product Humira. The studies included in vitro evaluation of the Fab- and Fc-related biological activities and additional biological properties and in vivo efficacy evaluation in TNF-α Transgenic Mouse Polyarthritis Model to demonstrate similarity of FKB327 and US Humira in improving the symptoms of TNF-α mediated pathology.

The similarity of FKB327 to reference product Humira was initially assessed by in vitro Fab-related mode of action characterisation studies (neutralization of soluble TNF-α induced cytotoxicity in L929 cells and induction of apoptosis in mTNF-α expressing cells), and in Fc-related functions (binding to Fcγ receptor I, IIa , IIb, IIIa(F-158 isoform), IIIa(V-158 isoform), IIIbNA1 and IIIbNA2 isoforms and FcRn; binding to C1q; ADCC activity and CDC activity in mTNF-α expressing cells). For receptor FcγRIIa, two isoforms (131H and H131R) are described depending on histidine or arginine at position 131 of FcγRIIa. The amino acid substitution arginine to histidine at position 131 is influencing the IgG1 affinity. The applicant clarified that the isoform of FcγRIIa used in the similarity assessment and presented in the initial application was the Arginine isoform (R 131) only. Considering that both the H or R variants are associated with an important role in IBD and in RA, the applicant was requested to provide comparative binding of the biosimilar vs reference to H131 as well. Those additional results performed with a qualified assay showed that the KD values were comparable, providing an additional confirmation that biosimilarity applies for polymorphic forms of FcγRIIa receptors as well.

The scope of testing is judged sufficient to compare Hulio and Humira. Testing needs to compare binding and functional consequences for each of the Fab and Fc regions and has been done.

In terms of experimental design, in general, the Applicant adopted an approach of nominating a reference batch of Hulio and comparing results with further batches of Hulio and results with Humira EU to results with this reference batch. This reduces the effect of inter-day assay variability or drift, and is supported. Testing included comparisons with Humira from US and Japanese markets.

The in vitro assays were completed by an in vivo efficacy study in TNF-α Transgenic Mouse Polyarthritis Model. No significant differences were seen in arthritic and histopathological scores between FKB327 and US Humira at dose levels of 1 and 10 mg/kg at the study termination.

A post hoc statistical analysis of the arthritis clinical scores at the end of the evaluation (Week 12; 1 week after the 5th dose) was conducted by the applicant for both dose levels and showed no statistical significance between FKB327 and EU-Humira at either the 1 mg/kg dose (p=0.55) or the 10 mg/kg dose (p=0.29). No further discussion was considered necessary by the CHMP.

Secondary pharmacodynamic studies

The studies on secondary pharmacodynamic were not conducted and are not deemed necessary by the CHMP.

Safety pharmacology programme

The studies on safety pharmacology were not conducted and are not deemed necessary by the CHMP.

Pharmacodynamic drug interactions

The studies on pharmacodynamic drug interactions were not conducted and are not deemed necessary by the CHMP.

2.3.3. Pharmacokinetics

The pharmacokinetic (PK) and toxicokinetic (TK) data for FKB327 were generated as part of a human TNF-α transgenic mouse (TTg mouse) arthritis study, a single dose PK preliminary study in cynomolgus

monkeys and a toxicokinetic profile comparison of FKB327 and US Humira in cynomolgus monkeys included as part of the 4-week repeat dose toxicity study. Although pharmacokinetics studies are not a formal request for a biosimilar, the toxicokinetic analysis was included for development of FKB327 for global registration purposes.

The studies were supported by validated electrochemiluminescence (ECL) methods to detect FKB327 and US Humira in mouse and non-human primate sera as well as antibodies to these products. Validation studies were also presented to support use of those assays to quantify adalimumab and antibodies to adalimumab.

The pharmacokinetic/toxicokinetic comparisons did not highlight any marked difference in the parameters between FKB327 and Humira. The in vivo pharmacokinetic/toxicokinetic studies were however performed on a limited number of animals therefore the applicant cannot claim 'bioequivalence' between FKB327 and Humira and reference is made to bioequivalence studies conducted in human (healthy volunteers and patients).

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).

2.3.4. Toxicology

Single dose toxicity

Full toxicity studies were not considered necessary as FKB327 is a proposed biosimilar to Humira in agreement with the CHMP guidelines on similar biological medicinal products, and studies on single-dose toxicity were not conducted.

Repeat dose toxicity

A 4-week comparative repeat-dose toxicity study in cynomolgus monkeys was conducted to support the similarity of FKB327 and originator Humira in a reduced toxicology study package for a biosimilar application. The comparison of toxicokinetics, local tolerance and potential immunotoxic profiles were included to the study. Cynomolgus monkey was selected as a relevant species and were also used in the originator studies to investigate the potential toxicities of adalimumab.

The administered dose was 30 mg/kg. This dose represents a 12-fold safety margin, based on the conversion of the dose in monkeys into human equivalent dose corresponding to a 40 mg dose. For doses of 80 and 160 mg, the safety margins are 6 and 3; respectively. In terms of exposures, the safety margin is approximately 17-18 comparing single doses (compared to a SD of 40 mg in human).

The weekly administration is twice as frequent as in patients. The selected s.c. route of administration is the intended route in humans for administration of FKB327.

FKB327 and US Humira were well tolerated at a dose level of 30 mg/kg (s.c., once weekly for 4 weeks), consistent with the results of originator adalimumab studies in cynomolgus monkeys and without unexpected findings. The toxicological assessment revealed no significant or biologically meaningful treatment -related effects or treatment-related differences between FKB327 and Humira in clinical observations, body weights, food consumption, ophthalmoscopy examinations, electrocardiographs, haematology, coagulation, clinical chemistry or urinalysis endpoints, or peripheral blood leukocyte

analysis, or macro/microscopic evaluations. There were no safety signals in either drug treatment group. Histopathological changes consisting of decreases in positive CD21 immunoreaction in the follicle of the spleen and mesenteric and submandibular lymph nodes were noted and were attributed to an exaggerated pharmacological effect rather than toxicity. Those changes were comparable among groups.

Anti-drug antibodies (ADA) were evaluated in the TTg mouse arthritis study and the GLP-repeat dose toxicity/TK study. In the TTg mouse arthritis study, most treated animals produced ADA which was expected due to administration of a heterologous therapeutic protein. In the monkey, the results showed that 1 monkey was positive for ADA at Day 56 in a recovery phase in FKB327 group. The immunogenicity seen in animals is however not considered relevant for humans.

Genotoxicity

Full toxicity studies were not considered necessary as FKB327 is a proposed biosimilar to Humira in agreement with the CHMP guidelines on similar biological medicinal products, and studies on genotoxicity were not conducted.

Carcinogenicity

Full toxicity studies were not considered necessary as FKB327 is a proposed biosimilar to Humira in agreement with the CHMP guidelines on similar biological medicinal products, and studies on carcinogenicity were not conducted.

Reproduction Toxicity

Full toxicity studies were not considered necessary as FKB327 is a proposed biosimilar to Humira in agreement with the CHMP guidelines on similar biological medicinal products, and studies on reproductive and developmental toxicity were not conducted.

2.3.5. Ecotoxicity / environmental risk assessment

The Applicant provided a justification for not submitting environmental risk assessment studies. FKB327 is a protein and therefore unlikely to pose a significant risk to the environment. This is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2). This justification was found acceptable by the CHMP.

2.3.6. Discussion on non-clinical aspects

The nonclinical programme of FKB327 included a series of head-to-head in vitro comparative studies including binding studies and cell based assays for characterisation of Fab and Fc-related effects. An in vivo PD (efficacy) study in human TNF-α transgenic (TTg) mouse model of polyarthritis and a repeated dose toxicity study including toxicokinetic assessment and the determination of the anti-drug antibody (ADA) development in cynomolgus monkeys were conducted to support the similarity demonstration between FKB327 (Hulio) and US Humira. The nonclinical in vivo testing strategy was designed to meet the requirements for a global development strategy.

Scientific advice was sought from EMA (initial advice EMA/CHMP/SAWP/549582/2013, 19 September 2013). The scientific advice concerning nonclinical development was not fully followed. The scientific

advice indeed recommended using representative drug product batches of FKB327 for the biosimilarity exercise. For some assays (TNFα binding assays), drug substance batches only were used. The applicant justified that since only an additional amount of methionine is added to the DP during the formulation process, performing biosimilarity exercise using drug substance batches is considered acceptable. In addition, the Applicant was suggested during the SA procedure to consider testing with NK cells, in addition to testing with PBMCs as these cells express CD16 and are key for ADCC. In the marketing authorisation application dossier, the Applicant presented studies with NK cells and with Hulio drug product.

Safety pharmacology, genotoxicity, carcinogenicity, reproductive and developmental toxicity studies were not submitted and are not required.

The similarity of FKB327 to reference product Humira was assessed by the in vitro Fab-related mode of action characterisation studies (neutralization of soluble TNF-α induced cytotoxicity in L929 cells and induction of apoptosis in mTNF-α expressing cells), and in Fc-related functions [binding to Fcγ receptor I, IIa(H), IIa (R), IIb, IIIa(F), IIIa(V), IIIbNA1 and IIIbNA2 and FcRn; binding to C1q; ADCC activity and CDC activity in mTNF-α expressing cells]. From a non-clinical point of view, the above biological function parameters were found to be similar between FKB327 and the reference product Humira.

Slight differences were noted in glycosylation profiles between Hulio and the reference product. The Applicant provided a review of literature data showing that the relative difference in glycosylation content between antibodies investigated is significantly larger than the one observed between FKB327 and EU-Humira and these minor differences were confirmed to have no impact on the primary biological activities. This was further supported by the evidence that the sensitivity of the biological assays is sufficient to detect any meaningful differences in the function of FKB327 as compared to Humira.

The pharmacokinetic (PK) and toxicokinetic (TK) data for FKB327 were generated as part of a human TNF-α transgenic mouse (TTg mouse) arthritis study, a single dose PK preliminary study in cynomolgus monkeys and a toxicokinetic profile comparison of FKB327 and US Humira in cynomolgus monkeys included as part of the 4-week repeat dose toxicity study. Although animal studies are not a formal request for a biosimilars, those studies have been included for global registration purposes. The results of those animal studies were found comparable between Hulio and the reference Humira and were provided as supportive information only.

The Applicant did not submit ERA studies but provided an adequate justification which is in line with EMA Guideline on the Environmental Risk assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr. 2).

2.3.7. Conclusion on the non-clinical aspects

Overall, the nonclinical biosimilarity and safety data demonstrate that FKB327 has a similar activity to the reference product Humira.

2.4. Clinical aspects

2.4.1. Introduction

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.

- Tabular overview of clinical studies

Table 2 Tabular listing of all clinical studies

Type of Study Study Centers	Study Identifier (Study / Report Number)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects entered/ completed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 1	FKB327-005	Healthy subjects: To assess relative bioavailability of FKB327 after a single SC dose delivered by vial/syringe (vial), PFS and AI. To compare the safety of FKB327 after a single SC dose delivered by vial, PFS and AI. To describe the effect of body weight on the single SC dose PK of FKB327. To describe the effect of injection site on the single SC dose PK of FKB327.	Phase 1, randomized, open-label, parallel group, single SC dose study in healthy male and female subjects.	FKB327: single 40 mg SC injection via vial/syringe, PFS or AI.	FKB327 vial/syringe: 66/65 FKB327 PFS: 63/63 FKB327 AI: 66/66	Healthy volunteers	Screening visit, single SC dose on Day 1 and Final Visit on Day 65	Complete; Final CSR
Phase 1 1	FKB327-001	Healthy volunteers: To compare the safety and PK of FKB327 and EU-approved and US-licensed Humira® after single SC injection. To assess immunogenicity and tolerability after single doses of FKB327 and EU-approved and US-licensed Humira, by SC injection.	Phase 1, randomized, double-blind, parallel group study in healthy male volunteers and healthy female volunteers of non-childbearing potential.	FKB327, EU-approved Humira or US-licensed Humira: single 40 mg SC injection.	FKB327: 60/59 EU-approved Humira: 60/60 US-licensed Humira: 60/60	Healthy volunteers	Screening visit, single SC dose on Day 1, followed by 10-day clinic stay and a Final Visit on Day 65.	Complete; Final CSR
Phase 3 109	FKB327-002	To assess the efficacy of FKB327 compared with Humira when in combination with MTX. To compare the safety profiles of FKB327 and Humira when in combination with MTX. To assess the efficacy profiles of FKB327 and Humira over time. To compare the proportions of patients on each treatment, who developed ADAs and to summarize the distribution of the level of ADA activity between patients on each treatment. To compare the steady state PK of FKB327 and Humira administered by multiple dosing.	Phase 3, multi-center, randomized, double-blind, parallel arm, active-comparator, equivalence study in patients with active RA taking concomitant MTX. To be randomized in a 1:1 ratio to receive either FKB327 or Humira.	FKB327: 40 mg e.o.w. by SC injection. US-licensed Humira 40 mg e.o.w. by SC injection.	FKB327: 367/333 Humira: 363/328	Patients with moderate to severe, active RA	Screening visit, followed by a Baseline visit where patients received their first study treatment. Treatment (eow) continued to Week 22. At Week 24, eligible patients entered the OLE study (FKB327-003). Patients not entering the OLE study returned for a safety follow-up visit at Week 26.	Complete; Final CSR

Phase 3 92	FKB327-003	Patients with RA: To compare the safety of long-term treatment with FKB327 and Humira. To compare the efficacy of long-term treatment with FKB327 and Humira. To compare the proportions of patients developing ADAs on long-term treatment with FKB327 and Humira. To compare the PK of long-term treatment with FKB327 and Humira. To evaluate safety, changes in efficacy, and changes in PK and immunogenicity in patients who were switched from Humira in the preceding FKB327-002 double-blind study to FKB327 in the FKB327-003 OLE study, and of patients who were switched from FKB327 to Humira, respectively. To evaluate safety, changes in efficacy, and changes in PK and immunogenicity in patients who were switched from FKB327 in the preceding FKB327-002 double-blind study to Humira in the FKB327-003 OLE study, and then switched back to FKB327 in the second part of the FKB327-003 OLE study (from Week 30; double switch).	Phase 3, Period 1: open-label, randomized, comparative, multi-center, 2-arm extension in patients with RA taking concomitant MTX who continued from the preceding Study FKB327-002. To be randomized in a 2:1 ratio either to continue the same treatment, or to switch to the alternative treatment. Period 2: open-label, multi-center, single arm extension in which all patients received prolonged FKB327 treatment.	Period 1: FKB327: 40 mg e.o.w. by SC injection using PFS. US-licensed Humira 40 mg e.o.w. by SC injection using PFS. Period 2: FKB327 40 mg e.o.w by SC injection using AI or PFS.	*Interim (Period I)* : FKB327: 324/149 Humira: 321/155	Patients with moderate to severe, active RA who had successfully completed Study FKB 327-002	Period 1: To be treated with FKB327 or Humira (e.o.w) from Week 0 to Week 28. Period 2: To be treated with FKB327 from Week 30 to Week 76. Follow-up visit at Week 80.	Ongoing; Interim CSR

Phase 1 1	FKB327-004	To compare the PK and safety of FKB327 and Humira after single dose SC injection in Japanese healthy male subjects. To assess immunogenicity and local tolerability of FKB327.	Phase 1, randomized, active-controlled, single-blind, parallel-group, clinical pharmacology study in Japanese healthy male subjects.	FKB327 or Humira: single 40 mg SC injection.	FKB327: 66/65 Humira: 65/65	Japanese healthy male volunteers	Screening visit, followed by 10-day clinic stay and a Final Visit on Day 65.	Complete; Final CSR (Supportive Study)

2.4.2. Pharmacokinetics

The pivotal clinical study program for this MAA includes two single-dose clinical pharmacology studies that have been completed in healthy subjects:

- Study FKB327-001: A randomized, double-blind, parallel-group single-dose study in healthy male and female subjects to compare the safety and PK of FKB327 and EU-approved and US-licensed Humira (40 mg by sc injection)
- Study FKB327-005: A randomized, open-label, parallel-group, single-dose study in healthy male and female subjects to compare the relative bioavailability of FKB327 (40 mg by sc injection) delivered via vial, PFS and AI presentations.

In addition, the sponsor conducted a Phase 1, healthy subject study in Japan comparing the PK of FKB327 and US-licensed Humira to enable a local product licence application (Study FKB327-004). A synopsis for this study was included in the dossier as it was considered a supportive rather than a pivotal study..

Bioanalytical methods

Adalimumab serum concentration measurements

Adalimumab drug concentration was measured by a sandwich electro-chemiluminescence (ECL) assay. The method detected equivalently FKB327 and reference products, EU-approved Humira and US-licensed Humira, using a single set of calibrators and quality controls made from FKB327. The lower limit of reliable

quantification was 100 ng/mL, which is sufficient to detect serum drug concentrations through to the terminal phase.

Evidence of audits of the laboratory where all the bioanalytical assays were performed is provided. For Study FKB327-001, results obtained for all parameters evaluated during the pre-study validation confirmed that the performance of the assay was acceptable for the intended purpose of concentration analysis of all analytes (FKB327, EU-approved Humira, and US-licensed Humira). No reanalysis of study samples has been made for a pharmacokinetic reason.

A validated immunoassay method was used for quantification of adalimumab in human serum from studies FKB327-002 to FKB327-005.Determination of anti-drug antibodies

The Applicant has used several bioanalytical methods for the determination of anti-drug antibodies (ADAs) and of neutralizing antibodies (NAbs) from the serum samples from healthy volunteers (studies FKB327-001, -004 and -005) and from patients with rheumatoid arthritis (RA, studies FKB327-002 and -003). In all of the clinical studies, when ADA screen results are negative, confirmatory assays do not need to be performed. As a result the ADA titer and the results of the neutralizing assay are not available for the samples found negative in the first screening. For the sake of analysis these samples are nevertheless stated as having a negative confirmatory ADA test.

An ADA screening test was initially developed and used for the analysis of the clinical samples from study FKB327-001. However, an insufficient drug tolerance limits the meaning of the results. The high proportions of inconclusive samples drive an uncertainty on the actual proportions of the positive samples. As a result, no sound conclusion can be drawn on the relative immunogenicity of FKB327 versus Humira for the study FKB327-001. Because these ADA and NAb assays were only used in the study FKB327-001 and because ADA or NAb were not included as a covariate of the ANCOVA model used to conclude the bioequivalence between all 3 treatments in the study FKB327-001, this issue was not pursued by the CHMP.

Before initiation of the Phase 3 program, the design/operating conditions of both the ADA and the nAb assays were modified to improve detection sensitivity/drug tolerance. These methods were used for detection of ADA/Nab for the studies FKB327-002, -003, -004 and -005 and were considered adequate by the CHMP. For the clinical study FKB327-002 and -003 with RA patients, due to the presence of rheumatoid factors (RF) in the RA study patients in pre-dose samples, the Applicant has re-determined a new screening for the ADA assay format. It is 20 fold higher than the anticipated pre-study validation cut point factor for RA patients. A further assay that allowed to recover part of the sensitivity was designed and a number of samples were tested.

The CHMP concluded that the use of this more sensitive method for the analysis of the samples would not significantly impact the overall comparability exercise between FKB327 and Humira.

Pivotal phase I PK study FKB327-001

The primary objective of this study was to compare the safety and PK of FKB327 and EU-approved and US-licensed Humira after single doses, by sc injection in healthy subjects. The secondary objective was to assess immunogenicity and tolerability after single doses of FKB327 and EU-approved and US-licensed Humira, by sc injection.

The study was performed at one centre in UK which has been subject to GCP inspections carried out by European and US competent authorities and no critical or major finding has been found. The FKB327-001 study itself has been audited by an ICH GCP audit.

The study FKB327-001 was a randomized, double-blind, parallel-group study performed in healthy male subjects and healthy female subjects of non-childbearing potential.

Test and reference products

- Reference product 1: EU-approved Humira (adalimumab) 40 mg/0.8 mL as a single subcutaneous injection,
- Reference product 2: US-approved Humira (adalimumab) 40 mg/0.8 mL as a single subcutaneous injection.
- Test product: Adalimumab 40 mg as a subcutaneous injection.

In total, 180 subjects were enrolled in the study across 3 treatment groups: 60 subjects in each of the FKB327, EU-Humira and US-Humira treatment groups, respectively. Consenting male and female healthy volunteers aged 18 to 65 years with a weight 60 to 90 kg and body mass index 18 to 30 kg/m^2 were enrolled.

Blood samples for serum drug concentration measurements and ADA titre were collected until 1536 hours (64 days) after dosing (0, 4, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 360, 528, 696, 864, 1032, 1200 and 1536h).

Considering the long half-life of approximately 14 days, the duration of 64 days is judged appropriate to evaluate the elimination phase of adalimumab and the anti-drug antibodies. PK sampling time points are considered appropriate for comparison of absorption and elimination period. The last sampling time is at 1536 hours post-dose which corresponds to 4.57 half-lives. The sampling schedule covers the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved as AUC(0-t) covers at least 80% of $AUC_{(0-\infty)}$.

Maximum concentrations of adalimumab were attained (tmax) at approximately 144 hours post-dose (median estimates) following single SC administration of FKB327 and US-licensed Humira, with tmax attained slightly later for EU-approved Humira at 192 hours post dose. Thereafter, serum concentrations declined with geometric mean elimination half-life (t1/2) of 324, 345 and 366 hours for FKB327, EU-approved and US-licensed Humira, respectively.

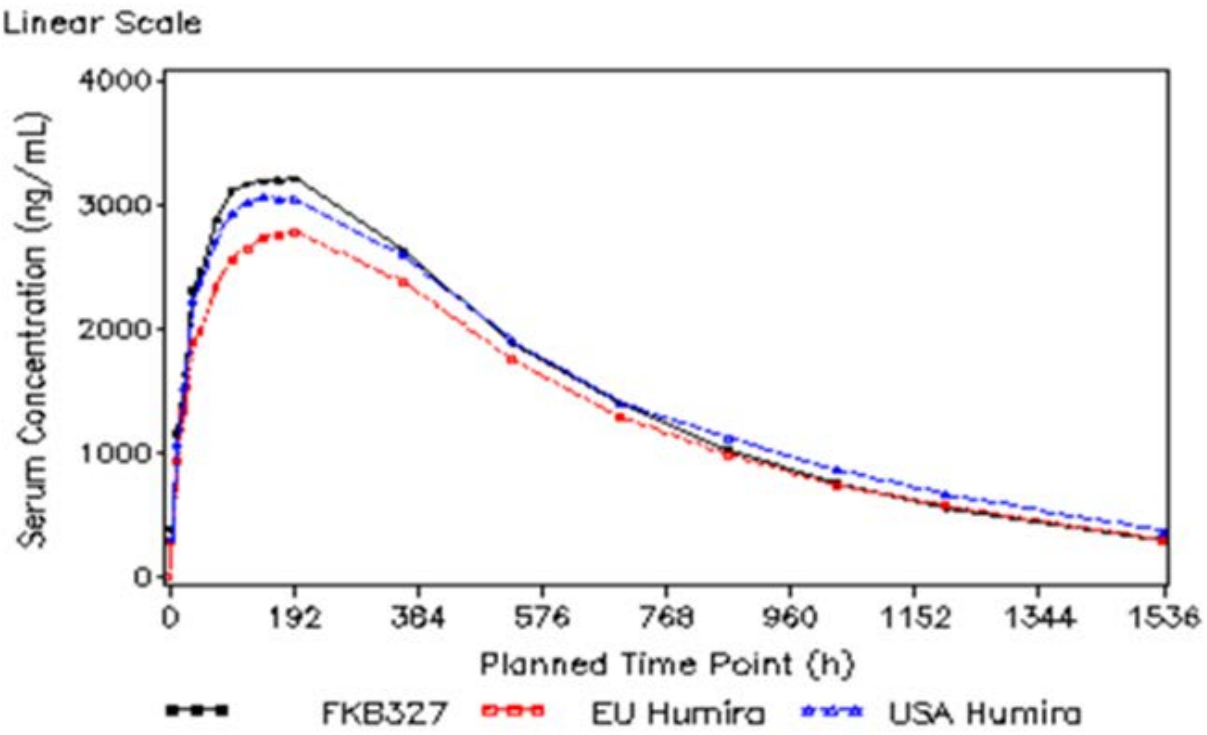


Figure 1 Study FKB327-001: Mean Serum Concentration Time Profiles of Adalimumab by Treatment: PK Analysis Set

Table 3 Study FKB327-001: Summary of Equivalence Analysis (ANCOVA) (PK Analysis Set)

Hypothesis	PK Parameter	FKB327/EU-Humira	FKB327/US-Humira	EU-Humira/US-Humira
Primary	$AUC_{0-\infty}$ (h*ng/mL)	1.06 (0.94, 1.18)[a]	0.98 (0.88, 1.10)[a]	0.93 (0.83, 1.04)[a]
	AUC_{0-t} (h*ng/mL)	1.08 (0.97, 1.20)[a]	1.01 (0.91, 1.12)[a]	0.93 (0.84, 1.03)[a]
	C_{max} (ng/mL)	1.13 (1.03, 1.23)[a]	1.07 (0.98, 1.17)[a]	0.95 (0.87, 1.04)[a]
Secondary	AUC_{0-360h} (h*ng/mL)	1.12 (1.02, 1.23)[a]	1.04 (0.95, 1.14)[a]	0.93 (0.85, 1.02)[a]
	$t_{1/2}$ (h)	0.95 (0.83, 1.10)[a]	0.90 (0.78, 1.03)	0.94 (0.82, 1.08)[a]

AUC_{0-360h}=area under concentration time curve up to 360 hours; AUC_{0-t}=area under concentration time curve up to last non zero value; $AUC_{0-\infty}$=area under concentration time curve extrapolated to infinity; C_{max}=peak serum concentration; EU=European Union; PK=pharmacokinetic; $t_{1/2}$=elimination half-life; US=United States.

Note: For C_{max}, age, weight and gender were included in the model; for both $AUC_{0-\infty}$ and AUC_{0-t}, age and weight were included in the model.

For the secondary parameters, the covariates were forced to be age and weight as per the primary AUC parameters.

[a] 90% CI within predefined limits (0.80, 1.25) concluding bioequivalence.

Based on the original ANCOVA analysis, bioequivalence between Hulio and Humira was demonstrated since the ratios (90% CI) of geometric means for both primary PK endpoints AUC0-last and Cmax was within the acceptability range of 80-125% in the study. However, some limitations were identified with this ANCOVA approach namely that the choice of covariates to include in the ANCOVA model was data driven.

As expected, the 90% CIs produced by the ANOVAs were wider than those produced by the ANCOVA and as a result for the FKB327/EU-approved Humira comparison, the primary endpoint Cmax and the secondary endpoint AUC0-360h had upper 90% CIs (1.29 for both) outside the bioequivalence criteria of

0.80 to 1.25. In this ANOVA analysis of FKB327-001, serum drug concentration was not adjusted for the protein content in each study drug. No such adjustments were pre-planned in the protocol and SAP.

Table 4 Summary of Equivalence Analysis (ANOVA Assuming Equal Variance) (PK Analysis Set)

		Ratio of Geometric Least Squares Means (90% Confidence Interval)		
Hypothesis	**PK Parameter**	**FKB327/US-Humira**	**FKB327/EU-Humira**	**EU-Humira/US-Humira**
Primary	$AUC_{0-\infty}$ (h*ng/mL)	0.98 (0.87, 1.10)[a]	1.08 (0.96, 1.22)[a]	0.90 (0.80, 1.01)[a]
	AUC_{0-t} (h*ng/mL)	1.00 (0.90, 1.11)[a]	1.10 (0.99, 1.23)[a]	0.91 (0.81, 1.01)[a]
	C_{max} (ng/mL)	1.07 (0.97, 1.18)[a]	1.17 (1.06, 1.29)	0.91 (0.83, 1.01)[a]
Secondary	AUC_{0-360h} (h*ng/mL)	1.04 (0.94, 1.15)[a]	1.16 (1.05, 1.29)	0.90 (0.81, 0.99)[a]
	$t_{1/2}$ (h)	0.89 (0.77, 1.02)	0.94 (0.82, 1.08)[a]	0.94 (0.82, 1.08)[a]

AUC_{0-360h}=area under concentration time curve up to 360 hours; AUC_{0-t}=area under concentration time curve up to last non zero value; $AUC_{0-\infty}$=area under concentration time curve extrapolated to infinity; C_{max}=peak serum concentration; EU=European Union; PK=pharmacokinetic; $t_{1/2}$=elimination half-life; US=United States.

[a] 90% CI within predefined limits (0.80, 1.25) concluding bioequivalence.

At the request of CHMP, the ANCOVA analyses has been repeated by the applicant forcing all pre-specified covariates (age, body weight, body surface area, and sex) into the model. After repetition, the 90% confidence intervals (CIs) around the ratio of geometric least squares means (LSMs) were still within the pre-specified limits of 0.80 to 1.25 for all treatment comparisons for the primary PK endpoints and bioequivalence was concluded between all 3 treatments. The 90% CIs for the ratios of the secondary endpoint AUC_{0-360h} were also within pre-specified limits for all three comparisons, as was the 90% CI for $t_{1/2}$ in the FKB327/EU-Humira comparison. The lower 90% CI for $t_{1/2}$ in the FKB327/US-Humira and EU-Humira/US-Humira comparisons fell slightly below the pre-specified limit at 0.77 and 0.79, respectively.

Table 5 Study FKB327-001: Summary of Bioequivalence Analysis (Analysis of Covariance) (PK Analysis Set)

Hypothesis	PK Parameter	FKB327/EU-Humira	FKB327/US-Humira	EU-Humira/US-Humira
Primary	$AUC_{0-\infty}$ (h*ng/mL)	1.07 (0.95, 1.20)*	0.98 (0.87, 1.10)*	0.92 (0.81, 1.03)*
	AUC_{0-t} (h*ng/mL)	1.09 (0.98, 1.21)*	1.00 (0.90, 1.11)*	0.92 (0.83, 1.02)*
	C_{max} (ng/mL)	1.13 (1.03, 1.24)*	1.07 (0.97, 1.17)*	0.94 (0.86, 1.04)*
Secondary	AUC_{0-360h} (h*ng/mL)	1.12 (1.02, 1.22)*	1.04 (0.95, 1.14)*	0.93 (0.85, 1.03)*
	$t_{1/2}$ (h)	0.98 (0.85, 1.13)*	0.89 (0.77, 1.02)	0.91 (0.79, 1.05)

Ratio of geometric least squares means (90% CI presented)
AUC_{0-360h} = area under concentration time curve up to 360 hours; AUC_{0-t} = area under concentration time curve up to last non zero value; $AUC_{0-\infty}$ = area under concentration time curve extrapolated to infinity; CI = confidence interval; C_{max} = peak serum concentration; EU = European Union; PK= pharmacokinetic; $t_{1/2}$ = elimination half-life; US=United States.
* 90% CI within predefined limits (0.80, 1.25) concluding bioequivalence.

In addition, for each paired comparison of interest for the primary endpoints, a separate analysis was conducted where the subjects on the third arm (not of interest) were excluded from the analysis. Both ANCOVA (including all pre-specified covariates) and analysis of variance (ANOVA) were performed. The results from the ANCOVA model for all paired comparisons met the pre-specified bioequivalence limits (0.80 to 1.25) for all 3 primary endpoints. As expected, the 90% CIs obtained using the ANOVA model were wider than those obtained from the ANCOVA model, and the 90% CIs of the primary endpoints C_{max} for FKB327/EU-approved Humira and $AUC_{0-\infty}$ for EU-approved Humira/US-licensed Humira fell slightly outside the pre-specified limits at 1.29 and 0.796, respectively, while all other 90% CI fell within limits.

Table 6 Summary of Bioequivalence Analysis Excluding Third Arm (PK Analysis Set)

Hypothesis	Paired Comparison of Interest	PK Parameter	ANCOVA Ratio (90% CI)	ANOVA Ratio (90% CI)
Primary	FKB327/EU-Humira	$AUC_{0-\infty}$ (h*ng/mL)	1.06 (0.95, 1.19)*	1.08 (0.97, 1.21)*
		AUC_{0-t} (h*ng/mL)	1.08 (0.98, 1.20)*	1.10 (1.00, 1.22)*
		C_{max} (ng/mL)	1.12 (1.02, 1.23)*	1.17 (1.06, 1.29)
Primary	FKB327/US-Humira	$AUC_{0-\infty}$ (h*ng/mL)	0.98 (0.88, 1.10)*	0.98 (0.86, 1.10)*
		AUC_{0-t} (h*ng/mL)	1.01 (0.91, 1.12)*	1.00 (0.90, 1.12)*
		C_{max} (ng/mL)	1.07 (0.97, 1.17)*	1.07 (0.96, 1.18)*
Primary	EU-Humira/US-Humira	$AUC_{0-\infty}$ (h*ng/mL)	0.91 (0.803, 1.03)*	0.90 (0.796, 1.02)
		AUC_{0-t} (h*ng/mL)	0.91 (0.81, 1.02)*	0.91 (0.81, 1.02)*
		C_{max} (ng/mL)	0.93 (0.85, 1.02)*	0.91 (0.83, 1.01)*

Ratio of geometric least squares means (90% CI presented). ANCOVA = analysis of covariance; ANOVA = analysis of variance; AUC_{0-360h} = area under concentration time curve up to 360 hours; AUC_{0-t} = area under concentration time curve up to last non zero value; $AUC_{0-\infty}$ = area under concentration time curve extrapolated to infinity; C_{max} = peak serum concentration; EU = European

Union; PK = pharmacokinetic; $t_{1/2}$ = elimination half-life; US = United States. ANCOVA: treatment group, Baseline values for age, body weight, body surface area, and sex as covariates. * 90% CI within predefined limits (0.80, 1.25) concluding bioequivalence.

ADA formation

ADA formation against adalimumab is known to be accompanied by increased clearance and reduced exposure, as well as possible loss of efficacy. The impact of ADA levels on PK parameters for FKB327 was compared to US-licensed Humira and EU-approved Humira in healthy volunteers in study FKB327-001. However, due to the uncertainties related to the numerous inconclusive samples in the assays, no conclusion can be drawn on the comparability of the immunogenicity profiles of FKB327 and EU-Humira and US-Humira for the healthy subjects included in the study FKB327-001. Because the deficient ADA and NAb assays were only used in the study FKB327-001 and because ADA or NAb are not included as a covariate of the ANCOVA model used to conclude the bioequivalence between all 3 treatments in the study FKB327-001, this issue was not pursued by the CHMP.

Study FKB327-005

This study is a Phase I, randomised, open-label, parallel, single-dose study to assess the relative bioavailability of a subcutaneous dose of FKB327 when administered using a pre-filled syringe, a pre-filled auto-injector or a vial with disposable syringe in healthy subjects.

The primary objective is to assess the relative bioavailability of FKB327 after a single SC dose delivered by vial/syringe (vial), PFS and AI in healthy subjects. The secondary objectives were to compare the safety of FKB327 after a single SC dose delivered by vial, PFS and AI in healthy subjects, to describe the effect of body weight on the single SC dose PK of FKB327 in healthy subjects and to describe the effect of injection site on the single SC dose PK of FKB327 in healthy subjects.

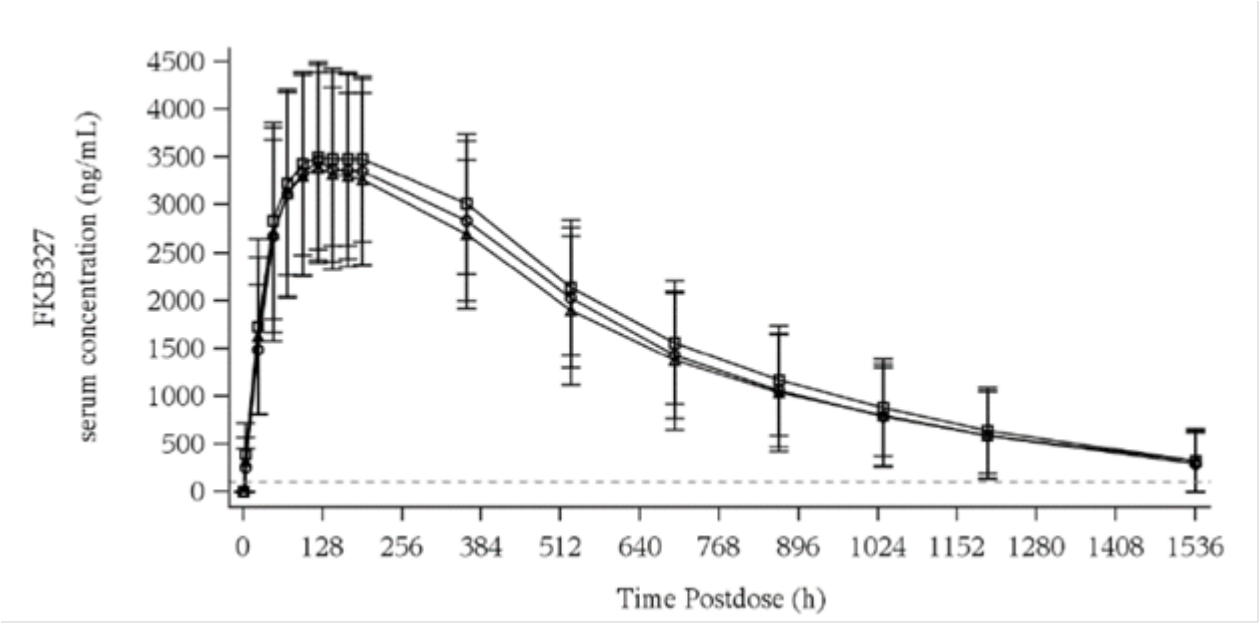


Figure 2 Arithmetic Mean (±SD) Serum Concentration-Time Profiles of FKB327 Following a Single 40-mg SC Dose of FKB327 Administered via Vial/Syringe, PFS and AI

The PK parameters were log-transformed prior to analysis and were analysed using a fixed-effects analysis of variance (ANOVA) model. The model included treatment as a fixed effect.

A secondary analysis also investigated the effect of adding body weight strata and injection site into the above ANOVA model individually and in combination as fixed effects. In addition, due to potential formation of FKB327 ADAs, AUC0-t, AUC0-∞, Cmax and t1/2 were analyzed using a fixed-effects ANOVA model, with a term for treatment and ADA titer results at the last sampling time point (the result was classified as being within the median, lower or upper quartiles), along with an ADA titer by treatment interaction term.

Table 7 Statistical Analysis of the Pharmacokinetic Parameters of FKB327 for FKB327 PFS / vial, FKB327 AI / vial and FKB327 AI / PFS

	Geometric LS Means			Ratio of Geometric LS Means (90% CI)		
Parameter	FKB327 vial	FKB327 PFS	FKB327 AI	FKB327 PFS / FKB327 vial	FKB327 AI / FKB327 vial	FKB327 AI / FKB327 PFS
AUC_{0-t} (h*ng/mL)	2149422 (n=65)	2137221 (n=63)	2378321 (n=65)	0.994 (0.877, 1.13)	1.11 (0.976, 1.254)	1.11 (0.981, 1.26)
$AUC_{0-\infty}$ (h*ng/mL)	2376682 (n=60)	2298611 (n=56)	2463195 (n=60)	0.967 (0.861, 1.09)	1.04 (0.925, 1.16)	1.07 (0.954, 1.20)
C_{max} (ng/mL)	3449 (n=65)	3447 (n=63)	3592 (n=65)	1.00 (0.918, 1.09)	1.04 (0.957, 1.13)	1.04 (0.957, 1.13)
$t_{1/2}$ (h)	305 (n=60)	308 (n=56)	306 (n=60)	1.01 (0.880, 1.16)	1.00 (0.877, 1.15)	0.995 (0.868, 1.14)
t_{max} (h) #	120 (n=65)	120 (n=63)	144 (n=65)	0 (-24.0, 0)	0 (-24.0, 23.9)	0 (0, 24.0)

Medians, median difference and approximate 90% CI for the difference are presented.
Abbreviations: AI = auto-injector; AUC_{0-t} = area under the concentration-time curve from time zero to the last detectable value; $AUC_{0-\infty}$ = area under the concentration-time curve from time zero extrapolated to infinity; CI = confidence interval; C_{max} = maximum concentration; LS = least squares; n = number of observations; PFS = pre-filled syringe; $t_{1/2}$ = elimination half-life; t_{max} = time to reach maximum concentration.
The ratio and corresponding CIs are back-transformed from the difference and CIs calculated on the log e scale.

The PFS was bioequivalent to the vial in terms of all primary PK parameters (AUC0-t, AUC0-∞ and Cmax), as the 90% CIs around the geometric means ratios were fully contained within the predefined bioequivalence (BE) limits of 0.80 to 1.25 using ANOVA. For the AI/vial and AI/PFS comparisons, the 90% CIs of the geometric LS means ratios for AUC0-∞ and Cmax were fully contained within the predefined BE limits of 0.80 to 1.25, although for both the AI/vial and AI/PFS comparisons, the upper limit of 90% CIs of the geometric LS means ratios for AUC0-t was slightly outside the predefined BE limits of 0.80 to 1.25. This was not considered as a concern by the CHMP and does not preclude any switch between the three presentations.

With regard to the injection site, the abdominal wall group showed a tendency for lower exposure compared to the thigh group. With regard to body weight, the exposure for the 50 to 75 kg group was higher than for the >75 to 100 kg group.

Study FKB327-004

The objective of the study was to compare PK and the safety of FKB327 and US-sourced Humira after single dose, by sc injection in Japanese healthy male subjects. Immunogenicity and local tolerability of FKB327 were also investigated.

This study is a Phase I, Randomized, Single-Blind, parallel group Single-Dose Study to Compare Pharmacokinetic Characteristics and Safety of FKB327 with those of Humira in Japanese Healthy Subjects.

Table 8 Summary of PK Similarity Analysis using ANOVA: PK Analysis Set

	PK Parameter	Geometric LS Mean		Ratio of Geometric LS Mean (90% CI)
		FKB327	Humira	FKB327/Humira
Primary	C_{max} (ng/mL)	3920	3650	1.07 (0.99, 1.16)
	$AUC_{0\text{-}360h}$ (h*ng/mL)	1170000	1070000	1.10 (1.01, 1.19)
	$AUC_{0\text{-}t}$ (h*ng/mL)	2540000	2180000	1.17 (1.05, 1.30)
Secondary	$AUC_{0\text{-}\infty}$ (h*ng/mL)	2770000	2380000	1.16 (1.03, 1.31)
	$t_{1/2}$ (h)	330.49	288.64	1.14 (0.97, 1.35)

ANOVA = analysis of variance; LS = least squares; CI = confidence interval; PK = pharmacokinetic; C_{max} = maximum serum concentration; $AUC_{0\text{-}360h}$ = area under concentration-time curve up to 360 hours; $AUC_{0\text{-}t}$ = area under concentration-time curve up to time of last quantifiable concentration; $AUC_{0\text{-}\infty}$ = area under concentration-time curve extrapolated to infinity; $t_{1/2}$ = elimination half-life.
PK parameters were logarithmically transformed prior to ANOVA including a term for treatment group.
PK similarity is demonstrated if the 90% CI of the log ratio Test/Reference is included within the range of 0.8 to 1.25 for the primary PK parameters (C_{max}, $AUC_{0\text{-}360h}$, and $AUC_{0\text{-}t}$).

The applicant was requested to present an ANCOVA using baseline covariates but not ADA level. The baseline subject characteristics of age, weight and body surface area were chosen for the requested post hoc analysis of covariance (ANCOVA) of results of study FKB327-004 because these parameters have been described as potentially influencing the PK of adalimumab (Humira EPAR). Gender was not relevant as a covariate in this study since all subjects were male. The same primary and secondary pharmacokinetic (PK) parameters and bioequivalence limits were chosen as used in the pre-specified PK analyses for this study.

The results of ANCOVA including age, weight, body surface area as covariates are shown in the table below:

Table 9 Summary of PK Similarity Analysis using ANCOVA (age, body weight, body surface area): PK Analysis set

	Pharmacokinetic Parameter	Geometric LS Mean		Ratio of Geometric LS Mean (90% CI)
		FKB327	Humira	FKB327/Humira
Primary	C_{max} (ng/mL)	3900	3660	1.06 (1.00, 1.13)[a]
	$AUC_{0\text{-}360h}$ (h*ng/mL)	1160000	1070000	1.09 (1.01, 1.16)[a]
	$AUC_{0\text{-}t}$ (h*µg/mL)	2530000	2190000	1.16 (1.04, 1.28)
Secondary	$AUC_{0\text{-}inf}$ (h*ng/mL)	2770000	2390000	1.16 (1.04, 1.30)
	$t_{1/2}$ (h)	329.83	289.19	1.14 (0.97, 1.34)

Considering the primary PK parameters, the 90% CIs of the geometric LS mean ratios for Cmax and AUC0-360h were fully contained within the pre-specified bioequivalence limits of 0.80 to 1.25, but the upper 90% CI of the geometric LS mean ratio for AUC0-t was slightly outside the pre-defined range.

For the secondary PK parameters, the upper limits of 90% CIs of the geometric LS mean ratios for both AUC0-∞ and t1/2 were outside the range.

In conclusion, the analyses requested support equivalence of Cmax and AUC0-360h but not of AUC0-t and AUC0-∞.

Study FKB327-002 and 003

In studies FKB327-002 and -003, a statistical comparison of the Ctrough concentrations pre-dose (PK Population) has been carried out.

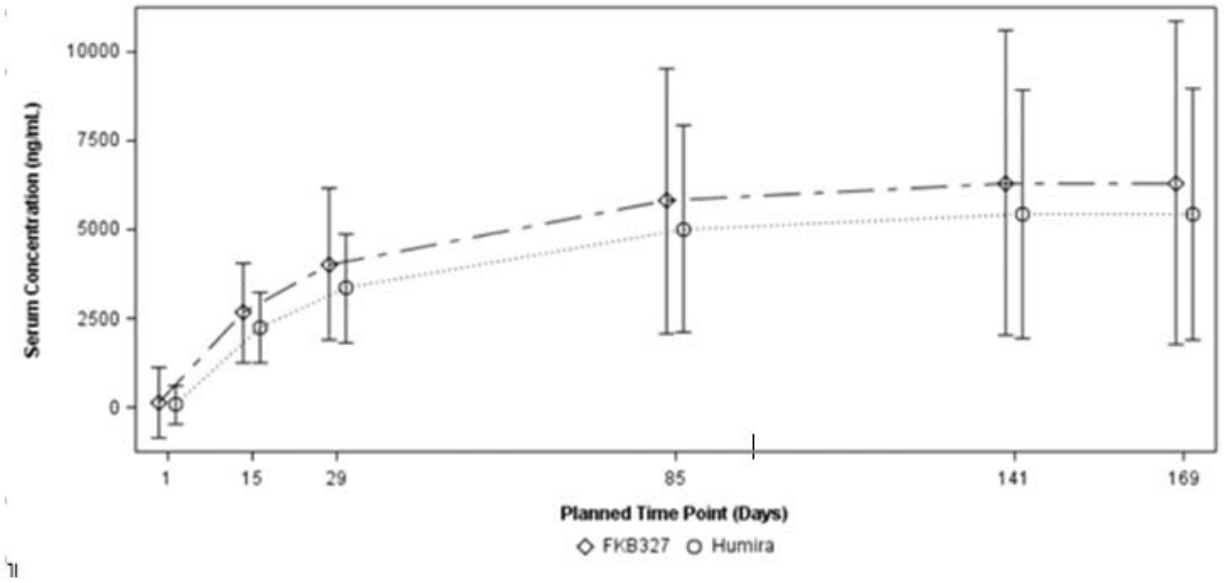


Figure 3 Study FKB327-002: Mean (±Standard Deviation) Serum Concentrations of Adalimumab by Treatment (PK Analysis Set)

In study FKB327-002, LSM serum trough concentrations of adalimumab were higher at all time points following FKB327 administration compared to Humira. LSM serum trough concentrations of adalimumab at Week 24 were slightly higher following FKB327 administration (4126.0 ng/mL) compared to Humira (3758.2 ng/mL). The ratio of geometric LSM (90% CI) serum trough adalimumab concentrations for FKB327/US-Humira at Weeks 20 and 24 and for the average of Weeks 20 and 24 (ie, after achieving steady state) were 1.13 (0.98, 1.30), 1.10 (0.94, 1.27) and 1.11 (0.97, 1.28), respectively, and all of these 90% CIs included unity.

Table 10 Study FKB327-002: Statistical Analysis of Serum Concentration Data (ng/mL) (PK Analysis Set)

	Geometric LSM (95% CI)		Ratio of Geometric LSM (90%CI)
Planned Relative Time (Week)	FKB327	Humira	FKB327/Humira
Week 2	2434.6 (2321.4, 2553.2)	2089.1 (1990.9, 2192.2)	1.17 (1.10, 1.23)
Week 4	3450.6 (3223.2, 3694.1)	2932.1 (2737.0, 3141.1)	1.18 (1.08, 1.28)
Week 12	4316.3 (3919.6, 4753.2)	3851.5 (3493.9, 4245.7)	1.12 (1.00, 1.26)
Week 20	4369.8 (3892.3, 4905.9)	3873.0 (3445.9, 4353.0)	1.13 (0.98, 1.30)
Week 24	4126.0 (3645.1, 4670.4)	3758.2 (3316.8, 4258.3)	1.10 (0.95, 1.27)
Average over Week 20 and Week 24	4246.1 (3774.9, 4776.3)	3815.1 (3388.0, 4296.2)	1.11 (0.97, 1.28)

CI=confidence interval; LSM=least squares mean; PK=pharmacokinetic.
Model fitted to log-transformed PK trough concentrations at Weeks 2, 4, 12, 20 and 24 with fixed effect terms for week, treatment group and week × treatment group.

Table 11 Study FKB327-003: Statistical Analysis of Trough Serum Concentration Data to Compare Treatment Averaged Across Period I Time-points: PK Analysis Set

Planned Relative Time (Week)	Geometric LSM (95% CI) H-H	Geometric LSM (95% CI) F-F	Ratio of Geometric LSM (90% CI) H-H/F-F
Week 12	4541.5 (3871.0, 5328.2)	4227.1 (3601.7, 4961.1)	1.07 (0.89, 1.30)
Week 24	4657.3 (4004.6, 5416.5)	4145.7 (3562.4, 4824.6)	1.12 (0.94, 1.34)
Week 30	4370.1 (3759.7, 5079.7)	4333.4 (3726.2, 5039.6)	1.01 (0.84, 1.21)
Average over all time points	4521.5 (3904.8, 5235.5)	4234.7 (3656.3, 4904.6)	1.07 (0.90, 1.27)

PKAS: PK Analysis Set, LSM: Least-squares means, CI: Confidence interval.
Repeated Measures model fitted to log-transformed PK trough concentrations at Weeks 12, 24 and 30 with fixed effect terms for week, treatment sequence and week × treatment sequence.
Covariance structure: unstructured. Since the treatment * week interaction effect was found to be significant at the 10% level (p-value = 0.0846) all estimates across all time-points are displayed.

As expected, the differences observed in ADA titres did impact on serum trough concentrations and efficacy parameters. ADA formation against adalimumab is known to be accompanied by increased clearance and reduced exposure, as well as possible loss of efficacy. However, there was no difference between FKB327 and Humira in terms of the effect of ADA titre on PK parameters by drug titre in patients with RA.

Special populations

Analyses in the special populations are not relevant in the Hulio MAA as the biosimilar relies on the information already known of the reference product. Renal and hepatic impairment are not expected to influence the PK of an antibody and dedicated PK studies in patients with renal or hepatic impairment have not been carried out.

No gender-related differences were observed with the reference product after correction for body-weight. According to the Humira SmPC, population pharmacokinetic analyses with data from over 1,300 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight.

Dedicated pharmacokinetic studies in the elderly have not been carried out. The amount of elderly subjects (> 65 years) in the clinical PK studies is very small and the Humira SmPC indicates that after adjustment for weight differences, age appeared to have a minimal effect on adalimumab clearance. No clinical studies have been conducted with Hulio in the paediatric patient population.

Drug-drug interactions

No formal interaction studies have been performed with Hulio and no interaction studies are needed in the biosimilarity exercise. By analogy to endogenous IgG, adalimumab clearance did not appear to occur by excretion and liver metabolism as conventional drugs, rendering classical mechanisms for pharmacokinetic interactions unlikely.

2.4.3. Pharmacodynamics

Mechanism of action

Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its 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 (ELAM 1, VCAM 1, and ICAM 1 with an IC50 of 0.1 0.2 nM).

Primary and Secondary pharmacology

After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation (C reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL 6) was observed, compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP 1 and MMP 3) that produce tissue remodelling responsible for cartilage destruction were also decreased after adalimumab administration. Patients treated with adalimumab usually experienced improvement in haematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis and hidradenitis suppurativa after treatment with adalimumab. In patients with Crohn's disease, a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNFα was seen. Endoscopic studies in intestinal mucosa have shown evidence of mucosal healing in adalimumab treated patients.

2.4.4. Discussion on clinical pharmacology

With respect to the clinical pharmacokinetics, the development program to demonstrate the similarity between Hulio and Humira is in general adequate and was performed according to the guidance on similar biological products and the recommendations given in the CHMP Scientific Advices. The comparability exercise was performed between EU/US sourced reference products and the formulation intended to be marketed in the European Union.

The Hulio PK program consists of two pivotal phase I studies carried out in healthy subjects (Clinical Studies FKB327-001 and FKB327-005) and the PK data collected in the pivotal phase III study in patients

with RA. In addition, the Applicant conducted a supportive Phase 1 study in Japan comparing the PK of FKB327 and US-licensed Humira to enable a local product licence application (Study FKB327-004).

In general, the assay format employed by the applicant for the measurement of adalimumab is considered acceptable. See below discussion on the ADA and Nab assays used in the study FKB327-001.

The use of a parallel design in Study FKB327-001 to demonstrate bioequivalence of Hulio and Humira primarily is considered appropriate by the CHMP for a monoclonal antibody with per definition a long half-life and a potential of immunogenicity. The population enrolled in this study is adequate since volunteers are the most sensitive population for initial and comparative investigation of PK.

Based on the data submitted in the initial application, biosimilarity of Hulio to Humira was not considered established because of uncertainties with respect to the PK data. In addition, discrepancies were seen between the N-glycan patterns of Hulio and EU-approved Humira, including differences in high mannose content, a quality attribute which was formerly reported to affect pharmacokinetic properties.

At the CHMP request, the applicant has therefore provided the reanalysis of the pivotal PK trial by ANCOVA forcing all pre-specified covariates into the model. The introduction of covariates in the statistical analysis (ANCOVA) helped to reduce the variability introduced by using different patients (with possibly different baseline characteristics) on each treatment arm and was used instead of ANOVA. Even if this method is not the standard approach to be used in bioequivalence testing and is not included in the EMA rules for bioequivalence (due to crossover design being the standard design for small molecules), ANCOVA was pre-specified in the SAP and is deemed justified by the CHMP for a parallel design of a monoclonal antibody with the aim to reduce variability and to increase precision. Using ANCOVA, the 90% CIs around the ratio of geometric LSMs are well within the pre-specified bioequivalence limits of 0.80 to 1.25 for all treatment comparisons for the primary PK endpoints, thus PK similarity was concluded between all 3 treatments (FKB327, EU-Humira and US-Humira).

At the CHMP request, the applicant has also further investigated the potential reasons for the observed PK differences discussing all the attributes known to have an impact on the PKs of mAbs (drug presentations, ethnic factors...). A special attention has been paid to the physicochemical and functional characteristics of FKB327 (glycan patterns, LMWS) and evidence has been provided that the relative difference in high mannose content (and/or other physicochemical/biological parameters) between test and reference products has negligible impact on pharmacokinetics.

With regard to the ADA and Nab assays used in the study FKB327-001, no conclusion can be drawn on the comparability of the immunogenicity profiles of FKB327 and EU-Humira and US-Humira for the healthy subjects included in this study due to the uncertainties related to the numerous inconclusive samples in the assays. However, because the deficient ADA and NAb assays were only used in the study FKB327-001 and because ADA or NAb are not included as a covariate of the ANCOVA model used to conclude the bioequivalence between all 3 treatments in the study FKB327-001, this issue was not pursued by the CHMP.

Supportive PK data from healthy volunteers are also provided with the results of a PK trial (FKB327-004) comparing FKB327 to US-Humira in Japanese subjects. The PK trial FKB327-005 comparing three modes of delivery of FKB327 from a vial, a PFS and an AI has also been carried out in healthy subjects. These trials used the same design as the pivotal trial.

Overall, the three presentations are considered equivalent for their intended clinical use in study FKB327-005.

The conclusion from study FKB327-004 is that equivalence has not been demonstrated for some important PK parameters. Indeed, the results of the requested ANCOVA analysis using baseline

covariates but not ADA level support equivalence of Cmax and AUC0-360h but not of AUC0-t and AUC0-∞ and are consistent with the ANOVA analysis previously presented. It should be noted that there is a substantial difference between study FKB327-001 and study FKB327-004 in demographic characteristics like mean body weight/BMI and race. The applicant points out a previous (pre-specified) analysis adjusting for ADA titre where the criteria for bioequivalence where met on all 3 primary parameters. However, this analysis cannot be considered reliable as the ADA titre may depend on the treatment taken. Indeed, the trend for slightly higher ADA titres with US-Humira could explain the slight difference in the tail of the exposure profile. In addition, the frequency of ADA occurrence cannot be compared directly since different ADA assays were used and the covariates used in study FKB327-001 were demographic while that used in study FKB327-004 was post-dose ADA titre. However, these data are only provided for completeness sake as this is a comparison of Hulio with US Humira, which is not directly relevant to this application.

According to literature, there are no significant differences in the PK characteristics in healthy subjects and RA patients. However, in the total comparability exercise, supportive PK data from clinical studies in patients are encouraged and could provide highly supportive evidence of a similarity. Target-mediated clearance can only be really investigated in patients. However, with the high variability linked to disease and to therapy, no reasonable bioequivalence approach can be proposed for a parallel group design in phase III trials in patients. In order to obtain valid data, high patient numbers would be required which is not feasible within a phase III trial and multiple sampling required for an adequate PK assessment of the test and reference product. Bearing in mind the complexity of performing a PK profile in patients in phase III, it is not realistic to establish pre-defined rules for bioequivalence on the basis of the limited blood sampling opportunities and number of patients in each treatment group. The phase I studies in healthy male subjects are used as the major studies for establishing bioequivalence.

Nevertheless, a statistical comparison for the Ctrough pre-dose concentrations in the target population (at weeks 4, 12, 20 and 24 and at weeks 12, 24 and 30 in the phase III studies FKB327-002 and 003 respectively) has been carried out by the applicant. The small differences in mean trough serum drug concentrations observed in the clinical studies are not expected to result in clinically meaningful differences in efficacy and safety.

As expected, the differences observed in ADA titres did impact on serum trough concentrations and efficacy parameters. ADA formation against adalimumab is known to be accompanied by increased clearance and reduced exposure, as well as possible loss of efficacy. However, there was no difference between FKB327 and Humira in terms of the effect of ADA titre on PK parameters by drug titre in patients with RA.

Analyses in the special populations are not relevant in the Hulio MAA as the biosimilar relies on the information already known of the reference product. No formal drug-drug interaction studies are considered needed by the CHMP.

2.4.5. Conclusions on clinical pharmacology

Typically, the comparability of the pharmacokinetic parameters is analysed using ANOVA, which is adequate for the analysis of a cross-over trial. However, for a parallel group study it may be desirable to adjust for baseline characteristics that could affect the PK results and which may be imbalanced between the two treatment arms. Therefore, analysis of comparability of the pharmacokinetic parameters by ANCOVA are acceptable in parallel group studies, provided that the choice of covariates is justified and provided that this is pre-specified in the statistical analysis plan. This is the case for study FKB327-001.

From a PK perspective, using an updated ANCOVA model, the 90% CIs around the ratio of geometric LSMs are well within the pre-specified bioequivalence limits of 0.80 to 1.25 for all treatment comparisons for the primary PK endpoints, thus PK similarity was concluded between all 3 treatments (FKB327, EU-Humira and US-Humira).

In conclusion, the applicant has provided adequate bridging data between Humira-US and Humira-EU. The Phase 1 FKB327-001 study provide a three-way comparison of FKB327 and both EU- and US-licenced Humira and the results demonstrate similarity between EU- and US-licenced Humira and the latter formulations are considered as equivalent.

2.5. Clinical efficacy

Two studies were performed to assess equivalence of Hulio with Humira in RA patients. A 24 week phase 3 trial (FKB327-002) was performed to assess efficacy and safety characteristics of both products. Patients that finished this study were invited to enter a long term 80 week follow up study after re-randomisation (FKB327-003).

2.5.1. Dose response study

No dose response studies were undertaken. Given that FKB327-002 was intended to prove similarity between products at equal doses and treatment schedules the lack of dose response studies is not an issue for the CHMP as the same scheduling routine that is used for Humira was implemented.

2.5.2. Main study

FKB327-002

A Phase 3 Randomised, Blinded, parallel arm Active-Controlled Study to Compare FKB327 Efficacy and Safety with the Comparator Humira in Rheumatoid Arthritis Patients Inadequately Controlled on Methotrexate (ARABESC), during which FKB327 or Humira was administered by multiple dosing every other week for 22 weeks in patients with active RA who were already taking MTX at a stable dose (10 to 25 mg/week) for a minimum of 8 weeks prior to Screening but who required additional therapy to control their disease.

Methods

Study Participants

Inclusion Criteria

Patients were to meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Men or women aged ≥18 years.
2. RA, diagnosed to revised ACR criteria (2010 version) at least 3 months prior to Screening.

3. Active RA, as confirmed by ≥6 tender and ≥6 swollen joint counts out of 68/66, respectively, at Screening and at Baseline.
4. CRP level ≥10 mg/L at Screening.
5. Were taking MTX (oral or parenteral) for at least 3 months prior to Screening and at a stable dose of between 10 and 25 mg/week for at least 8 weeks, with concomitant folic/folinic acid of at least 5 mg/week. Patients could start treatment with folic acid at Screening if not already receiving it.
6. If the patient was currently taking oral steroids (≤10 mg/day prednisone or equivalent) or NSAIDs, the patient was to be on a stable dose ≥4 weeks prior to Screening and during the study.
7. Females of childbearing potential were to have a negative pregnancy test at Screening, in the 3 weeks prior to study dosing, and every 4 weeks during dosing.

Both sexes were to be willing to take adequate contraceptive precautions throughout the study period and continuing for at least 5 months after the last dose of study drug. Acceptable methods of contraception in this study were: surgical sterilisation, intrauterine devices, oral contraceptives, contraceptive patch, long-acting injectable contraceptives, partner's vasectomy, a double-barrier protection method (condom or diaphragm with spermicide).

Exclusion Criteria

Patients presenting with any of the following were not included in the study:

1. Prior treatment with adalimumab.
2. Prior treatment with more than 1 biologic or 1 protein kinase inhibitor DMARD for RA, either as part of clinical management or during a clinical study.
3. Prior treatment with TNF inhibitors for RA with lack of efficacy as per clinical judgment (primary failure). Patients who had received 1 TNF inhibitor other than adalimumab at a therapeutic dose and for an adequate period of time, and discontinued it for any reason other than lack of efficacy, were not excluded.
4. Prior treatment with cyclophosphamide.
5. Treatment with an investigational agent within 12 weeks or 5 half-lives of the drug prior to Screening, whichever was longer.
6. Immunisation with a live or attenuated vaccine within 4 weeks prior to study drug dosing.
7. Intra-articular or parenteral steroids within 28 days prior to Screening.
8. Treatment with any DMARDs, other than MTX, within a period prior to Screening appropriate to the pharmacodynamic profile of the drug concerned, as specified in the protocol.
9. History of relevant allergy/hypersensitivity to monoclonal antibodies or any of the excipients of FKB327 or Humira, or history of clinically significant contact allergy/hypersensitivity to latex or rubber.
10. Presence of active autoimmune disease or joint disease other than RA (eg, mixed connective tissue disorder, gout) which may have confounded efficacy assessments such as joint count evaluations or CRP/erythrocyte sedimentation rate (ESR).
11. ACR functional Class IV.

12. Major surgery (including joint surgery) within 8 weeks prior to Screening or planned to take place during the study period.
13. Presence of chronic or acute infection at Screening including positive result for human immunodeficiency virus (HIV) 1 or 2, hepatitis B virus (HBV), hepatitis C virus (HCV), and active tuberculosis (TB) or untreated latent TB where the patient was not willing to undergo prophylactic treatment, as per protocol.
14. Acute infection requiring parenteral antibiotics within 4 weeks of study dosing or requiring oral/topical antibiotics within 2 weeks of study dosing.
15. Presence of serious, uncontrolled disease of another body system including cardiovascular, neurological, pulmonary, renal and hepatic disease.
16. Presence of New York Heart Association (NYHA) Class III/IV heart failure.
17. Presence of any uncontrolled disease for which steroid treatment was regularly required for flares, eg, asthma.
18. Presence of any malignancy or history of malignancy in the 5 years prior to Screening which had not been curatively treated, with the exception of carcinoma in situ of the cervix or basal cell carcinoma of the skin that had been fully excised.
19. Patients with aspartate transaminase (AST) or alanine transaminase (ALT) >1.5 × upper limit of normal (ULN), haemoglobin (Hb) <8 g/dL (<80 g/L), absolute neutrophil count <1500/µL (<1.5 thou/µL or <1.5 GI/L), platelets <100,000/µL (<100,000/cumm or <100 GI/L), and/or creatinine >1.5 × ULN. In case of isolated exclusionary values, the test could be repeated once, at the discretion of the Investigator, and the new value used for eligibility.
20. Patients with demyelinating diseases (eg, multiple sclerosis).
21. Pregnant or breastfeeding women.
22. Patients with any condition or circumstances, which, in the opinion of the Investigator, made them unsuitable for the study, unlikely or unable to comply with study procedures and requirements.
23. Body weight >120 kg.
24. Prior or current treatment with an agent which might have confounded efficacy or safety evaluation in this study, eg, RANKL inhibitors for osteoporosis, immunomodulators for asthma within 5 half-lives of the drug concerned prior to the first dose of study treatment.

Treatments

Patients received either FKB327 40 mg eow or US-licensed Humira 40 mg eow by sc injection for up to 22 weeks.

FKB327 was manufactured by Kyowa Hakko Kirin Co., Ltd., Japan and the vial presentation was provided by the Sponsor. US-licensed Humira PFSs were provided by the Sponsor.

FKB327 was supplied as a vial containing a clear, colourless, and preservative-free solution for sc administration. Each sterile vial was filled with 0.8 mL deliverable volume of 50 mg/mL FKB327 formulated in monosodium glutamate, sorbitol, methionine, polysorbate 80, hydrochloric acid and water for injection at pH 5.2. Each vial was for single use only.

In each kit a disposable masking unit was provided by the Sponsor for the blinded administration of every dose of FKB327 or Humira.

Prior Concomitant Therapy

Permitted Concomitant Medication

Patients were to have taken MTX (oral or parenteral) for at least 3 months and at a stable dose of 10 to 25 mg/week for the last 8 weeks immediately prior to Screening. Patients were to continue to take this stable dose during the study. The route of administration of MTX was not to change throughout the study. The patient's MTX dose could be reduced for toxicity only. If toxicity occurred, this was to be recorded as an AE. Patients were also to have taken folic/folinic acid at a dose of at least 5 mg/week during the study.

Folic/folinic acid could be started at Screening if the patient was not already receiving it. Oral corticosteroids (≤10 mg/day prednisone or equivalent) were permitted during the study if the dose had been stable for at least 4 weeks prior to Screening and the same dose was continued during the study. An increase in oral steroid dose was permitted to treat concomitant conditions, e.g., asthma, only. The reason for any such increase in dose was to be recorded as an AE (e.g., asthma flare). The dose was to be tapered back down as soon as medically viable and within 2 weeks.

NSAIDs up to the maximum approved dose were permitted during the study if the dose had been stable for at least 4 weeks prior to Screening and during the study. Patients were to continue to take this stable dose during the study. The NSAID dose could be increased (not above the maximum approved dose) for up to 2 weeks to treat an RA flare. This was to be documented as a change in the concomitant medication. The dose was to be tapered back down as soon as medically viable and within 2 weeks. Patients who were not receiving NSAIDs could be treated with an NSAID for up to 2 weeks or an additional NSAID could be added to an existing NSAID regimen for up to 2 weeks to treat an RA flare.

Analgesics up to the maximum approved dose were permitted during the study but were not to be taken in the 24 hours prior to efficacy evaluations.

Patients with evidence or suspicion of latent TB at Screening, could be enrolled providing that they commenced prophylactic anti-mycobacterial treatment at least 3 weeks prior to randomisation (or longer, if local guidelines specified) and committed to completing the course of treatment. The treatment was to be according to local guidelines. If needed, such patients could be re-screened.

All concomitant medications (including over-the-counter medications, herbal medications, preventative vaccines, vitamins and food supplements) and procedures were to be recorded in the electronic Case Report Form (eCRF). Concomitant medications for chronic conditions were to be kept stable throughout the study wherever possible.

Prohibited Concomitant Medication

Immunisation with a live or attenuated vaccine was prohibited within 4 weeks prior to study dosing, for the duration of study, and for 3 months after administration of the last dose.

Treatment with an investigational agent within 12 weeks or 5 half-lives of the drug prior to Screening, whichever was longer, was prohibited.

Treatment with intra-articular and parenteral steroids within 28 days prior to study dosing or during the study was prohibited.

Treatment with other DMARDs (apart from MTX) was prohibited for the duration of the study. In the event the Investigator wished to treat a patient with a DMARD (other than MTX) during the study, the patient was to be withdrawn from study treatment and the reason for withdrawal documented.

Treatment with an agent which might confound efficacy or safety evaluation in this study (e.g., RANKL inhibitors for osteoporosis, immunomodulators for asthma) was prohibited within 5 half-lives of the drug concerned prior to the first dose of study treatment or during the study period.

Objectives

The primary objective was to assess the efficacy of FKB327 compared with Humira, when each was administered in combination with MTX.

The secondary objectives were:

- To compare the safety profiles of FKB327 and Humira, each in combination with MTX treatment.
- To assess the efficacy profiles of FKB327 and Humira over time, including initial onset of effect.
- To compare the proportions of patients on FKB327 and Humira, who developed ADAs and to summarise the distribution of the level of ADA activity between patients on FKB327 and Humira.
- To compare the steady-state PK of FKB327 and Humira administered by multiple dosing in patients with RA receiving concomitant treatment with MTX.

Outcomes / endpoints

Primary Efficacy Endpoint

ACR20 response rate at Week 24.

Secondary Efficacy Endpoints

The key secondary efficacy endpoint is as follows:

- DAS28 based on C-reactive protein (DAS28-CRP) score at Week 24.

Other secondary efficacy endpoints are as follows:

- ACR20, ACR50 and ACR70 response rates over time.

Values of the individual ACR core set variables (swollen joint count, tender joint count, CRP, patient"s assessment of disease activity, physician's assessment of disease activity, patient"s assessment of pain, HAQ-DI) over time.

- DAS28-CRP score and change in DAS28-CRP score over time.
- DAS28 score based on erythrocyte sedimentation rate (DAS28-ESR) at Weeks 12 and 24.

Other Endpoints

- Proportion of patients developing ADAs.
- Trough adalimumab concentration.

Safety Endpoints

- Safety as assessed by AEs, SAEs, serious infections, malignancies, vital signs, and laboratory abnormalities.

Sample size

A total of 680 patients were to be randomised to FKB327 and Humira treatment in a 1:1 allocation ratio. This sample size has been calculated based on being able to show equivalence of the ACR20 response rate in FKB327 and Humira, with 80% power and an equivalence margin of ±13%, an estimated ACR20 response rate of 57% to 63% and a maximum of 15% of patients ineligible for the PPAS. In order for biosimilarity to be demonstrated using these criteria, the two-sided 95% CI of the difference in ACR20 response rate between the 2 treatment groups must lie entirely within the bounds of -13% to +13%. With this sample size, the asymmetric equivalence margin of -12% to +15% using the 90% CI would provide approximately 88% power in being able to show equivalence between FKB327 and Humira.

Randomisation

Patients were to be randomised in a 1:1 ratio to receive either FKB327 40 mg eow or Humira 40 mg eow using the following stratification factors: prior biological treatment for RA (yes/no) and Screening disease activity (DAS28-CRP ≤5.1/>5.1). In order to balance treatment allocation as far as possible within strata and by site, a dynamic randomisation was used (as defined in the randomisation specification document).

Blinding (masking)

A blinded kit containing a single dose of either FKB327 or Humira was supplied by the Sponsor. The person preparing the injection (pharmacist or other suitably qualified member of staff not otherwise involved in the study) was unblinded once the treatment kit was opened. As FKB327 was provided in vials and Humira was provided in PFSs, the following measures were taken to ensure the blinding of patients and study site staff:

- In the event that the kit contained FKB327, on the day of administration the unblinded pharmacist (or other suitably qualified member of staff not otherwise involved in the study) withdrew 0.8 mL (40 mg) FKB327 from the vial using the syringe provided in the kit. The filled syringe was then placed into a masking unit (which allowed the dose to be administered without revealing the appearance of the syringe) before being taken to the location of the patient.
- If the kit contained Humira, no assembly was necessary as the Humira PFS was already inserted into a masking unit at the investigational medicinal product (IMP) packing facility.
- The masking units for both FKB327 and Humira were identical in external appearance.
- A nurse (unblinded) who was not otherwise involved in the study assessments administered the injections without allowing the patient to see the syringe before, during or after administration. In advance of administering the first dose the nurse explained to the patient how this procedure would be conducted. It was essential that the nurse did not inadvertently communicate to the patient which treatment they were receiving or show them the study treatment out of the masking unit.

Statistical methods

Efficacy analyses sets

The Full Analysis Set (FAS) was defined as the set of patients who received at least 1 dose of the randomised treatment and who had at least 1 evaluable primary efficacy measurement after their first dose of randomised treatment and was derived programmatically. The criteria leading to exclusion from the FAS were fully defined prior to unblinding the study data. The FAS was used for the primary efficacy analysis and other efficacy endpoints and analyses. Patients were analysed according to the randomised treatment in the primary analysis.

The Per-protocol Analysis Set (PPAS) was defined as the set of patients in the FAS that had not deviated sufficiently from the protocol as to impact on the primary efficacy endpoint and was derived programmatically. The criteria leading to exclusion from the PPAS were fully defined prior to unblinding the study data. These criteria were assessed and documented within the Analysis Sets Specification Form, which was finalised during a data review meeting prior to database lock.

The FAS and the PPAS were both relevant analysis sets for demonstrating equivalence so both were utilised for the equivalence tests of ACR20 response rate and DAS28-CRP score at Week 24. For other efficacy endpoints and analyses, the FAS was used.

Statistical tests

The percentage of patients achieving an ACR20 response at Week 24 was summarised using percentages and their 95% CIs, via the Clopper-Pearson method, by treatment for the FAS and the PPAS. The CIs for the differences in treatments (FKB327 – Humira) were calculated using a normal approximation with no continuity correction.

For the FAS analysis, patients without an ACR20 response recorded at Week 24 or those patients who had been withdrawn from the study or treatment had efficacy data imputed depending on reason for missingness.

The secondary hypothesis involved equivalence of the difference between FKB327 and Humira in DAS28-CRP at Week 24. The LSM for week × treatment group from the marginal model for repeated measures were estimated with 95% CIs and the difference in LSMs of FKB327-Humira at Week 24 was estimated with 95% CI. Baseline DAS28-CRP, previous biological treatment for RA (yes/no) and site were included as covariates. To handle missing DAS28-CRP, a repeated measures analysis model was used. This method was consistent with assuming that any missing values were missing at random.

Results

Participant flow

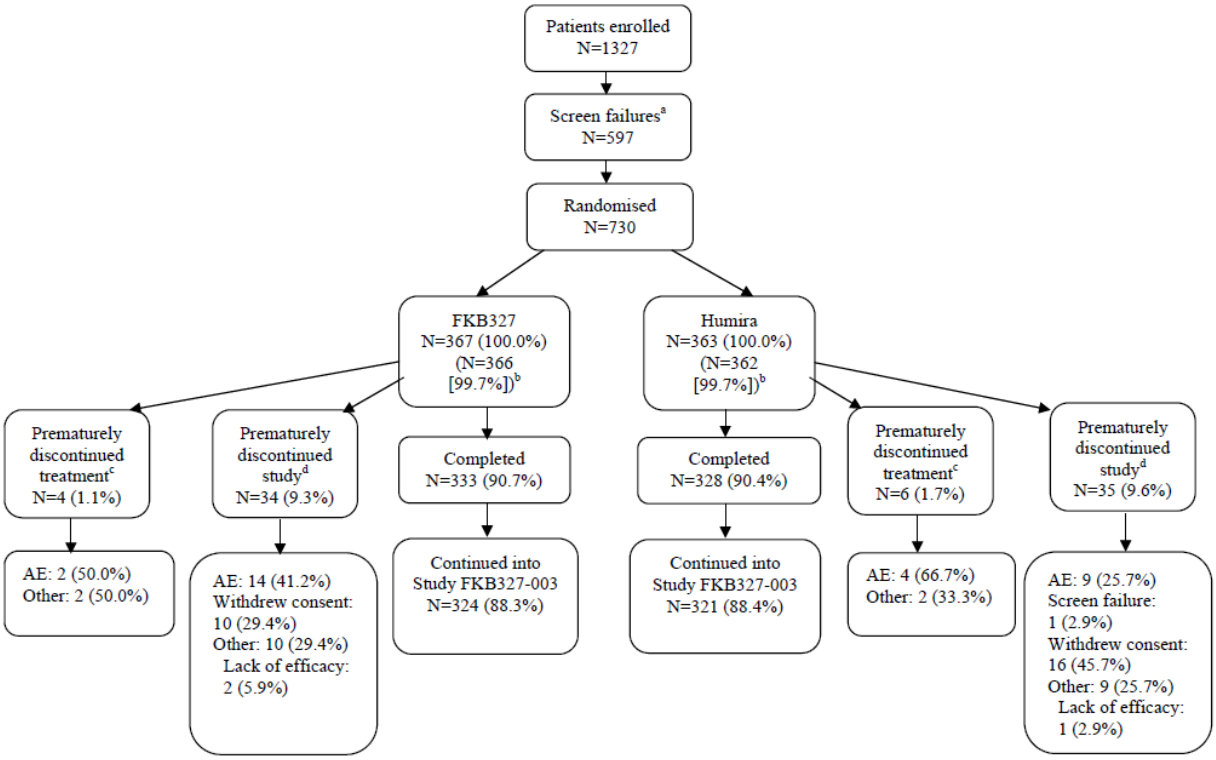


Figure 4 Patient disposition: all enrolled patients

Recruitment

The first patient was enrolled on 05 January 2015 and the last patient completed the study on 12 July 2016. Patients were enrolled from 109 sites in 12 countries. For the purposes of randomisation, the countries were assigned to 3 geographical regions: North America (US and Canada), Europe (Bulgaria, Czech Republic, Germany, Poland, Romania and Spain) and Rest of World (Chile, Peru, Russia and the Ukraine). Overall, 728 patients were recruited with the proportion of patients recruited in each region being similar for the FKB327 and Humira treatment groups. The most important contribution to patient enrolment was from the EU (38%) and Eastern Europe (31%). Four countries recruited the majority of patients (63%): Poland, Ukraine, Russia and Peru.

Conduct of the study

There were three substantial amendments to the protocol but only two after study initiation. These were numerous clarifications, change of sample size and rationale after interaction with regulatory authorities, definitions of FAS and PKAS populations. In addition, the exclusion of patients with a history of clinically significant contact allergy/hypersensitivity to latex or rubber was added after a potential safety issue regarding the handling of Humira was identified as the needle cover on Humira PFS contains dry natural rubber.

In total, 89 patients (12%) had at least one 'major significant' protocol deviation leading to exclusion from the PPAS: 52 patients (14%) and 37 patients (10%) in the FKB327 and Humira treatment arms, respectively. The most common 'major significant' protocol deviations were:

- missed visit (Week 0 or Week 24 visits, affecting primary efficacy endpoint), reported for 24 patients (6.5%) and 21 patients (5.8%) in the FKB327 and Humira treatment arms, respectively
- violation of efficacy inclusion/exclusion criteria, reported for 10 patients (2.7%) and 7 patients (1.9%) in the FKB327 and Humira treatment arms, respectively.

Although there were slightly more 'major significant' protocol deviations for patients in the FKB327 treatment arm compared to Humira, there was no trend in the type of protocol deviations reported.

In addition, 129 patients (35%) and 120 patients (33%) in the FKB327 and Humira treatment arms, respectively, had at least one 'major' protocol deviation, the most common being visit out-of-widow and stratification error.

Baseline data

Demographics

Demographics are summarised in the table below. The treatment groups were well balanced with respect to the demographic characteristics.

Overall, mean age was 53.3 years (range 18 to 93 years) and was well matched in both the FKB327 and Humira treatment groups. The majority of patients were female (77.6%) and White (85.0%). Mean weight (73.46 kg overall) and height (163.30 cm overall) were also similar in both treatment groups.

Table 12 Summary of Demographics: Safety Analysis Set

	FKB327 N=366	Humira N=362	Total N=728
Age (years)			
n	366	362	728
Mean (SD)	53.0 (12.04)	53.6 (12.32)	53.3 (12.18)
Range	18, 85	21, 93	18, 93
Age (years), n (%)			
<65	302 (82.5)	299 (82.6)	601 (82.6)
≥65	64 (17.5)	63 (17.4)	127 (17.4)
Gender, n (%)			
Male	85 (23.2)	78 (21.5)	163 (22.4)
Female	281 (76.8)	284 (78.5)	565 (77.6)
Race, n (%)			
American Indian or Alaska Native	1 (0.3)	1 (0.3)	2 (0.3)
Asian	1 (0.3)	1 (0.3)	2 (0.3)
Black or African American	2 (0.5)	4 (1.1)	6 (0.8)
White	311 (85.0)	308 (85.1)	619 (85.0)
Other	51 (13.9)	48 (13.3)	99 (13.6)
Height (cm)			
n	366	362	728
Mean (SD)	163.591 (9.7184)	162.999 (8.8645)	163.297 (9.3019)
Range	141.00, 193.00	144.00, 192.00	141.00, 193.00
Weight (kg)[a]			
n	366	362	728
Mean (SD)	73.337 (15.9765)	73.590 (15.6127)	73.463 (15.7863)
Range	39.90, 118.60	40.50, 116.20	39.90, 118.60

N=number of patients in the Safety Analysis Set; n=total number of patients with observation; SD=standard deviation.
a Weight at Screening.
Percentages based on the number of patients in the Safety Analysis Set with data.

Baseline characteristics

Baseline characteristics are summarised in the table below. Treatment groups were well matched for most baseline RA characteristics, including those variables in the ACR Core Set and Baseline DAS28. The majority of patients were positive (76.4%) for rheumatoid factor, mean serum MMP-3 concentration was 76.9 ng/mL (range 4 to 753 ng/mL), mean CRP 25.8 mg/L (range 1 to 230 mg/L), mean ESR 40.0 mm/hr (range 2 to 110 mm/hr), mean TJC (68 joint count) 26.1 joints (range 0 to 68 joints), mean SJC (66 joint count) 16.1 joints (range 0 to 66 joints), mean TJC (28 joint count) 15.8 joints (range 0 to 28 joints), mean SJC (28 joint count) 11.7 joints (range 0 to 28 joints), mean Patient's assessment of disease activity VAS 68.1 (range 0 to 100), mean Physician's assessment of disease activity VAS 67.3 (range -1 to 99), mean HAQ-DI 1.8 (range 0 to 3), mean DAS28-CRP 6.1 (range 4 to 8) and mean DAS28-ESR 6.5 (range 3 to 9).

Table 13 Summary of Baseline Patient Characteristics – RA Disease Status: Safety Analysis Set

	FKB327 N=366	Humira N=362	Total N=728
Rheumatoid factor status, n (%)			
Positive	277 (75.9)	277 (76.9)	554 (76.4)
Negative	88 (24.2)	83 (23.1)	171 (23.6)
Missing (n)	1	2	3
Serum MMP-3 concentration (ng/mL)			
n	361	358	719
Mean (SD)	73.4 (78.54)	80.5 (95.35)	76.9 (87.33)
Range	5, 687	4, 753	4, 753
Anti-CCP antibody concentration (units)			
n	287	287	574
Mean (SD)	1907.9 (3375.46)	1651.2 (2032.77)	1779.6 (2786.74)
Range	18, 41728	22, 13888	18, 41728
CRP level (mg/L)			
n	365	362	727
Mean (SD)	25.0 (26.66)	26.6 (28.43)	25.8 (27.55)
Range	1, 193	1, 230	1, 230
ESR (mm/hr)			
n	364	359	723
Mean (SD)	38.8 (19.20)	41.2 (20.66)	40.0 (19.96)
Range	2, 98	4, 110	2, 110
Tender joint count (68 joint count)			
n	365	362	727
Mean (SD)	26.2 (14.45)	25.9 (14.47)	26.1 (14.45)
Range	0, 68	6, 68	0, 68
Swollen joint count (66 joint count)			
n	365	362	727
Mean (SD)	16.2 (9.10)	16.0 (8.95)	16.1 (9.02)
Range	0, 66	0, 58	0, 66
Tender joint count (28 joint count)			
n	365	362	727
Mean (SD)	15.9 (6.95)	15.6 (6.58)	15.8 (6.77)
Range	0, 28	1, 28	0, 28
Swollen joint count (28 joint count)			
n	365	362	727
Mean (SD)	11.8 (5.38)	11.6 (5.04)	11.7 (5.21)
Range	0, 28	2, 28	0, 28
Patient's assessment of disease activity			
n	365	362	727
Mean (SD)	68.0 (17.93)	68.2 (18.15)	68.1 (18.03)
Range	7, 100	0, 100	0, 100

	FKB327 N=366	Humira N=362	Total N=728
Physician's assessment of disease activity			
n	364	362	726
Mean (SD)	68.4 (14.56)	66.2 (15.43)	67.3 (15.03)
Range	30, 99	-1, 99	-1, 99
Patient's assessment of pain			
n	365	362	727
Mean (SD)	66.7 (18.68)	67.9 (18.59)	67.3 (18.63)
Range	8, 100	1, 100	1, 100
Health Assessment Questionnaire			
n	365	362	727
Mean (SD)	1.8 (0.54)	1.8 (0.54)	1.8 (0.54)
Range	0, 3	0, 3	0, 3
DAS28-CRP			
n	364	362	726
Mean (SD)	6.1 (0.91)	6.1 (0.85)	6.1 (0.88)
Range	3, 9	4, 8	3, 9
DAS28-ESR			
n	363	359	722
Mean (SD)	6.5 (0.94)	6.6 (0.90)	6.5 (0.92)
Range	4, 9	4, 9	4, 9

CCP=cyclic citrullinated peptide; CRP=C-reactive protein; DAS=disease activity score; ESR=erythrocyte sedimentation rate; MMP-3=matrix metalloproteinase-3; N= number of patients in the Safety Analysis Set; n=total number of patients with observation; RA=rheumatoid arthritis; SD=standard deviation.
Percentages based on the number of patients in the Safety Analysis Set with data.
The rheumatoid factor values are categorised as 'negative' if <12 kU/l and 'positive' if ≥12 kU/l.

Prior anti-rheumatic drugs

Prior anti-rheumatic drugs for RA are summarised in the tables below. Prior anti-rheumatic drugs for RA were classified as those used and discontinued at least once prior to Screening in this study. Overall, approximately two-thirds of patients had received at least 1 DMARD for RA prior to study entry and the FKB327 and Humira treatment groups were well matched with respect to prior DMARD use for RA. The most commonly used DMARDs were MTX (43.0%), sulfasalazine (16.8%) and leflunomide (16.6%). It should be noted that the MTX dose was adjusted prior to study start according to the protocol and patients were required to be on a stable dose for a minimum of 8 weeks prior to Screening.

Fewer patients overall had received a prior biologic treatment for RA (18.1%), with a similar proportion of patients in the FKB327 (17.8%) and Humira (18.5%) treatment groups having received at least 1 prior biologic treatment. The most commonly used biologic treatment was abatacept (4.0%).

Only 6.7% of patients overall had received a prior anti-TNF treatment for RA, with a similar proportion of patients in the FKB327 and Humira treatment groups having received 1 prior anti-TNF. The most commonly used anti-TNF was etanercept (2.7%).

Per protocol, none had previously received adalimumab.

Table 14 Summary of Most Common Prior DMARDs for RA (Reported for ≥3% of Patients): Safety Analysis Set

	FKB327 N=366 n (%)	Humira N=362 n (%)	Total N=728 n (%)
Number of prior DMARDs per patient			
0	130 (35.5)	133 (36.7)	263 (36.1)
1	80 (21.9)	74 (20.4)	154 (21.2)
2	50 (13.7)	59 (16.3)	109 (15.0)
≥3	106 (29.0)	96 (26.5)	202 (27.7)
Number of patients with at least 1 prior DMARD for RA	236 (64.5)	229 (63.3)	465 (63.9)
Methotrexate[a]	156 (42.6)	157 (43.4)	313 (43.0)
Sulfasalazine	63 (17.2)	59 (16.3)	122 (16.8)
Leflunomide	67 (18.3)	54 (14.9)	121 (16.6)
Hydroxychloroquine	28 (7.7)	44 (12.2)	72 (9.9)
Abatacept	17 (4.6)	12 (3.3)	29 (4.0)

DMARD=disease modifying anti-rheumatic drug; N= number of patients in the Safety Analysis Set; MTX=methotrexate; n=total number of patients with observation; RA=rheumatoid arthritis; WHO-DD=World Health Organization-Drug Dictionary.
a Prior medications were defined as medications that started and ended before Screening; therefore, the protocol-required MTX dosing the study is not captured here as dosing continued throughout the study.
Both biologic and non-biologic prior DMARDs included.
Prior DMARDs defined as DMARDs taken prior to Screening.
Percentages based on the total number of patients in the Safety Analysis Set.
Medications were coded using WHO-DD Version June 2014.

Table 15 Summary of Most Common Prior Biologic Treatment for RA (Reported for ≥2% of Patients): Safety Analysis Set

	FKB327 N=366 n (%)	Humira N=362 n (%)	Total N=728 n (%)
Number of patients with at least 1 prior biologic treatment for RA	65 (17.8)	67 (18.5)	132 (18.1)
Abatacept	17 (4.6)	12 (3.3)	29 (4.0)
Etanercept	8 (2.2)	12 (3.3)	20 (2.7)
Infliximab	9 (2.5)	9 (2.5)	18 (2.5)
Tocilizumab	7 (1.9)	11 (3.0)	18 (2.5)

RA=rheumatoid arthritis; N= number of patients in the Safety Analysis Set; n=total number of patients with observation; WHO-DD=World Health Organization-Drug Dictionary.
Prior biologic treatments defined as those taken prior to Screening.
Percentages based on the total number of patients in the Safety Analysis Set.
Medications were coded using WHO-DD Version June 2014.

Table 16 Summary of Prior Anti-TNF Treatment for RA: Safety Analysis Set

	FKB327 N=366 n (%)	Humira N=362 n (%)	Total N=728 n (%)
Number of patients with at least 1 prior anti-TNF treatment for RA	22 (6.0)	27 (7.5)	49 (6.7)
Etanercept	8 (2.2)	12 (3.3)	20 (2.7)
Infliximab	9 (2.5)	9 (2.5)	18 (2.5)
Golimumab	2 (0.5)	3 (0.8)	5 (0.7)
Certolizumab	1 (0.3)	1 (0.3)	2 (0.3)
Certolizumab pegol	2 (0.5)	0	2 (0.3)
TNF-α inhibitors	0	2 (0.6)	2 (0.3)

N=number of patients in the Safety Analysis Set; n=total number of patients with observation; RA=rheumatoid arthritis; TNF=tumour necrosis factor; WHO-DD=World Health Organization-Drug Dictionary.
Prior anti-TNFs defined as those taken prior to Screening.
Percentages based on the total number of patients in the Safety Analysis Set.
Medications were coded using WHO-DD Version June 2014.

Concomitant Medication for Rheumatoid Arthritis (RA)

Concomitant oral steroids and NSAIDs and concomitant MTX are summarised in the table below. Again, the FKB327 and Humira treatment groups were well matched with respect to concomitant, stable, background treatment for RA. The average concomitant MTX dose was 15.8 mg/week in both treatment groups (range 4.26 to 25.00 mg/week) with the majority of patients receiving their MTX dose orally. Overall, 442 patients (60.7%) were receiving at least 1 concomitant oral steroid for RA during the study, 424 patients (58.2%) were receiving at least 1 concomitant NSAID for RA during the study and 286 patients (39.3%) were receiving both concomitant oral steroids and NSAIDs during the study.

Table 17 Summary of Concomitant Use of MTX, Oral Steroids and NSAIDs for RA: Safety Analysis Set

	FKB327 N=366	Humira N=362	Total N=728
Average dose of concomitant MTX (mg/week)			
n	366	362	728
Mean (SD)	15.762 (5.0071)	15.802 (4.6373)	15.782 (4.8235)
Range	4.26, 25.00	4.40, 25.00	4.26, 25.00
Route of concomitant MTX (mg/week) n (%)			
Oral	283 (76.7)	290 (79.9)	573 (78.3)
Subcutaneous	65 (17.6)	55 (15.2)	120 (16.4)
Other	21 (5.7)	18 (5.0)	39 (5.3)
Number of patients with at least 1 concomitant oral steroid for RA, n (%)	219 (59.8)	223 (61.6)	442 (60.7)
Number of patients with at least 1 NSAID for RA, n (%)	212 (57.9)	212 (58.6)	424 (58.2)
Number of patients with at least 1 concomitant oral steroid and at least 1 NSAID for RA	137 (37.4)	149 (41.2)	286 (39.3)

MTX=methotrexate; N=number of patients in the Safety Analysis Set; n=total number of patients with observation; NSAID=non-steroidal anti-inflammatory drug; RA=rheumatoid arthritis; SD=standard deviation.
Concomitant oral steroids and NSAIDs defined as those taken on or at any time after Screening.
Percentages based on the total number of patients in the Safety Analysis Set.

Concomitant oral steroids for RA are summarised in the table below. A similar proportion of patients in the FKB327 and Humira treatment groups was receiving concomitant oral steroids for RA. The most common concomitant oral steroids for RA were methylprednisolone and prednisone and were taken by similar proportions of patients in the FKB327 and Humira treatment groups.

More patients in Europe (58.8%) and the Rest of World (69.5%) received concomitant oral steroids for RA compared to patients in North America (29.4%). The most common concomitant oral steroid used in Europe was methylprednisolone whereas the most common concomitant oral steroid used in North America and the Rest of World was prednisone. The average concomitant prednisone equivalent dose was 46.62 mg/week overall (range: 2.0 to 140.0 mg/week) and was similar in the FKB327 and Humira treatment groups.

Table 18 Summary of Concomitant Oral Steroids and Glucocorticoids for RA: Safety Analysis Set

Preferred Term	FKB327 N=366 n (%)	Humira N=362 n (%)	Total N=728 n (%)
Number of patients with at least 1 concomitant oral steroid or glucocorticoid for RA	219 (59.8)	223 (61.6)	442 (60.7)
Methylprednisolone	102 (27.9)	110 (30.4)	212 (29.1)
Prednisone	81 (22.1)	83 (22.9)	164 (22.5)
Prednisolone	29 (7.9)	24 (6.6)	53 (7.3)
Deflazacort	7 (1.9)	6 (1.7)	13 (1.8)
Methylprednisolone sodium succinate	1 (0.3)	1 (0.3)	2 (0.3)
Cortisone acetate	0	1 (0.3)	1 (0.1)
Dexamethasone sodium phosphate	1 (0.3)	0	1 (0.1)

N=number of patients in the Safety Analysis Set; n=total number of patients with observation; RA=rheumatoid arthritis; WHO-DD=World Health Organization-Drug Dictionary.
Concomitant oral steroids and glucocorticoids defined as those taken on or at any time after Screening.
Percentages based on the total number of patients in the Safety Analysis Set.
Medications coded using WHO-DD Version June 2014.
Conversion factors from prednisone to other glucocorticoids were extracted from the British National Formulary.

Concomitant NSAIDs for RA are summarised in the table below. A similar proportion of patients in the FKB327 and Humira treatment groups were receiving concomitant NSAIDs for RA. The most common concomitant NSAIDs for RA were meloxicam and diclofenac, which were taken by a similar proportion of patients in the FKB327 and Humira treatment groups.

As with concomitant oral steroids, more patients in Europe (58.1%) and the Rest of World (64.0%) received concomitant NSAIDs for RA compared to patients in North America (34.1%). The most common concomitant NSAIDs used in Europe and North America was meloxicam and in the Rest of World were meloxicam and celecoxib.

Table 19 Summary of Most Common Concomitant NSAIDs for RA (Reported for ≥3% of Patients Overall): Safety Analysis Set

Preferred Term	FKB327 N=366 n (%)	Humira N=362 n (%)	Total N=728 n (%)
Number of patients with at least 1 concomitant NSAID for RA	212 (57.9)	212 (58.6)	424 (58.2)
Meloxicam	58 (15.8)	47 (13.0)	105 (14.4)
Diclofenac	36 (9.8)	32 (8.8)	68 (9.3)
Celecoxib	28 (7.7)	25 (6.9)	53 (7.3)
Nimesulide	19 (5.2)	30 (8.3)	49 (6.7)
Diclofenac sodium	17 (4.6)	19 (5.2)	36 (4.9)
Ketoprofen	15 (4.1)	10 (2.8)	25 (3.4)
Ibuprofen	9 (2.5)	15 (4.1)	24 (3.3)

N=number of patients in the Safety Analysis Set; n=total number of patients with observation; NSAID=non-steroidal anti-inflammatory drug; RA=rheumatoid arthritis; WHO-DD=World Health Organization-Drug Dictionary.
Concomitant NSAIDs defined as those taken on or at any time after Screening.
Percentages based on the total number of patients in the Safety Analysis Set.
Medications coded using WHO-DD Version June 2014.

Numbers analysed

Analysis sets are summarised in the table below. Overall, 1 patient (0.3%) in each of the FKB327 and Humira treatment groups was excluded from the Safety Analysis Set because they did not receive a dose of study drug.

In total, 9 patients (1.2%) were excluded from the FAS, either because they did not receive study drug or because they did not have a primary efficacy measurement after the first study drug dose). Overall, 91 patients (12.5%) were excluded from the PPAS, with the main reasons for exclusion being missed visit, missed/invalid efficacy procedure and violation of efficacy inclusion/exclusion criterion (classified in a blinded fashion as a 'major significant' protocol deviation). In total, 8 patients (1.1%) were excluded from the PKAS because they did not receive a dose of study drug or did not have a serum adalimumab concentration measurement after dosing.

Table 20 Summary of Analysis Sets: All Randomised Patients

	FKB327 n (%)	Humira n (%)	Total n (%)
Number of patients randomised	367 (100.0)	363 (100.0)	730 (100.0)
Safety Analysis Set			
Number of patients included	366 (99.7)	362 (99.7)	728 (99.7)
Number of patients excluded	1 (0.3)	1 (0.3)	2 (0.3)
Reasons for exclusion			
Did not dose IMP	1 (0.3)	1 (0.3)	2 (0.3)
Full Analysis Set			
Number of patients included	363 (98.9)	358 (98.6)	721 (98.8)
Number of patients excluded	4 (1.1)	5 (1.4)	9 (1.2)
Reasons for exclusion			
Did not dose IMP	1 (0.3)	1 (0.3)	2 (0.3)
No primary efficacy measurement after first study drug dose	3 (0.8)	4 (1.1)	7 (1.0)
PP Analysis Set			
Number of patients included	314 (85.6)	325 (89.5)	639 (87.5)
Number of patients excluded	53 (14.4)	38 (10.5)	91 (12.5)
Reasons for exclusion			
Did not meet criteria for Full Analysis Set	1 (0.3)	1 (0.3)	2 (0.3)
Inadequate IMP dosing	3 (0.8)	1 (0.3)	4 (0.5)
Incorrect MTX dosing	5 (1.4)	4 (1.1)	9 (1.2)
Missed visit	24 (6.5)	21 (5.8)	45 (6.2)
Missed/invalid efficacy procedure	20 (5.4)	13 (3.6)	33 (4.5)
Prohibited concomitant medication	4 (1.1)	3 (0.8)	7 (1.0)
Violated efficacy inclusion / exclusion criterion	11 (3.0)	8 (2.2)	19 (2.6)
Violated efficacy or safety inclusion / exclusion criterion	1 (0.3)	0	1 (0.1)
Violated safety inclusion / exclusion criterion	1 (0.3)	0	1 (0.1)
Visit OOW	5 (1.4)	3 (0.8)	8 (1.1)
PK Analysis Set			
Number of patients included	364 (99.2)	358 (98.6)	722 (98.9)
Number of patients excluded	3 (0.8)	5 (1.4)	8 (1.1)
Reasons for exclusion			
Did not dose IMP	1 (0.3)	1 (0.3)	2 (0.3)
No serum adalimumab concentration measured after taking IMP	2 (0.5)	4 (1.1)	6 (0.8)

IMP=investigational medicinal product; MTX=methotrexate; n=total number of patients with observation; PK=pharmacokinetic; PP=per-protocol; OOW=out-of-window.
Percentages based on the number of randomised patients.
Patients may be counted in more than 1 reason for exclusion category.

Outcomes and estimation

Primary efficacy evaluation

The ACR20 response rate at Week 24 is summarised in the table below. For the root cause imputation (FAS), as the 95% CI was within the pre-defined limits of ±13% (CHMP), equivalence was concluded between FKB327 and Humira. In total, 270 patients (74.4%) in the FKB327 treatment group achieved an ACR20 response at Week 24, compared to 271 patients (75.7%) in the Humira treatment group. The 95% CI for FKB327-Humira was -7.6, 5.0. Equivalence for ACR20 was also indicated between FKB327 and Humira for the non-responder imputation (FAS), where the 90% CI was contained within the pre-defined limits of -12% and 15% (FDA). For this analysis, 263 patients (72.5%) in the FKB327 treatment group achieved an ACR20 response at Week 24 compared to 266 patients (74.3%) in the Humira treatment group. The 90% CI for FKB327-Humira was -7.3, 3.6. For the PPAS, the CI for FKB327-Humira was also contained within the pre-defined limits. Overall, efficacy equivalence was demonstrated.

The results from the sensitivity analysis of the ACR20 response rate using a mixture of non-responder imputation and multiple imputation support the conclusions from the primary efficacy analysis. The ACR20 response rate for FKB327 and Humira was 75.7% (95% CI: 71.1, 80.3) and 78.4% (95%CI: 74.0, 82.7), respectively. The estimated FKB327-Humira difference was -2.6%, where the 90% CI (-7.9, 2.6) was contained within the pre-defined limits of -12% and 15% (FDA) and the 95%CI (-9.0, 3.7) was contained within the pre-defined limits of ±13% (CHMP).

The results from tipping-point analysis of the ACR20 response rate in the FAS using both root cause and non-responder imputations indicate that even severe deviations from the missing at random assumption underlying the sensitivity analysis described in the previous paragraph do not lead to a change in the interpretation of the results. In fact, even shifting all imputed responders to non-responders in the FKB327 treatment group and leaving the imputed values untouched in the Humira group (i.e., shift values of 1.0 and 0.0 for FKB327 and Humira, respectively) leads to an estimated FKB327-Humira difference of -6.18%, where the 90%CI (-11.52, -0.83) was contained within pre-defined limits of -12% and 15% (FDA) and 95%CI (-12.54, 0.19) was contained with the pre-defined limits of ±13% (CHMP). These findings provide further robustness to the primary analysis results and point to the conclusion for equivalence between FKB327 and Humira.

Table 21 Analysis of the ACR20 Response Rate at Week 24: Full Analysis Set and Per-Protocol Analysis Set

	FKB327	Humira	Total
FAS (root cause imputation)[a], N	363	358	721
Number of patients with an evaluable ACR20 response at Week 24	363	358	721
Patients achieving ACR20 response at Week 24			
n (%)[b]	270 (74.4)	271 (75.7)	541 (75.0)
95% CI[c]	69.6, 78.8	70.9, 80.1	71.7, 78.2
FKB327 – Humira[d]		-1.3	
95% CI		-7.6, 5.0	
95% CI contained in ±13% equivalence margin?		Yes	
FAS (non-responder imputation)[e], N	363	358	721
Number of patients with an evaluable ACR20 response at Week 24	363	358	721
Patients achieving ACR20 response at Week 24			
n (%)[b]	263 (72.5)	266 (74.3)	529 (73.4)
95% CI[c]	67.5, 77.0	69.4, 78.8	70.0, 76.6
FKB327 – Humira[d]		-1.8	
90% CI		-7.3, 3.6	
90% CI contained in -12% to +15% equivalence margin?		Yes	
PPAS, N	314	325	639
Number of patients with an evaluable ACR20 response at Week 24	314	325	639
Patients achieving ACR20 response at Week 24			
n (%)[f]	249 (79.3)	259 (79.7)	508 (79.5)
95% CI[c]	74.4, 83.6	74.9, 83.9	76.2, 82.6
FKB327 – Humira[d]		-0.4	
90% CI		-5.6, 4.9	
90% CI contained in -12% to +15% equivalence margin?		Yes	
95% CI		-6.7, 5.9	
95% CI contained in +/- 13% equivalence margin?		Yes	

ACR=American College of Rheumatology; CI=confidence interval; FAS=Full Analysis Set; N=number of patients in Full Analysis Set; n=total number of patients with observation; PPAS=Per-protocol Analysis Set; RA=rheumatoid arthritis.
a Missing responses for the ACR and responses for patients who discontinued the treatment prior to Week 24 were imputed as follows: if the patient withdrew due to lack of efficacy, withdrawal of consent, an adverse event (non-infection), medical reason (non-infection) or if the patient had taken a prohibited treatment for RA and had been withdrawn from study treatment, they were regarded as 'non-responders'; for all other patients with a missing ACR response at Week 24, last observation carried forward was used on the ACR to determine whether they were 'responders' or 'non-responders'.
b Percentages based on the number of patients with an evaluable ACR20 result at Week 24, after imputation.
c 95% CI calculated using the Clopper-Pearson method.
d CIs calculated using a normal approximation with no continuity correction.
e Missing Week 24 responses for the ACR and responses for patients who discontinued the treatment prior to Week 24 were imputed using non-responder imputation.
f Percentages based on the number of patients with an evaluable ACR20 result at Week 24.
The ACR20 response rate is defined as a 20% improvement in tender and swollen joint counts and at least 3 out of 5 other indicators.

Secondary efficacy variables

Disease Activity Score (DAS)28-C-Reactive Protein (CRP)

The DAS 28-CRP LSM and LSM change from baseline is summarised for the FAS in the figures below. For both the FAS and PPAS, the LSM DAS28-CRP were similar in both the FKB327 and Humira treatment groups at all visits and the 95% CI for the difference at Week 24 was within the pre-defined limits of -0.6 to +0.6 confirming equivalence. For the FAS, at Week 24, the LSM was 3.43 and 3.42 for the FKB327 and Humira treatment groups, respectively, and the 95% CI for FKB327-Humira was -0.17, 0.18. For the

PPAS, at Week 24, the LSM was 3.38 and 3.41 for the FKB327 and Humira treatment groups, respectively, and the 95% CI for FKB327-Humira was -0.21, 0.15.

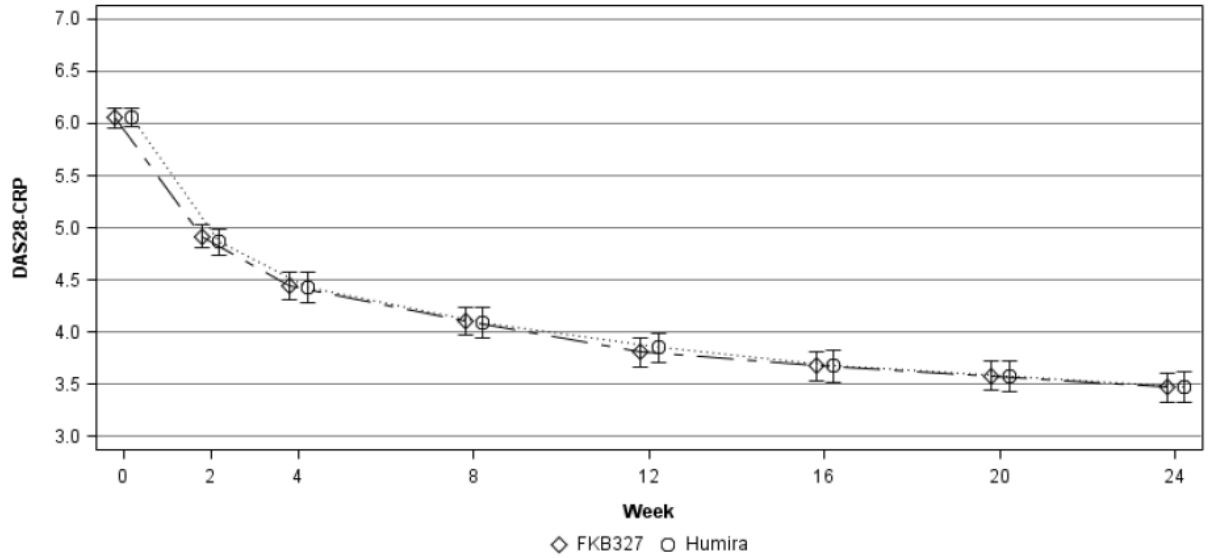


Figure 5 Mean and 95% CI DAS28-CRP (FAS). DAS28-CRP, Disease Activity Score 28-C reactive protein; CI, confidence interval.

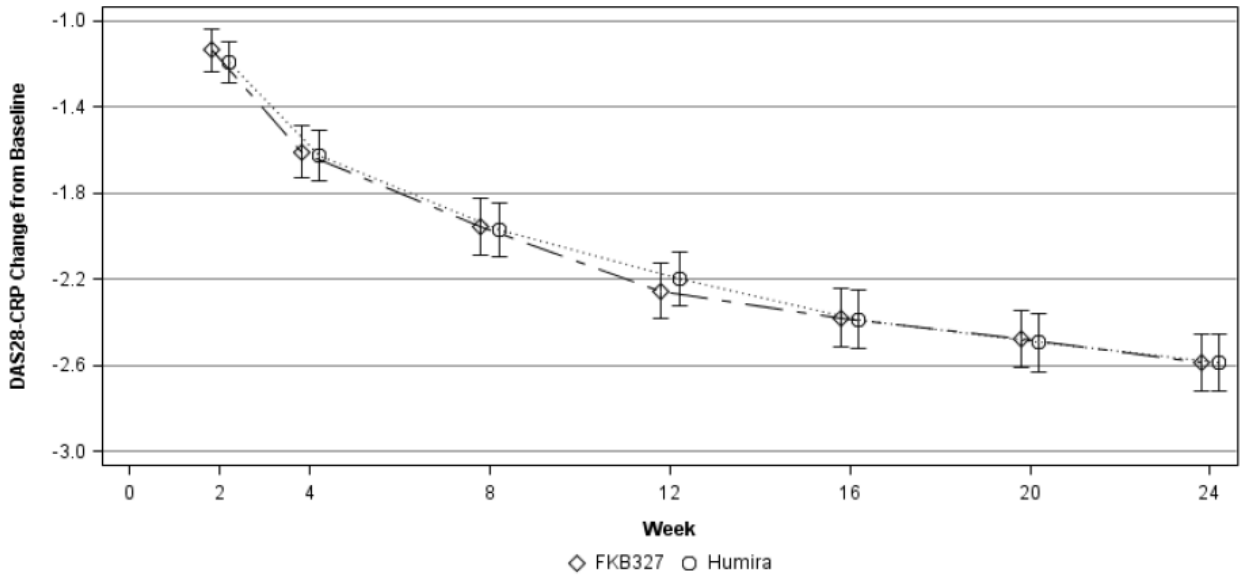


Figure 6 Mean change from baseline and 95% CI DAS28-CRP (FAS). DAS28-CRP, Disease Activity Score 28-C reactive protein; CI, confidence interval.

ACR20 response rate

The ACR20 response rate by time is presented in the figure below. The proportion of patients considered to be responders was similar in the FKB327 and Humira treatment groups at all visits from Week 4 onwards. Prior to Week 4, the number of responders in the FKB327 treatment group was slightly higher (37.3%) than in the Humira group (31.0%). By Week 24, the proportion of responders had increased in both treatment groups (77.1% and 79.3% in the FKB327 and Humira treatment groups, respectively).

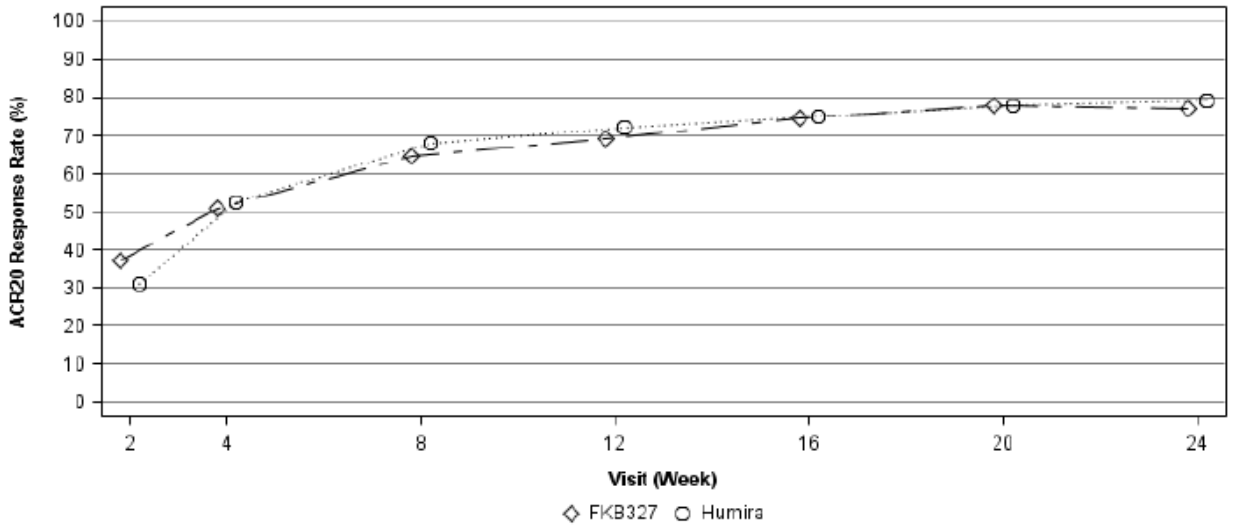


Figure 7 ACR20 Response Rate, by Time: Full Analysis Set. ACR=American College of Rheumatology.

The ACR20 response rate is defined as a 20% improvement in tender and swollen joint counts and at least 3 out of 5 other indicators. Response rate calculated based on patients with an evaluable ACR20 at each given visit.

The ACR20 response rate at Week 24 was also analysed for the following sub-groups used as stratification factors: Prior Biologic Treatment for RA (yes/no), Screening DAS28-CRP (≤5.1/>5.1) and Geographical Region (North America/Europe/Rest of World). The subgroup analysis within use of prior biologics (yes/no), Screening DAS28-CRP and geographical region provided no evidence of heterogeneity of strata in terms of differential ACR20 response between the treatment groups.

ACR50 response rate

The ACR50 response rate is defined as a 50% improvement in tender and swollen joint counts and at least 3 out of 5 other indicators.Response rate calculated based on patients with an evaluable ACR50 at each given visit.

The ACR50 response rate is presented in the figure below. The proportion of responders was similar in the FKB327 and Humira treatment groups at all visits. By Week 24, 49.0% of patients in the FKB327 treatment group and 49.4% of patients in the Humira treatment group were responders.

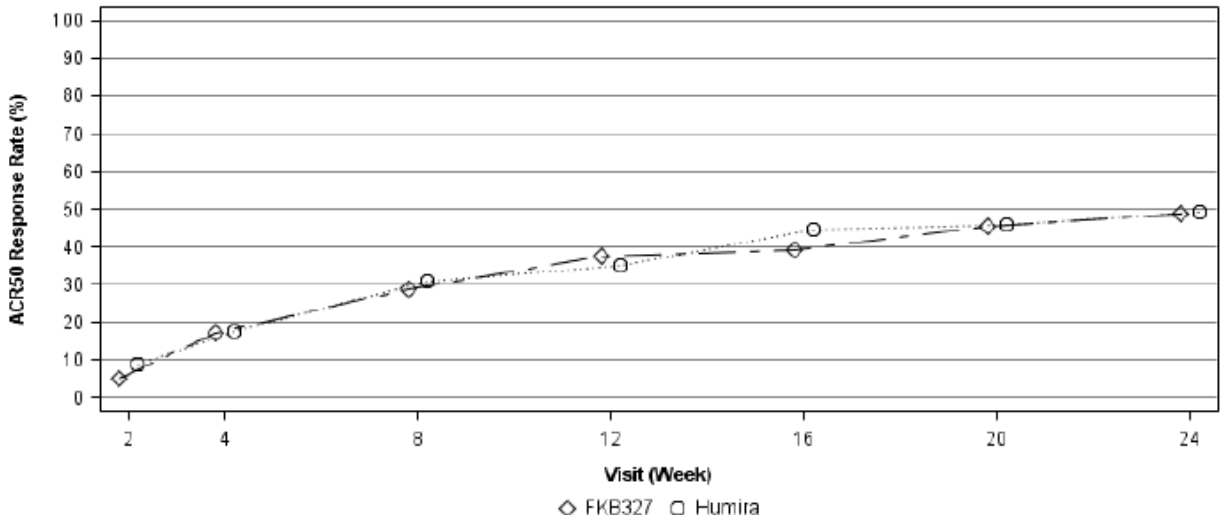


Figure 8 ACR50 Response Rate, by Time: Full Analysis Set. ACR=American College of Rheumatology.

ACR70 response rate

The ACR70 response rate is defined as a 70% improvement in tender and swollen joint counts and at least 3 out of 5 other indicators. Response rate calculated based on patients with an evaluable ACR70 at each given visit.The ACR70 response rate is presented in the figure below.

The proportion of responders was similar in the FKB327 and Humira treatment groups at all visits. By Week 24, 21.3% of patients in the FKB327 treatment group and 25.1% of patients in the Humira treatment group were responders.

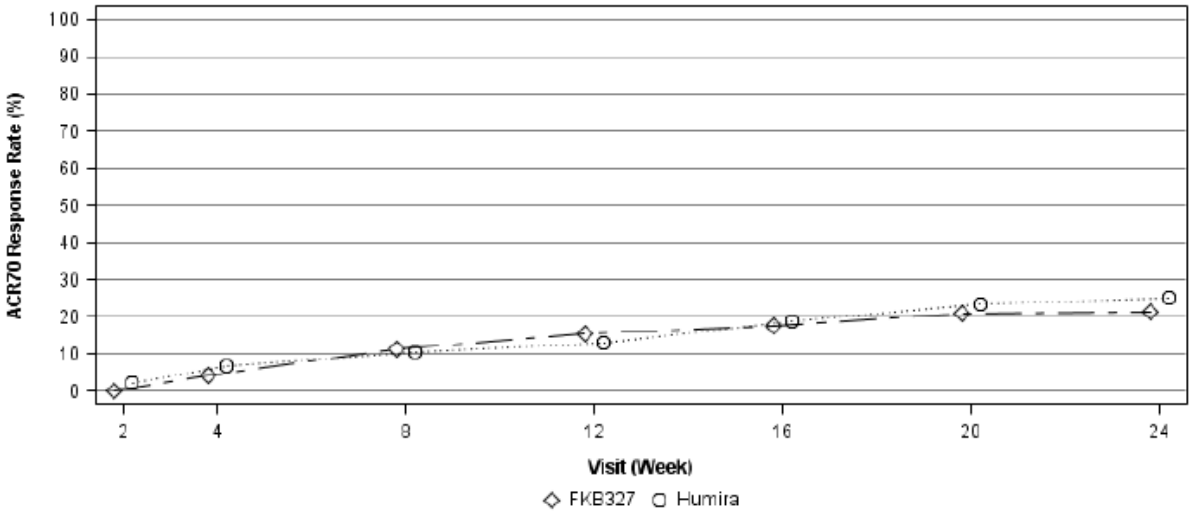


Figure 9 ACR70 Response Rate, by Time: Full Analysis Set. ACR=American College of Rheumatology.

C-reactive protein (CRP)

CRP values are summarised in the figure below. Mean (SD) CRP values were similar in both the FKB327 and Humira treatment groups at all time points and the mean (SD) changes from baseline were comparable between the treatment groups. The mean (SD) change from Baseline at Week 24 was -14.62

(26.540) and -14.34 (25.733) for the FKB327 and Humira treatment groups, respectively. CRP results fluctuated more than the results for the other efficacy parameters. This is to be expected given that CRP is a non-specific measure of inflammation and could be affected by concurrent medical conditions such as infections.

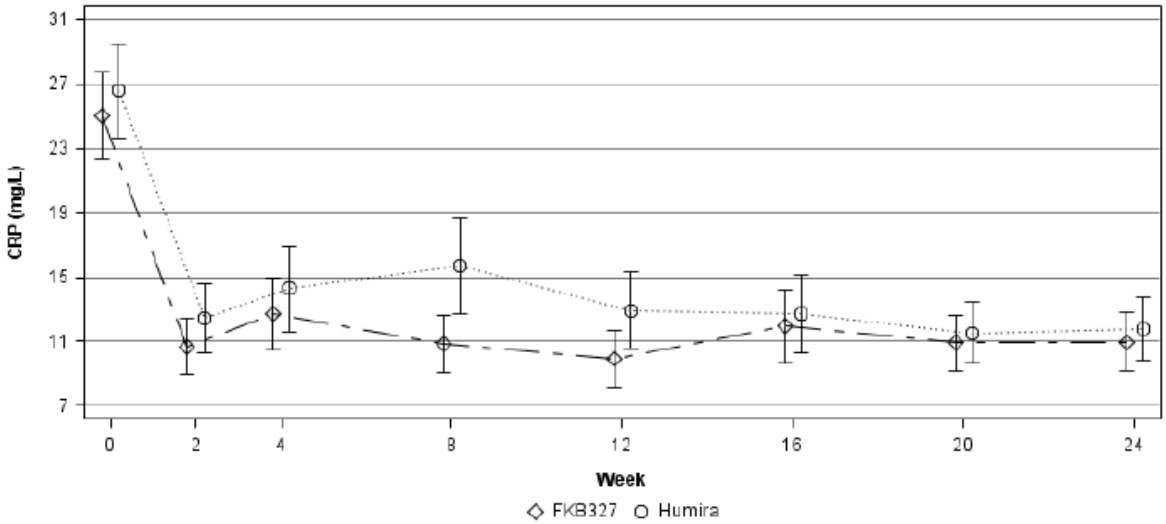


Figure 10 Mean (95% CI) CRP Values, by Time: Full Analysis Set. CI=confidence interval; CRP=C-reactive protein.

Health Assessment Questionnaire Disability Index (HAQ-DI)

HAQ-DI is summarised in the figure below. The mean (SD) values for the HAQ-DI decreased in both the FKB327 and Humira treatment groups throughout the study, with the largest decreases seen at Week 24 for both groups. The decreases in mean (SD) values were similar for both treatment groups at all time points. The mean (SD) change from Baseline at Week 24 was -0.55 (0.615) and -0.53 (0.594) for the FKB327 and Humira treatment groups, respectively. It should be noted that larger decreases in mean (SD) values were observed in the FKB327 treatment group to Week 8 compared with the Humira treatment group.

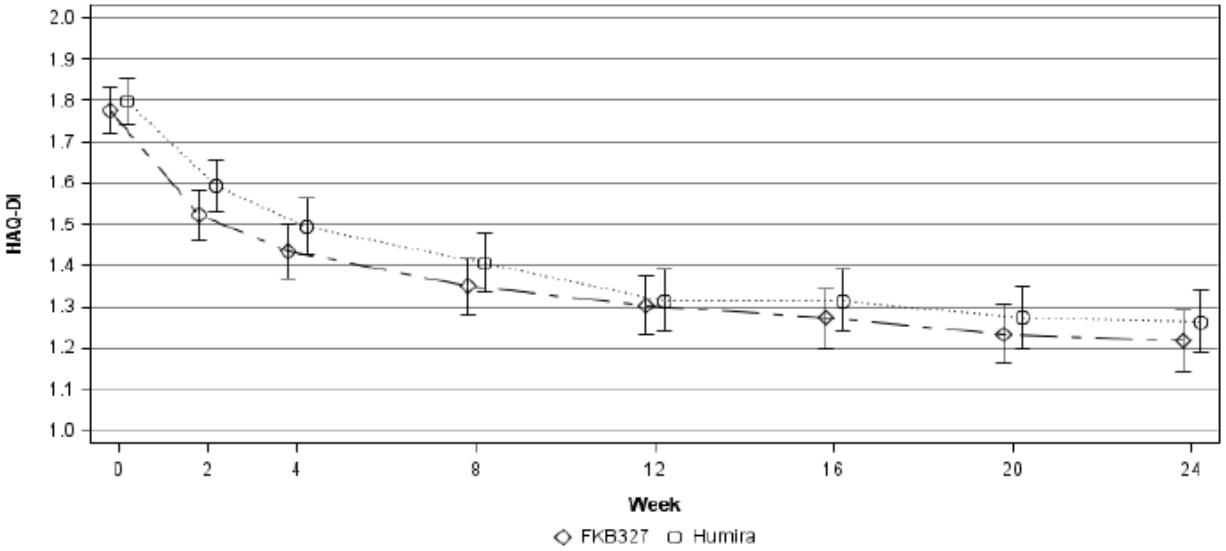


Figure 11 Mean (95% CI) HAQ-DI, by Time: Full Analysis Set. CI=confidence interval; HAQ-DI=Health Assessment Questionnaire Disability Index.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22 Summary of efficacy for trial FKB327-002

Title: A Randomised, Blinded, Active-Controlled Study to Compare FKB327 Efficacy and Safety with the Comparator Humira in Rheumatoid Arthritis Patients Inadequately Controlled on Methotrexate (ARABESC)			
Study identifier	NCT02260791 - 2014-000109-11		
Design	Refer to title. Multicenter study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24-26 weeks 4 weeks Long term extension FU study FKB327-003
Hypothesis	Equivalence		
Treatments groups	FKB327		Hulio (N=367)
	Humira		Humira (N=363)
Endpoints and definitions	Co-Primary endpoint	ACR20 FAS-RCI w24	ACR20 RR at w24 in FAS with root cause imputation
	Co-Primary endpoint	ACR20 FAS-NRI w24	ACR20 RR at w24 in FAS with non-responder imputation
	Co-Primary endpoint	ACR20 PPAS w24	ACR20 RR at w24 in PPAS
	Secondary endpoint	DAS28-CRP FAS	DAS28-CRP score at w24 in FAS

	Secondary endpoint	DAS28-CRP PPAS	DAS28-CRP score at w24 in PPAS
	Secondary endpoint	ACR20	ACR20 RR week 0 – week 24
	Secondary endpoint	ACR50	ACR50 RR week 0 – week 24
	Secondary endpoint	ACR70	ACR70 RR week 0 – week 24
	Secondary endpoint	CRP	C-Reactive protein
	Secondary endpoint	HAQ-DI	Health assessment questionnaire – disability index

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS)		
Descriptive statistics and estimate variability	Treatment group	FKB327	Humira
	Number of subject	363	358
	ACR20 RCI w24 RR (%)	74.4	75.7
	95% CI	69.6,78.8	70.9,80.1
	ACR20 NRI w24 RR (%)	72.5	74.3
	95% CI	67.5,77.0	69.4,78.8
	DAS28-CRP w24 (LSM)	3.43	3.42
	95% CI	3.29,3.57	3.28,3.56
Analysis population and time point description	Per protocol analysis set (PPAS)		
Descriptive statistics and estimate variability	Treatment group	FKB327	Humira
	Number of subject	314	325
	ACR20 PPAS w24 RR (%)	79.3	79.7
	95% CI	74.4,83.6	74.9,83.9
	DAS28-CRP w24 (LSM)	3.38	3.41
	95% CI	3.23,3.53	3.27,3.55
Analysis population and time point description	Full analysis set (FAS)		

Descriptive statistics and estimate variability	Treatment group	<group descriptor>	<group descriptor>
	Number of subject	363	358
	ACR50 w24 RR (%)	49	49.4
	95% CI	43.6,54.4	44.0,54.9
	ACR70 w24 RR (%)	21.3	25.1
	95% CI	17.1,26.1	20.6,30.1
	CRP w24 (mean) SD	10.98 16.82	11.78 18.53
	HAQ-DI w24 (mean)	1.21	1.26
	SD	0.70	0.72
Effect estimate per comparison	Co-Primary endpoint ACR20 FAS-RCI w24 (CHMP endpoint)	Comparison groups	FKB327-Humira
		difference	-1.3
		95% CI	-7.6,5.0 (equivalence margin 95% CI +/- 13%)
	Co-Primary endpoint ACR20 FAS NRI w24 (FDA endpoint)	Comparison groups	FKB327-Humira
		difference	-1.8
		90% CI	-7.3,3.6 (equivalence margin 90% CI -12%,+15%)
	Co-Primary endpoint ACR20 PPAS w24 (CHMP endpoint)	Comparison groups	FKB327-Humira
		difference	-0.4
		90% CI	-5.6,4.9
		95% CI	-6.7,5.9 (equivalence margin 95% CI +/- 13%)
	Secondary endpoint DAS28-CRP FAS (CHMP endpoint)	Comparison groups	FKB327-Humira
		difference	0.01
		95% CI	-0.17,0.18 (equivalence margin 95% CI +/- 0.6)
	Secondary endpoint DAS28-CRP PPAS (CHMP endpoint)	Comparison groups	FKB327-Humira
		difference	-0.03
		95% CI	-0.21,0.15 (equivalence margin 95% CI +/- 0.6)
	Secondary endpoint CRP w24	Comparison groups	FKB327 * Humira
		Change from BL	-14.62 * -14.34
		range	-189.20,70.80 * -126.60,95.00

	Secondary endpoint HAQ-DI w24	Comparison groups	FKB327 * Humira

Clinical studies in special populations

No studies were undertaken in special or subpopulations

Supportive study

Study FKB327-003 was an Open-label Extension Study to Compare the Long term Efficacy, Safety, Immunogenicity and Pharmacokinetics of FKB327 and Humira in Patients with Rheumatoid Arthritis on Concomitant Methotrexate (ARABESC-OLE). It included RA patients that completed all 24 weeks of study procedures (including dosing) according to protocol FKB327-002, with a minimum of 9 doses of study drug received, and were continuing with stable concomitant MTX and folate, and in the investigator's opinion, had shown a clinical response to treatment during Study FKB327-002.

Patients received either FKB327 40 mg eow or Humira 40 mg eow from Week 0 to Week 28 (Period I) in an open fashion using PFS presentations of both FKB327 and Humira. From Week 30 onwards (Period II), all patients received FKB327 40 mg eow.

The study was designed to assess long term safety and efficacy of both adalimumab presentations up to 1 year of treatment (period I), including patients who switched formulations. Final efficacy data from period I are presented in the present application and support the long term efficacy of FKB327.

Maintenance of efficacy, based on ACR20 RR, ACR50 RR and ACR70 RR, was demonstrated for patients on continuous FKB327 or Humira treatment. Similar observations were done for the DAS28-CRP and HAQ-DI endpoints.

Maintenance of efficacy, based on ACR20 RR, ACR50 RR and ACR70 RR, was demonstrated in the patient groups that switched between adalimumab presentations. Similar observations were done for the DAS28-CRP and HAQ-DI endpoints.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Main equivalence study FKB327-002

Study FKB327-002 served to demonstrate equivalence between two adalimumab presentations, i.e. FKB327 and US-sourced Humira. This study was a phase 3 randomised, double blinded, parallel arm active-controlled study to compare FKB327 efficacy and safety with the comparator Humira in rheumatoid arthritis patients inadequately controlled on methotrexate, during which FKB327 or Humira was administered by multiple dosing every other week for 22 weeks in patients with active RA who were already taking MTX at a stable dose (10 to 25 mg/week) for a minimum of 8 weeks prior to screening but who required additional therapy to control their disease.

The trial was conducted in 12 countries. The most important contribution to patient enrolment was from the EU (38%) and Eastern Europe (31%), the rest of the world including North America, Peru and Chile. Four countries recruited the majority of patients (63%): Poland, Ukraine, Russia and Peru. Provided similar results are shown across geographical regions, this is acceptable in the context of a biosimilar application.

The CHMP had no concern about the amendments to the study protocol. Deviations were slightly more frequent (2-4%) in all categories (without specific pattern) in the FKB327 arm than in the Humira arm but this is not considered to have significant impact on the results.

The applicant requested scientific advice on its phase III clinical programme with both the CHMP and the FDA and has implemented the recommendations received from both agencies in its study programme.

The choice of the indication (rheumatoid arthritis) is in line with the CHMP guidance on similar biological products and was endorsed in CHMP Scientific Advice. Indeed, this clinical model was considered sufficiently sensitive to enable the detection of differences between the two products.

The RA population selected is considered appropriate for equivalence investigation purposes of adalimumab presentations (biosimilars).

Patients that had been previously treated with adalimumab were excluded from the study. The proposed blinding approach was considered adequate by the CHMP.

The primary efficacy endpoint of the study is the ACR20 response rate at week 24, and the main secondary endpoint is DAS28-CRP at week 24 of treatment, as favoured by the CHMP. The +/- 13% equivalence range on the PE was agreed upon by the CHMP (FDA preferred -12%/+15%), as was the +/- 0.6 equivalence range for the DAS28-CRP endpoint. In addition, analyses of the PE were performed on the FAS with different handling of missing data (both RCI and NRI) and on the PPAS, and were supplemented with a sensitivity analysis and a tipping point analysis.

Considering the results from study FKB327-001, the CHMP acknowledged that FKB327 is highly similar to both EU-Humira and US-Humira in physicochemical and biological properties. Hence, a single pivotal equivalence trial comparing the test and US-sourced reference product is considered adequate to support this biosimilar application.

Open label extension study FKB327-003

An extension trial was performed with re-randomisation in each treatment arm for an additional 28 weeks of treatment with either product, before all patients were switched to FKB327 for an additional 48 weeks of treatment.

Efficacy data and additional analyses

Main equivalence study FKB327-002

Treatment groups were well balanced for demographics and most baseline RA characteristics, and prior use of anti-rheumatic drugs. Only 6.7% had received prior anti-TNF therapy for RA, equally distributed over both treatment groups, and none had received prior adalimumab. Concomitant RA medications remained stable and comparable throughout the study. Overall, 728 patients were randomised with 366 patients being treated with FKB327 and 362 with US-Humira. About 10% of patients discontinued

treatment with the most frequent reasons being withdrawal of consent and occurrence of adverse events (about 3-4% each) in both treatment arms.

The PE ACR20 RR difference CI at week 24 was within the predefined +/- 13% equivalence range, both in the FAS (RCI for missing data) and PPAS: -1.3 (95% CI -7.6,5.0) and -0.4 (95% CI -6.7,5.9), respectively.

Similarly, the difference in DAS28-CRP values CI was within the predefined equivalence margins both in the FAS and the PPAS populations: 0.01 (95% CI -0.17,0.18) and -0.03 (95% CI -0.21,0.15), respectively, which was confirmed in a post-hoc sensitivity analysis.

There were no notable differences between both treatment groups in ACR20, ACR50 and ACR70 RR over the 24w treatment period.

Open label extension study FKB327-003 (period I completed data)

Maintenance of efficacy, based on ACR20 RR, ACR50 RR and ACR70 RR, was demonstrated for patients on continuous FKB327 or Humira treatment. Similar observations were done for the DAS28-CRP and HAQ-DI endpoints.

Maintenance of efficacy, based on ACR20 RR, ACR50 RR and ACR70 RR, was demonstrated in the patient groups that switched between adalimumab presentations. Similar observations were done for the DAS28-CRP and HAQ-DI endpoints.

2.5.4. Conclusions on the clinical efficacy

Considering the results from study FKB327-001, the CHMP acknowledged that FKB327 is highly similar to both EU-Humira and US-Humira in physicochemical and biological properties. Hence, a single pivotal equivalence trial comparing the test and US-sourced reference product is considered adequate to support this biosimilar application.

Equivalent efficacy is shown for US-Humira and FKB327 in the selected RA patient population up to one year of treatment.

2.6. Clinical safety

Comparative safety data between FKB327 and Humira were collected in RA patients in the pivotal Phase 3 studies (FKB327-002 and FKB327-003). Additional supportive safety data are provided from the Phase 1 studies in healthy subjects (FKB327-001 and FKB327-005).

Table 23 Summary of Clinical Studies with FKB327 Set

Protocol No./ Status	Study Design	Study Objectives (Related to Safety)	Study Drug and Dose	No. of Subjects/Patients Assigned to Treatment
FKB327-001/ Completed	Phase 1, randomized, double-blind, parallel group study in healthy male volunteers and healthy female volunteers of non-childbearing potential.	To compare the safety of FKB327 and EU-approved and US-licensed Humira after single doses, by SC injection in healthy volunteers. To assess tolerability after single doses of FKB327 and EU-approved and US-licensed Humira, by SC injection.	FKB327 (from vial), EU-approved Humira (from PFS) or US-licensed Humira (from PFS): single 40 mg SC injection.	FKB327: 60 EU-approved Humira: 60 US-licensed Humira: 60
FKB327-005/ Completed	Phase 1, randomized, open-label, parallel group, single SC dose study in healthy male and female subjects.	To compare the safety of FKB327 after a single SC dose delivered by vial, PFS and AI in healthy subjects.	FKB327: single 40 mg SC injection via vial/syringe, PFS or AI.	FKB327 vial/syringe: 66 FKB327 PFS: 63 FKB327 AI: 66
FKB327-002/ Completed	Phase 3, multi-center, randomized, double-blind, parallel arm, active-comparator, equivalence study in patients with active RA taking concomitant MTX.	To compare the safety profiles of FKB327 and Humira.	FKB327 (vial): 40 mg eow by injection. Humira (PFS) 40 mg eow by SC injection.	FKB327: 367 [treated=366] Humira: 363 [treated=362]
FKB327-003/ Completed	Phase 3. Period 1: open-label, randomized, comparative, multi-center, 2-arm extension in patients with RA taking concomitant MTX who continued from the preceding Study FKB327-002. Period 2: open-label, multi-center, single arm extension in which all patients received prolonged FKB327 treatment.	To compare the safety of long-term treatment with FKB327 and Humira in patients with RA. To evaluate safety in patients who were switched from Humira in the preceding FKB327-002 double-blind study to FKB327 in the FKB327-003 OLE study, and of patients who were switched from FKB327 to Humira, respectively. To evaluate safety in patients who were switched from FKB327 in the preceding FKB327-002 double-blind study to Humira in the FKB327-003 OLE study, and then switched back to FKB327 in the second part of the FKB327-003 OLE study (from Week 30; double switch).	FKB327 (PFS or AI): 40 mg eow SC by injection. Humira (PFS) 40 mg eow by SC injection.	FKB327: 324 Humira: 321

ADA=anti drug antibody; AI=auto injector; eow=every other week; EU=European Union; MTX=methotrexate; OLE=open label extension; PFS=pre filled syringe; RA=rheumatoid arthritis; SC=subcutaneous; US=United States.

Healthy Subjects

The Phase 1 study FKB327-001 (40mg, single dose) was meant to allow comparison of safety between FKB327 and Humira, and the healthy immunocompetent subjects allowed assessment of immunogenicity.

The Phase 1 study FKB327-005 (40mg, single dose) allowed comparison of tolerability between vial, prefilled syringe (PFS), and auto-injector (AI) presentations.

Studies in Rheumatoid Arthritis Patients

In the randomized double-blind Study FKB327-002, safety versus US-Humira was compared over a 24-week treatment period using the vial presentation. Patients could enter the OLE (Study FKB327-003) after study ending, and were thus re-randomized (2:1 to continuation of treatment versus switch to alternate treatment) and switched to PFS presentation. In Period II of the OLE (W30) all were switched to FKB327 compound and the majority received the AI presentation of the study compound. The PFS presentation of Humira was used in all clinical studies.

Patient exposure

Healthy Subjects

The patient assignment for the PhI FKB327-001 and FKB327-005 are shown in the table below.

Studies in Rheumatoid Arthritis Patients

Three presentations of FKB327 were used in the clinical program (while only Humira PFS was used): vials (FKB327-002), PFS (mainly FKB327-003 Period I) and the auto-injector (AI) (FKB327-003 Period II). In Period II, 65 patients in the United States (US) used the FKB327 PFS (pending regulatory approval of the AI in that country) whereas the other 507 patients used the FKB327 AI.

Patient disposition and exposure in Studies FKB327-002 and FKB327-003 are summarized in the figure and table below.

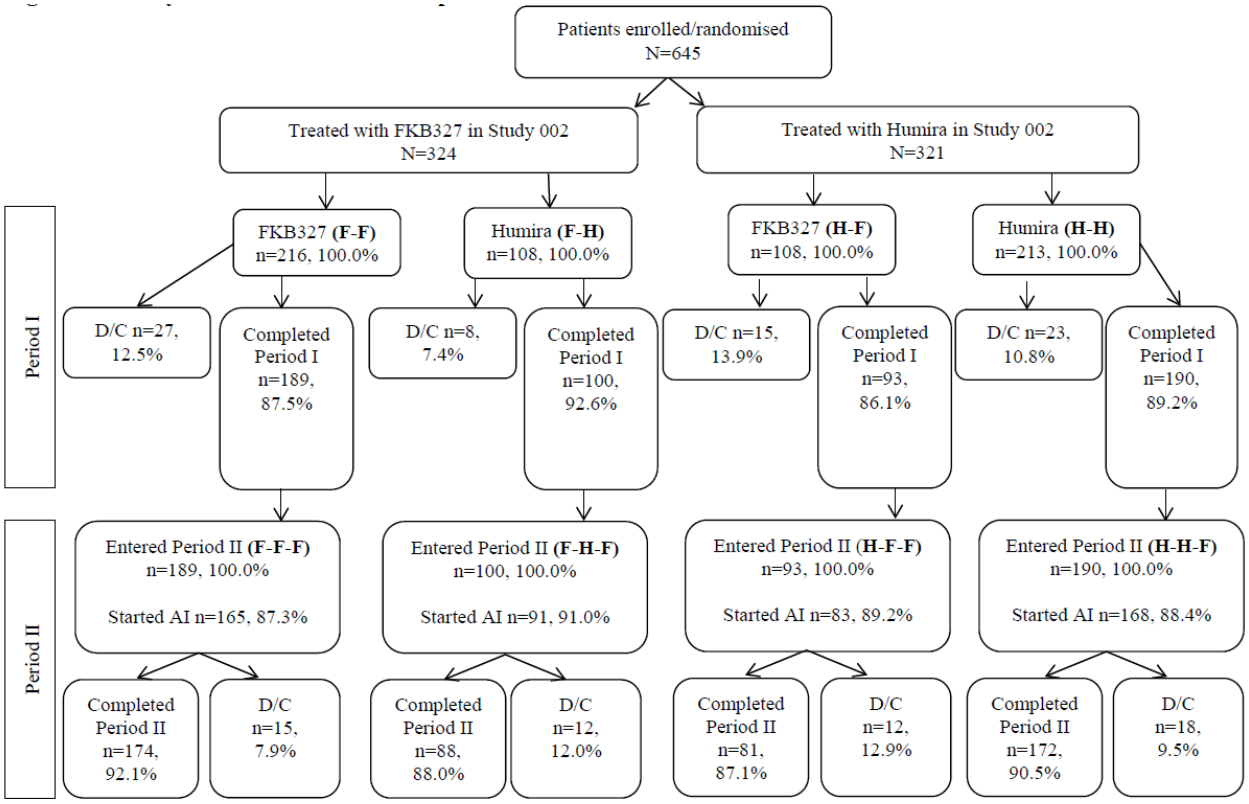


Figure 12 Study FKB327-003: Patient Disposition: All Enrolled Patients

In study FKB327-002, overall, more patients received delayed or interrupted dosing with FKB327. However, this imbalance is due to an imbalance of other reasons attributed to investigational medicinal product (IMP) shipment delay issues. There is no major issue for imbalance between FKB327 and Humira in study FKB327-002.

The mean duration of treatment per patient was 163.2 days for FKB327 and 162.1 days for Humira, giving a total overall exposure across patients of 163.52 patient-years for the FKB327 treatment group and

160.63 patient-years for the Humira treatment group. The number of patients dosed at each week was similar in the FKB327 and Humira treatment groups.

Table 24 Study FKB327-002: Summary of Exposure to Study Medication (SAS)

	FKB327 N=366	Humira N=362	Total N=728
Duration of treatment (days)			
n	366	362	728
Mean (SD)	163.2 (22.30)	162.1 (25.79)	162.6 (24.09)
Range	14, 191	14, 185	14, 191
Overall exposure (patient-years)	163.52	160.63	324.15
Patients who received delayed or interrupted dosing, n (%)[a]	100 (27.3)	80 (22.1)	180 (24.7)
Study drug stopped due to adverse event	18 (4.9)	24 (6.6)	42 (5.8)
Other	58 (15.8)	23 (6.4)	81 (11.1)
Missing	31 (8.5)	35 (9.7)	66 (9.1)
Number of doses received			
n	366	362	728
Mean (SD)	11.4 (1.63)	11.3 (1.88)	11.4 (1.76)
Range	1, 12	1, 12	1, 12

N=number of patients in Safety Analysis Set; n=total number of patients with observation; SD=standard deviation.
[a] Patients may have had more than 1 reason for delayed or interrupted dosing.

In Study FKB327-003, overall exposure was 673.7 patient-years for FKB327 and 175.4 patient-years for Humira. The difference in exposure between the 2 treatments is due to the fact that all patients switched to FKB327 for Period II of the study.

In Study FKB327-003 part II, 507 patients used the FKB327 AI for a mean duration of 317.6 days (range: 14 to 371 days, equating approximately to between 1 and 27 doses), and overall exposure of 440.9 patient-years. Duration of exposure across F-F-F, F-H-F, H-F-F and H-H-F groups was broadly comparable.

Table 25 Study FKB327-003: Summary of Exposure to Study Medication for Patients using the Auto-Injector (Part II): Safety Analysis Set

	F-F-F N=216	F-H-F N=108	H-F-F N=108	H-H-F N=213	Total N=645
Patients starting the auto-injector, n (%)[a]	165 (76.4)	91 (84.3)	83 (76.9)	168 (78.9)	507 (78.6)
Duration of exposure, days					
n	165	91	83	168	507
Mean (SD)	319.3 (59.98)	314.0 (65.82)	316.7 (63.22)	318.4 (58.91)	317.6 (61.10)
Range	14, 348	14, 350	14, 371	14, 351	14, 371
Overall exposure (patient-years)	144.3	78.2	72.0	146.4	440.9

F=FKB327; H=Humira; N=number of patients in Safety Analysis Set; n=total number of patients with observation; SD=standard deviation.
[a] Percentages are based on the number of patients in the Safety Analysis Set.

The Safety Analysis Set in Study FKB327-002 comprised 366 patients treated with FKB327 and 362 patients treated with Humira. Of these patients, 216 patients on FKB327 and 213 on Humira proceeded to the FF and HH treatment sequences in Study FKB327-003, respectively, and 189 patients on FKB327 and 190 on Humira completed Period I (1-year data).

For the 1-year safety comparison, the safety profile for 258 patients in the FF sequence (including 216 patients from FKB327-003 FF and 42 patients who received FKB327 in Study FKB327-002 but did not enter Study FKB327-003) has been compared to the safety profile for 254 patients in the HH sequence (including 213 patients from FKB327-003 HH and 41 patients who received Humira in Study FKB327-002 but did not enter Study FKB327-003).

Table 26 Summary of Patient Disposition during Studies FKB327-002 and FKB327-003 part I: All Enrolled Patients

FKB327-002	FKB327 n (%)	Humira n (%)	Total n (%)
Patients randomised to treatment	367 (100.0)	363 (100.0)	730 (100.0)
Patients with study drug administered	366 (99.7)	362 (99.7)	728 (99.7)
Patients who completed the study	333 (90.7)	328 (90.4)	661 (90.5)
Patients who prematurely discontinued	34 (9.3)	35 (9.6)	69 (9.5)
Patients who continued into Study FKB327-003	324 (88.3)	321 (88.4)	645 (88.4)
Randomised patients who did not continue into Study FKB327-003[a]	43 (11.7)	42 (11.6)	85 (11.6)

FKB327-003	F-F n (%)	F-H n (%)	H-F n (%)	H-H n (%)	Total n (%)
Patients randomised to treatment	216 (100.0)	108 (100.0)	108 (100.0)	213 (100.0)	645 (100.0)
Patients with study drug administered	216 (100.0)	108 (100.0)	108 (100.0)	213 (100.0)	645 (100.0)
Patients who completed Period I	189 (87.5)	100 (92.6)	93 (86.1)	190 (89.2)	572 (88.7)
Patients who prematurely discontinued during Period I	27 (12.5)	8 (7.4)	15 (13.9)	23 (10.8)	73 (11.3)

F=FKB327; H=Humira; n=number of patients
Percentages are based on the number of randomised patients.
[a] Other than 2 patients who were randomised but not treated with study drug in Study FKB327-002, 42 patients receiving FKB327 and 41 patients receiving Humira, giving a total of 83 patients, received at least 1 dose of study drug and were included in the FKB327-002 Safety Analysis Set.

In the integrated safety analysis, data from the 2 phase 3 studies were pooled (Safety Analysis Set for FKB327-002 and FKB327-003). Overall exposure was 837.26 patient-years for FKB327 and 336.01 patient-years for Humira.

Demographic and Other Characteristics of Study Population:

Phase 1 Studies

For both studies, demographic characteristics were broadly comparable between treatments.

Approximately a third of subjects in each treatment group were taking concomitant medications, the most common concomitant medications being paracetamol and ibuprofen.

In Study FKB327-005, there were no clinically significant findings in the medical history.

Table 27 Studies FKB327-001 and FKB327-005: Demographic Characteristics

	FKB327-001			FKB327-005		
	FKB327 N=60	EU-Humira N=60	US-Humira N=60	FKB327 Vial N=66	FKB327 PFS N=63	FKB327 AI N=66
Mean age, years (SD)	31.0 (10.95)	35.2 (14.08)	32.3 (12.35)	38 (13.6)	40 (12.9)	37 (12.5)
Gender, n (%)						
Male	58 (96.7)	55 (91.7)	57 (95.0)	50 (75.8)	45 (71.4)	50 (75.8)
Female	2 (3.3)	5 (8.3)	3 (5.0)	16 (24.2)	18 (28.6)	16 (24.2)
Race, n (%)						
Asian	6 (10.0)	5 (8.3)	12 (20.0)	2 (3.0)	4 (6.3)	3 (4.5)
Black or African American	14 (23.3)	9 (15.0)	8 (13.3)	2 (3.0)	1 (1.6)	9 (13.6)
White	34 (56.7)	45 (75.0)	38 (63.3)	62 (93.9)	58 (92.1)	53 (80.3)
Other	6 (10.0)	1 (1.7)	2 (3.3)	0	0	1 (1.5)
Mean BMI, kg/m^2 (SD)	24.01 (2.281)	23.75 (2.297)	24.24 (2.750)	25.2 (3.06)	25.2 (2.62)	24.8 (2.85)
Mean weight, kg (SD)	74.59 (7.924)	74.87 (7.466)	73.67 (8.352)	76.2 (10.37)	75.2 (10.98)	75.5 (11.56)

Source: [illegible]

AI=auto-injector; BMI=body mass index; EU=European Union; N=number of patients in Safety Analysis Set; n=number of subjects with observation; PFS=pre-filled syringe; SD=standard deviation; US=United States

Phase 3 Studies

Study FKB327-002: The treatment groups were well balanced with respect to the demographic characteristics as shown in the table below.

Table 28 Study FKB327-002: Demographic Characteristics: Safety Analysis Set

	FKB327 N=366	Humira N=362	Total N=728
Mean age, years (SD)	53.0 (12.04)	53.6 (12.32)	53.3 (12.18)
<65 years, n (%)	302 (82.5)	299 (82.6)	601 (82.6)
≥65 years, n (%)	64 (17.5)	63 (17.4)	127 (17.4)
Gender, n (%)			
Male	85 (23.2)	78 (21.5)	163 (22.4)
Female	281 (76.8)	284 (78.5)	565 (77.6)
Race, n (%)			
American Indian or Alaska Native	1 (0.3)	1 (0.3)	2 (0.3)
Asian	1 (0.3)	1 (0.3)	2 (0.3)
Black or African American	2 (0.5)	4 (1.1)	6 (0.8)
White	311 (85.0)	308 (85.1)	619 (85.0)
Other	51 (13.9)	48 (13.3)	99 (13.6)
Mean height, cm (SD)	163.591 (9.7184)	162.999 (8.8645)	163.297 (9.3019)
Mean weight, kg (SD)[a]	73.337 (15.9765)	73.590 (15.6127)	73.463 (15.7863)

Source: [illegible]

N=number of patients in the Safety Analysis Set; n=total number of patients with observation; SD=standard deviation.

[a] Weight at Screening.

Study FKB327-003: Demographics by Period I treatment were similar for FKB327 and Humira. There was a higher proportion of patients aged ≥65 years in the H-H-F treatment sequence (20.7%) and a lower proportion in the H-F-F treatment sequence (11.1%); however, this did not greatly impact the mean age, which was 54.0 years in the H-H-F sequence compared to between 52.1 and 52.7 years in the other sequences. Overall mean age was 52.9 years (range 18 to 93 years). The majority of patients were female (77.7%) and White (85.6%). Mean weight (74.6 kg overall) and height (163.3 cm overall) were also similar across the treatment sequences.

Table 29 Study FKB327-003: Demographic Characteristics by Treatment Sequence: Safety Analysis Set

	F-F-F N=216	F-H-F N=108	H-F-F N=108	H-H-F N=213	Total N=645
Age (years)					
Mean (SD)	52.7 (12.35)	52.1 (11.35)	52.3 (11.93)	54.0 (12.60)	52.9 (12.20)
Range	18, 85	24, 77	23, 82	21, 93	18, 93
Age (years), n (%)					
<65	183 (84.7)	92 (85.2)	96 (88.9)	169 (79.3)	540 (83.7)
≥65	33 (15.3)	16 (14.8)	12 (11.1)	44 (20.7)	105 (16.3)
Gender, n (%)					
Male	54 (25.0)	23 (21.3)	25 (23.1)	42 (19.7)	144 (22.3)
Female	162 (75.0)	85 (78.7)	83 (76.9)	171 (80.3)	501 (77.7)
Race, n (%)					
American Indian or Alaska Native	1 (0.5)	0	0	1 (0.5)	2 (0.3)
Asian	1 (0.5)	0	1 (0.9)	0	2 (0.3)
Black or African American	1 (0.5)	1 (0.9)	2 (1.9)	2 (0.9)	6 (0.9)
White	187 (86.6)	90 (83.3)	90 (83.3)	185 (86.9)	552 (85.6)
Other	26 (12.0)	17 (15.7)	15 (13.9)	25 (11.7)	83 (12.9)
Height (cm)					
Mean (SD)	164.156 (10.2915)	163.272 (9.1952)	163.701 (8.3560)	162.295 (9.0680)	163.317 (9.4173)
Range	141.00, 193.00	141.00, 189.00	144.00, 180.00	144.00, 192.00	141.00, 193.00
Weight (kg)					
Mean (SD)	74.309 (15.9874)	74.936 (15.8638)	75.347 (16.5520)	74.267 (15.4225)	74.574 (15.8474)
Range	41.30, 116.30	42.50, 122.70	44.00, 115.50	41.00, 122.20	41.00, 122.70

F=FKB327; H=Humira; N=number of patients in the Safety Analysis Set; n=total number of patients with observation; SD=standard deviation
Percentages based on the number of patients in the Safety Analysis Set with data.
Results from the Screening visit from the FKB327-002 study are summarized, apart from weight, which is from the Week 24 assessment of the FKB327-002 study

Concomitant Anti-rheumatic Drugs

Phase 3 study FKB327-002

The FKB327 and Humira treatment groups were well matched with respect to concomitant, stable, background treatment for RA, with the average concomitant MTX dose being 15.8 mg/week in both treatment groups.

A similar proportion of patients in the FKB327 and Humira treatment groups were receiving concomitant oral steroids for RA, the most common being methylprednisolone and prednisone.

A similar proportion of patients in the FKB327 and Humira treatment groups were receiving concomitant NSAIDs for RA. The most common concomitant NSAIDs for RA were meloxicam and diclofenac.

Phase 3 study FKB327-003

Overall, 403 patients (62.5%) were receiving concomitant oral steroids for RA, 394 patients (61.1%) were receiving concomitant NSAIDs for RA and 268 (41.6%) were receiving both NSAIDs and oral steroids concomitantly for RA. The use of these medications was not balanced across the treatment sequences and was higher for the F-H-F treatment sequence and lower for the F-F-F treatment sequence compared to the other treatment sequences. The mean concomitant MTX dose was 15.9 mg/week (range 7.50 to 25.00 mg/week) overall, with a higher mean dose of 16.2 mg/week seen in the F-F-F and H-F-F treatment sequences. The majority of patients in each treatment sequence received their MTX dose orally.

Table 30 Study FKB327-003: Summary of Concomitant Use of MTX, Oral Steroids and NSAIDs for RA by Treatment Sequence: Safety Analysis Set

	F-F-F N=216	F-H-F N=108	H-F-F N=108	H-H-F N=213	Total N=645
Average dose of concomitant MTX (mg/week)					
n	216	108	108	213	645
Mean (SD)	16.215 (5.1509)	15.493 (4.9309)	16.172 (4.6233)	15.733 (4.6071)	15.928 (4.8495)
Range	10.00, 25.00	7.50, 25.00	10.00, 25.00	10.00, 25.00	7.50, 25.00
Route of concomitant MTX , n (%)					
Oral	164 (75.9)	87 (80.6)	84 (77.8)	170 (79.8)	505 (78.3)
Subcutaneous	38 (17.6)	18 (16.7)	19 (17.6)	32 (15.0)	107 (16.6)
Other	16 (7.4)	3 (2.8)	5 (4.6)	11 (5.2)	35 (5.4)
Patients with at least 1 concomitant oral steroid for RA, n (%)	127 (58.8)	70 (64.8)	69 (63.9)	137 (64.3)	403 (62.5)
Patients with at least 1 NSAID for RA, n (%)	128 (59.3)	72 (66.7)	68 (63.0)	126 (59.2)	394 (61.1)
Patients with at least 1 concomitant steroid and at least 1 NSAID for RA, n (%)	77 (35.6)	51 (47.2)	49 (45.4)	91 (42.7)	268 (41.6)

F=FKB327; H=Humira; MTX=methotrexate; N=number patients in the Safety Analysis Set; n=total number of patients with observation; NSAID=non-steroidal anti-inflammatory drug; RA=rheumatoid arthritis; SD=standard deviation.
Concomitant oral steroids and NSAIDs are defined as those taken on or at any time after the first day of study drug dosing.
Duration of Prior MTX is the duration for which MTX was taken before Screening. Concomitant MTX is defined as MTX taken on or at any time after the first day of study drug dosing.
Percentages are based on the total number of patients in the Safety Analysis Set.

Approximately 60% of patients in total received concomitant oral steroids, with no notable differences observed across groups; the most common being methylprednisolone and prednisone. More patients in Europe (62.0%) and the Rest of World (70.0%) received concomitant oral steroids for RA compared to patients in North America (31.6%).

Approximately 60% of patients in total received NSAIDs; the most common being meloxicam and diclofenac. As with concomitant NSAIDs, more patients in Europe (64.5%) and the Rest of World (64.8%) received concomitant NSAIDs for RA compared to patients in North America (34.2%).

Medical History and Concurrent Medical Conditions

Phase 3 study FKB327-002

Overall, 54.1% of patients, at similar proportion between treatment groups, reported a past medical history with the most common being related to Surgical and medical procedures.

Excluding RA, the most common concurrent medical conditions, included menopause, hypertension, osteoporosis, osteoarthritis, and were reported for similar proportions of patients in the FKB327 and Humira treatment groups.

Phase 3 study FKB327-003

A total of 57.5% of patients reported past medical history, the most being Surgical and medical procedures and Infections and infestations. No obvious differences could be noted between the different treatment schedule subgroups.

As expected, all patients reported having ongoing RA, while other frequently reported concurrent medical conditions included menopause, hypertension, osteoporosis, and osteoarthritis. Fewer patients in the F-H-F sequence reported concurrent Infections and infestations, and more patients in the H-H-F sequence reported concurrent Endocrine disorders compared to the other sequences.

Adverse events

Phase 1 Study FKB327-001

Overall, 110 subjects (61.1%) experienced at least 1 TEAE, with similar numbers of subjects experiencing TEAEs across the treatment groups. There were no deaths and no TEAEs leading to study discontinuation.

Table 31 Study FKB327-001: Summary of Adverse Events

	FKB327 N=60 n (%)	EU-Humira N=60 n (%)	US-Humira N=60 n (%)	Total N=180 n (%)
Subjects with at least 1 TEAE	35 (58.3)	39 (65.0)	36 (60.0)	110 (61.1)
Subjects with at least 1 TESAE	1 (1.7)	0	1 (1.7)	2 (1.1)
Subjects with at least 1 Severe TEAE	1 (1.7)	1 (1.7)	1 (1.7)	3 (1.7)
Subjects with at least 1 Related TEAE	30 (50.0)	35 (58.3)	32 (53.3)	97 (53.9)
Subjects with at least 1 TEAE Leading to Discontinuation	0	0	0	0
Subjects without any TEAEs	25 (41.7)	21 (35.0)	24 (40.0)	70 (38.9)

EU=European Union; US=United States; N=total number of subjects; n=number of subjects per group; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.

The most commonly reported TEAEs were headache, upper respiratory tract infection, nasopharyngitis, oropharyngeal pain and injection site hematoma, which were generally reported for similar numbers of subjects in each treatment group.

The most common treatment-related TEAEs, experienced by about half of the study population, were headache, upper respiratory tract infection, oropharyngeal pain, nasopharyngitis and injection site haematoma. Most TEAEs were mild or moderate in intensity.

Phase 1 Study FKB327-005

A higher proportion in the AI group compared to the vial and PFS groups experienced at least 1 TEAE, driven by a greater incidence of nasopharyngitis, injection site rash, vessel puncture site pain and vessel puncture site bruising.

Moderate intensity TEAEs were reported rarely, and no severe TE(S)AEs or discontinuations occurred.

Table 32 Study FKB327-005: Summary of Adverse Events

	FKB327 vial N=66 n (%)	FKB327 PFS N=63 n (%)	FKB327 AI N=66 n (%)	Overall N=195 n (%)
Subjects with at least 1 TEAE	40 (60.6)	37 (58.7)	48 (72.7)	125 (64.1)
Number of TEAEs	86	83	107	276
Subjects with at least 1 TESAEs	0	0	0	0
Subjects Discontinued due to TEAEs	0	0	0	0
Subjects with at least 1 Severe TEAE	0	0	0	0
Subjects with at least 1 Related TEAE				
Possibly Related	34 (51.5)	30 (47.6)	41 (62.1)	105 (53.8)
Related	2 (3.0)	1 (1.6)	4 (6.1)	7 (3.6)
Subjects with at least 1 Device-related TEAE				
Possibly Related	2 (3.0)	3 (4.8)	1 (1.5)	6 (3.1)
Related	0	0	0	0

AI=auto-injector; PFS=pre-filled syringe; N=total number of subjects; n=number of subjects per group; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.

The most common TEAEs in all 3 groups were nasopharyngitis and headache, the former occurring in higher numbers in the AI group while for the latter this was the opposite.

TEAEs related to the injection site showed low incidence and included injection site pain, bruising, rash and reaction. Some of these were considered more related to the administration device than to the product itself.

A higher incidence of TEADRs was observed for the AI group, driven by events that were considered related to the study drug in the AI group.

Of note is the fact that very few subjects had TEAEs that were considered device-related, with the related TEAEs being identified as injection site bruising and injection site pain.

Phase 3 Study FKB327-002

Overall, TEAE treatment related TEAE incidence is shown in the table below.

Table 33 Study FKB327-002: Summary of Adverse Events: Safety Analysis Set

	FKB327 N=366 n (%)	Humira N=362 n (%)	Total N=728 n (%)
Deaths	1 (0.3)	0	1 (0.1)
Treatment-emergent deaths	1 (0.3)	0	1 (0.1)
Patients with at least 1 TEAE	203 (55.5)	223 (61.6)	426 (58.5)
Patients with at least 1 severe TEAE	10 (2.7)	7 (1.9)	17 (2.3)
Patients with at least 1 treatment-related TEAE	74 (20.2)	84 (23.2)	158 (21.7)
Patients who prematurely discontinued treatment due to a TEAE	14 (3.8)	10 (2.8)	24 (3.3)
Patients who prematurely discontinued treatment due to a TESAE	8 (2.2)	7 (1.9)	15 (2.1)
Patients who had a treatment interruption due to a TEAE	27 (7.4)	38 (10.5)	65 (8.9)
Patients who had a treatment interruption due to a TESAE	5 (1.4)	5 (1.4)	10 (1.4)
TESAEs, n	19	20	39
Patients with at least 1 TESAE	15 (4.1)	19 (5.2)	34 (4.7)
Patients with at least 1 SAE	15 (4.1)	19 (5.2)	34 (4.7)

N=number of patients in Safety Analysis Set; n=total number of patients with observation; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.

In both groups, the most common TEAEs occurred in the SOC Infections and infestations, Gastrointestinal disorders, and Musculoskeletal and connective tissue disorders with similar rate in both groups.

The most common individual TEAEs were nasopharyngitis, upper respiratory tract infection, urinary tract infection and hypercholesterolaemia.

Overall, 21.7% of subjects experienced a TEAE related to study drug (3% difference in favour of FKB327), the most common ones being injection site erythema, nasopharyngitis and hypercholesterolaemia; all in similar proportion for both treatment groups.

Phase 3 Study FKB327-003 – Period I

Comparison of the incidence of AEs by treatment sequence H-F, F-H, F-F and H-H allows the evaluation of safety of treatment switch. TEAEs incidences in the different treatment combinations are presented in the table below. Although the safety profile was slightly better with F-F treatment sequence compared to the others, the incidence of severe TEAEs, treatment-related TEAEs, TESAEs, discontinuations due to TEAEs, and treatment interruptions due to TEAEs was generally comparable between treatment sequences (with switch or not). There was no outstanding difference between patients who remained on Humira (H-H) compared to patients who switched to FKB327 (H-F).

Table 34 Study FKB327-003: Summary of Adverse Events During Period I by Treatment Sequence: Safety Analysis Set

	F-F N=216 n (%)	F-H N=108 n (%)	H-F N=108 n (%)	H-H N=213 n (%)	Total N=645 n (%)
Deaths	0	0	1 (0.9)	1 (0.5)	2 (0.3)
Treatment-emergent deaths	0	0	1 (0.9)	1 (0.5)	2 (0.3)
Patients with at least 1 TEAE	103 (47.7)	59 (54.6)	59 (54.6)	117 (54.9)	338 (52.4)
Patients with at least 1 severe TEAE	5 (2.3)	2 (1.9)	3 (2.8)	2 (0.9)	12 (1.9)
Patients with at least 1 treatment-related TEAE	39 (18.1)	21 (19.4)	27 (25.0)	49 (23.0)	136 (21.1)
Patients who prematurely discontinued treatment due to a TEAE	10 (4.6)	0	4 (3.7)	11 (5.2)	25 (3.9)
Patients who prematurely discontinued treatment due to a TESAE	0	0	0	2 (0.9)	2 (0.3)
Patients who had a treatment interruption due to a TEAE	19 (8.8)	9 (8.3)	14 (13.0)	20 (9.4)	62 (9.6)
Patients who had a treatment interruption due to a TESAE	3 (1.4)	2 (1.9)	4 (3.7)	2 (0.9)	11 (1.7)
Number of TESAEs, n	7	9	9	7	32
Patients with at least 1 TESAE	5 (2.3)	7 (6.5)	5 (4.6)	7 (3.3)	24 (3.7)
Patients with at least 1 SAE	5 (2.3)	7 (6.5)	5 (4.6)	7 (3.3)	24 (3.7)

Source: [redacted]

F=FKB327; H=Humira; N=number of patients in Safety Analysis Set; n=total number of patients with observation/number of events; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event; SAE=serious adverse event

The most common TEAEs were in the Infections and infestations SOC regardless of treatment sequence: 20.8% in F-F, 25% in F-H and in H-F, and 29.6% in H-H. Musculoskeletal and connective tissue disorders were also observed frequently (13% in F-F, 13.9% in F-H, 15.7% in H-F, and 7.5% in H-H). There was no individual preferred term that appeared notably less frequently in the H-H arm compared with the arms receiving FKB327. Minor differences were observed, but, for even for the most common TEAEs, patient and event numbers per sequence are too low for these differences to be regarded as clinically relevant in the absence of a consistent trend.

The Treatment-related TEAE (or TE-ADR) were not presented by the applicant for period I between sequence (F-F and H-H).

Phase 3 Study FKB327-003 – Period II and whole study period

Data are available to allow for an evaluation of the comparative safety for patients who were switched from FKB327 in the preceding FKB327-002 double-blind study to Humira in the FKB327-003 OLE study (F-H), and then switched back to FKB327 in the second part of the FKB327-003 OLE study (from Week 30; double switch F-H-F).

Discontinuations due to TEAEs, and treatment interruptions due to TEAEs was generally comparable between treatment sequences. The proportion of patients experiencing severe TEAEs and TESAEs was slightly higher in the F-H-F treatment sequence compared to the remaining treatment sequences.

Table 35 Study FKB327-003: Summary of Adverse Events during the Period II, by Treatment Sequence: Safety Analysis Set

	F-F-F N=189 n (%)	F-H-F N=100 n (%)	H-F-F N=93 n (%)	H-H-F N=190 n (%)
Number of deaths	0	0	1 (1.1)	1 (0.5)
Number of treatment-emergent deaths	0	0	1 (1.1)	1 (0.5)
Number of patients with at least one TEAE	114 (60.3)	61 (61.0)	51 (54.8)	114 (60.0)
Number of patients with at least one severe TEAE	2 (1.1)	8 (8.0)	4 (4.3)	5 (2.6)
Number of patients with at least one treatment-related TEAE	43 (22.8)	24 (24.0)	22 (23.7)	37 (19.5)
Number of patients who prematurely discontinued treatment due to a TEAE	4 (2.1)	5 (5.0)	6 (6.5)	10 (5.3)
Number of patients who prematurely discontinued treatment due to a TESAE	2 (1.1)	2 (2.0)	3 (3.2)	3 (1.6)
Number of patients who had a treatment interruption due to a TEAE	14 (7.4)	5 (5.0)	8 (8.6)	9 (4.7)
Number of patients who had a treatment interruption due to a TESAE	2 (1.1)	0	2 (2.2)	2 (1.1)
Number of patients with at least one TESAE	8 (4.2)	8 (8.0)	6 (6.5)	11 (5.8)
Number of patients with at least one SAE	8 (4.2)	8 (8.0)	6 (6.5)	11 (5.8)

AE=adverse event; F=FKB327; H=Humira; N=number of patients in Safety Analysis Set; n=total number of subjects per group; PFS=pre-filled syringe; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.
Percentages are based on the number of patients in the Safety Analysis Set that entered Period II.
Death is defined as the fatal outcome of an (S)AE.
SAEs are defined as AEs which are fatal, life threatening, require or prolong inpatient treatment, result in persistent or significant disability or incapacity, are a congenital anomaly or birth defect, or are medically important events that may jeopardise the patient.
TEAEs are defined as AEs that started or increased in severity after the first study medication administration.
Severe TEAEs are defined as SAEs occurring or increasing in severity after the first dose of study medication was taken.
Related TEAEs are defined as TEAEs where the relationship to study medication was recorded as 'Related', 'Possibly related' or missing.
AEs are counted under the treatment arm and period in which the event started

Table 36 Study FKB327-003: Summary of Adverse Events during the Whole Study Period, by Treatment Sequence: Safety Analysis Set

	F-F-F N=216 n (%)	F-H-F N=108 n (%)	H-F-F N=108 n (%)	H-H-F N=213 n (%)
Number of deaths	0	0	2 (1.9)	2 (0.9)
Number of treatment-emergent deaths	0	0	2 (1.9)	2 (0.9)
Number of patients with at least one TEAE	163 (75.5)	81 (75.0)	73 (67.6)	166 (77.9)
Number of patients with at least one severe TEAE	7 (3.2)	9 (8.3)	7 (6.5)	7 (3.3)
Number of patients with at least one treatment-related TEAE	65 (30.1)	35 (32.4)	40 (37.0)	68 (31.9)
Number of patients who prematurely discontinued treatment due to a TEAE	14 (6.5)	5 (4.6)	10 (9.3)	21 (9.9)
Number of patients who prematurely discontinued treatment due to a TESAE	2 (0.9)	2 (1.9)	3 (2.8)	5 (2.3)
Number of patients who had a treatment interruption due to a TEAE	32 (14.8)	13 (12.0)	20 (18.5)	26 (12.2)
Number of patients who had a treatment interruption due to a TESAE	5 (2.3)	2 (1.9)	6 (5.6)	4 (1.9)
Number of patients with at least one TESAE	13 (6.0)	15 (13.9)	11 (10.2)	18 (8.5)
Number of patients with at least one SAE	13 (6.0)	15 (13.9)	11 (10.2)	18 (8.5)

AE=adverse event; F=FKB327; H=Humira; N=number of patients in Safety Analysis Set; n=total number of subjects per group; PFS=pre-filled syringe; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.
Percentages are based on the number of patients in the Safety Analysis Set.
Death is defined as the fatal outcome of an (S)AE.
SAEs are defined as AEs which are fatal, life threatening, require or prolong inpatient treatment, result in persistent or significant disability or incapacity, are a congenital anomaly or birth defect, or are medically important events that may jeopardise the patient.
TEAEs are defined as AEs that started or increased in severity after the first study medication administration.
Severe TEAEs are defined as SAEs occurring or increasing in severity after the first dose of study medication was taken.
Related TEAEs are defined as TEAEs where the relationship to study medication was recorded as 'Related', 'Possibly related' or missing.
AEs are counted under the treatment arm and period in which the event started

In period II, the most common TEAEs were for the Infections and infestations SOC and were reported for fewer patients who double-switched (F-H-F; 26.0%) compared to the remaining treatment sequences. The most common treatment-related TEAEs were for the same SOC.

Integrated Analysis of Phase 3 Studies

The safety profiles of FKB327 and Humira, overall, are comparable with regards to the treatment-emergent adverse events (TEAEs), severe TEAE, treatment-emergent serious adverse events TEAE (TESAE), treatment-related TEAE, and discontinuation or interruption (due to TEAE or TESAE). However, the incidence was slightly lower with FKB327 compared to Humira for TEAE (2.00 vs. 2.69, respectively) and treatment related TEAE (0.56 vs. 0.74).

There were 5 deaths, of which 4 patients in the FKB327 treatment group and 1 patient in the Humira treatment group.

Table 37 Integrated Analysis of FKB327-002 and FKB327-003: Summary of Adverse Events: FKB327-002 Safety Analysis Set

	FKB327 N=664 837.26 patient-years		Humira N=470 336.01 patient-years		Total N=728
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)
Deaths	4 (0.6)	NC	1 (0.2)	NC	5 (0.7)
Patients with ≥1 TEAE	481 (72.4)	2.00 (1.91-2.10)	311 (66.2)	2.69 (2.52-2.87)	595 (81.7)
Patients with at least 1 severe TEAE	36 (5.4)	NC	12 (2.6)	NC	47 (6.5)
Patients with at least 1 treatment-related TEAE	207 (31.2)	0.56 (0.51-0.61)	132 (28.1)	0.74 (0.66-0.84)	286 (39.3)
Patients who prematurely discontinued due to a TEAE	53 (8.0)	0.09 (0.08-0.12)	21 (4.5)	0.07 (0.04-0.10)	74 (10.2)
Patients who prematurely discontinued due to a TESAE	18 (2.7)	NC	9 (1.9)	NC	27 (3.7)
Patients who had a treatment interruption due to a TEAE	86 (13.0)	NC	62 (13.2)	NC	137 (18.8)
Patients who had a treatment interruption due to a TESAE	18 (2.7)	NC	9 (1.9)	NC	26 (3.6)
TESAEs, n	80	NC	37	NC	117
Patients with ≥1 TESAE	58 (8.7)	0.10 (0.08-0.12)	34 (7.2)	0.11 (0.08-0.15)	88 (12.1)

CI=confidence interval; IR=incidence rate (events/patient-year); N=total number of patients in Safety Analysis Set; n=number of patients with observation/number of events; NC=not calculated; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.
Percentages based on the number of patients ever receiving a given treatment in the Safety Set. Hence, switching patients (either at Week 24 or Week 54 or both) are included in the N count, and can be summarized, for both treatments.

TEAEs were most frequently reported for the SOC Infections and infestations and Musculoskeletal and connective tissue disorders. Overall, the most common TEAEs were nasopharyngitis (submitted clinical safety summary).

Treatment related TEAEs were most frequently reported for the SOC Infections and infestations (submitted clinical safety summary). The most common treatment related TEAEs were injection site erythema, nasopharyngitis, urinary tract infection, latent tuberculosis, upper respiratory tract infections, bronchitis, pharyngitis, pneumonia, sinusitis, Mycobacterium tuberculosis complex test positive, alanine aminotransferase increased, hypercholesterolaemia, and RA flare. The incidence rates of these treatment-related TEAEs were broadly comparable between treatments.

Long-term (1-Year) Safety Comparison (FKB327-002 / FKB327-003 period I)

Overall, the safety profiles are similar for FF and HH (although it might be slightly better for FF). There was no outstanding difference, and FF is comparable to HH with regard to the TEAE (67.1% vs. 71.7%, respectively), treatment-related TEAEs (29.1% vs. 33.1%, respectively), treatment-emergent serious adverse events (TESAEs: 7% vs. 7.9%, respectively), prematurely discontinuation due to TEAEs (9.3% vs. 8.3%, respectively), prematurely discontinuation due to TESAEs (3.5% each), and deaths (1 each).

Table 38 Summary of Adverse Events until the End of FKB327 003 Period I: FKB327-002 Safety Analysis Set

	F-F[a] N=258[b] n (%)	F-H N=108 n (%)	H-F N=108 n (%)	H-H[a] N=254[c] n (%)
Deaths	1 (0.4)	0	1 (0.9)	1 (0.4)
At least 1 TEAE	173 (67.1)	80 (74.1)	87 (80.6)	182 (71.7)
At least 1 treatment-related TEAE	75 (29.1)	32 (29.6)	40 (37.0)	84 (33.1)
At least 1 TESAE	18 (7.0)	7 (6.5)	12 (11.1)	20 (7.9)
Prematurely discontinued due to a TEAE[d]	24 (9.3)	0	4 (3.7)	21 (8.3)
Prematurely discontinued due to a TESAE[d]	9 (3.5)	0	0	9 (3.5)

AE=adverse event; eCRF=electronic case report form; F=FKB327; H=Humira; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SAE=serious adverse event; SOC=System Organ Class; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event
[a] Patients who discontinued in the FKB327-002 study but received Humira are included in the H-H treatment sequence. Similarly, those who discontinued but received FKB327 are included in the F-F treatment sequence.
[b] N includes 216 patients from FKB327-003 (F-F) and 42 patients who received FKB327 in Study FKB327-002 but did not enter Study FKB327-003.
[c] N includes 213 patients from FKB327-003 (H-H) and 41 patients who received Humira in Study FKB327-002 but did not enter Study FKB327-003.
[d] Events summarised are those where 'Action Taken' = 'DRUG WITHDRAWN' in the eCRF.
Percentages are based on the number of patients in the Safety analysis Set in the FKB327-002 study.
SAEs are defined as AEs which are fatal, life threatening, require or prolong inpatient treatment, result in persistent or significant disability or incapacity, are a congenital anomaly or birth defect, or are medically important events that may jeopardize the patient.
TEAEs are defined as AEs that started or increased in severity after the first study medication administration.
Each patient is counted only once within each SOC and PT. TEAEs were coded using MedDRA Version 17.1.

For both treatment sequences, TEAEs were most frequently reported in the System Organ Class (SOC) Infections and Infestations (36.4% FF vs. 43.3% HH), musculoskeletal and connective tissue disorders (15.9% vs. 12.6%, respectively), investigations (14.3% vs. 11.4%, respectively), and gastrointestinal disorders (12.8% vs. 13.8%, respectively). The TEAEs most frequently reported were nasopharyngitis (9.3% vs. 10.6%, respectively), unary tract infection (7% vs. 4.3%, respectively), bronchitis (5.4% vs. 7.9%, respectively), upper respiratory tract infection (3.1% vs. 7.1%, respectively), and RA flare (7% vs. 5.1%, respectively). The difference in patient number experiencing TEAEs (fewer patients receiving FKB327 FF than Humira HH) is mostly due to fewer non-serious infections.

For both treatment sequences, treatment-related TEAEs were most frequently reported in the Infections and Infestations SOC (15.1% vs. 17.7%, respectively) (bronchitis: 2.3% for FF vs 3.5% for HH), General disorders and administration site conditions (injection site reaction: 0.4% vs. 0.8%, respectively), and Blood and lymphatic system disorders (anaemia: 0.8% vs. 1.2%, respectively).

Serious adverse event / deaths / other significant events

Deaths

Phase 1 Studies in Healthy Subjects

There were no deaths during the Phase 1 studies.

Phase 3 Studies in Rheumatoid Arthritis Patients

A total of 5 patients died (4 patients receiving FKB327 at the time of death and 1 patient receiving Humira, corresponding to death rates of 0.006 and 0.003 per patient-year, respectively).

During study FKB327-002 and Period I of study FKB327-003, 2 patients died while on FKB327 and 1 patient died on Humira: one patient receiving FKB327 (vial) died from disseminated TB thought to be

related to FKB327 by the investigator (possibly related for the sponsor); one patient receiving FKB327 (PFS) died from cervical carcinoma and sudden death thought to be related to FKB327 by the investigator (possibly related for the sponsor); and one patient receiving Humira died, but the death was ruled possibly due to pre-existing cardiovascular morbidity (hypertension, ischaemic heart disease).

Another 2 patients died during extended single arm treatment with FKB327 in Period II of study FKB327-003 (AI): one patient died from pneumonia and chronic sepsis, considered by the Investigator as unrelated to FKB327 (possibly related for the sponsor); and one patient died suddenly from either cardiac arrest related to arrhythmia or massive cerebrovascular accident, considered as unrelated to FKB327 by investigator and sponsor. It is possible that the slightly higher death rate on FKB327 than Humira observed in these studies was due to chance finding during the longer term exposure to FKB327.

Other Serious Adverse Events

Phase 1 Studies in Healthy Subjects

In Study FKB327-001, 1 subject in the FKB327 treatment group experienced the SAE of loss of consciousness and 1 subject in the US-Humira treatment group experienced psychotic disorder and both events were considered possibly related to study drug. There were no SAEs in Study FKB327-005. One pregnancy was reported for a healthy subject, who elected to undergo termination.

Phase 3 Study FKB327-002

No pertinent difference in TESAE was noted between FKB327 vial and Humira PFS presentations, with most TESAEs being experienced by only 1 patient. The 3 most reported SOC were infections and infestations, Injury/poisoning/procedural complications and neoplasms benign, malignant and unspecified.

Phase 3 Study FKB327-003 – period I and II

Generally there was no significant difference in TESAEs reported by any of the treatment schedule groups and most SAEs were only reported once. The most reported SOC were infections/infestations and Musculoskeletal & Connective Tissue disorders.

In period I of study FKB327-003, the incidence of TESAEs was generally comparable for patients who remained on FKB327 (F-F, 2.3%, 5 patients) compared to those who remained on Humira (H-H: 3.3%, 7 patients) as well as for patients who switched from Humira to FKB327 (H-F: 4.6%, 5 patients).

Integrated Analysis of Phase 3 Studies

The incidence of TESAEs was similar for FKB327 (0.10 events per patient-year) compared to Humira (0.11 events per patient-year). The most reported SOC were infections/infestations and Musculoskeletal & Connective Tissue disorders.

Long-term (1-Year) Safety Comparison (FKB327-002 / FKB327-003 period I)

TESAEs were experienced by 18 patients (7.0%) who remained on FKB327 (F-F) and by 20 patients (7.9%) who remained on Humira (H-H) for up to 1 year. The most frequently reported TESAEs were in the Infections and Infestations SOC (4.3% vs. 2.8%, respectively). Finally, Infections and Infestations TEAE were also the most frequent reason for treatment discontinuation (3.1% vs. 3.9%, respectively).

Adverse Events of Special Interest

Phase 3 Study FKB327-002

Table 39 Study FKB327-002: Summary of Adverse Events of Special Interest: Safety Analysis Set

	FKB327 N=366 n (%)	Humira N=362 n (%)	Total N=728 n (%)
Patients with at least 1 infection	106 (29.0)	108 (29.8)	214 (29.4)
Patients with at least 1 serious infection (including tuberculosis)	10 (2.7)	5 (1.4)	15 (2.1)
Patients with at Least 1 malignancy or lymphoproliferative disorder	3 (0.8)	2 (0.6)	5 (0.7)
Patients with at least 1 injection site reaction to study drug (related or possibly related)	8 (2.2)	14 (3.9)	22 (3.0)
Patients with at least 1 hypersensitivity reaction to study drug or anaphylaxis to study drug (related or possibly related)	14 (3.8)	7 (1.9)	21 (2.9)
Patients with at least 1 haematological event	0	0	0
Patients with at least neutropenia event	1 (0.3)	0	1 (0.1)
Patients with at least 1 thrombocytopenia event	1 (0.3)	1 (0.3)	2 (0.3)
Patients with at least 1 new or worsening congestive heart failure event	2 (0.5)	0	2 (0.3)
Patients with at least 1 demyelination event	0	0	0
Patients with at least 1 lupus-like reaction	0	0	0

N=number of patients in Safety Analysis Set; n=total number of patients with observation.

Overall, 106 patients (29%) with FKB327 and 108 patients (29.8%) with Humira had at least 1 TEAE of infection during the study. The most common infections were nasopharyngitis, upper respiratory tract infection and urinary tract infection and are expected in this treatment setting. There was no major difference in the pattern of occurrence of the most common infections across the treatment groups.

Ten patients (2.7%) with FKB327 and 5 patients (1.4%) with Humira had infections that were considered serious. Most serious infections were reported only once, making it difficult to compare patterns of occurrence.

Hypersensitivity or anaphylaxis to study drug occurred in 14 patients (3.8%) with FKB327 and 7 patients (1.9%) with Humira. There were no events of anaphylaxis reported.

Two patients (0.6%) in the FKB327 group and 2 patients (0.6%) in the Humira group are shown to have at least 1 malignancy or lymphoproliferative disorder.

One patient (0.3%) experienced mild neutropenia with FKB327 (none with Humira).

Thrombocytopenia occurred in 1 patient (0.3%) with both treatments.

New or worsening of congestive heart failure were reported for 2 patients (0.5%) with FKB327 (none with Humira).

No patient had pancytopaenia or aplastic anaemia, demyelination, or a lupus-like event.

Phase 3 Study FKB327-003

Table 40 Study FKB327-003: Summary of Treatment-emergent Adverse Events of Interest: Safety Analysis Set

	Period I			Period II
	FKB327 N=324	Humira N=321	Total N=645	FKB327 N=572
	n (%)	n (%)	n (%)	n (%)
Patients with at least 1 infection	72 (22.2)	90 (28.0)	162 (25.1)	189 (33.0)
Patients with at least 1 serious infection (including tuberculosis)	3 (0.9)	5 (1.6)	8 (1.2)	7 (1.2)
Patients with at least 1 malignancy or lymphoproliferative disorder	1 (0.3)	0	1 (0.2)	2 (0.3)
Patients with at least 1 injection site reaction to study drug (related or possibly related)	4 (1.2)	5 (1.6)	9 (1.4)	7 (1.2)
Patients with at least 1 hypersensitivity reaction or anaphylaxis to study drug (related to possibly related)	1 (0.3)	6 (1.9)	7 (1.1)	4 (0.7)
Patients with at least 1 pancytopaenia or aplastic anaemia	0	0	0	0
Patients with at least 1 neutropenia event	4 (1.2)	1 (0.3)	5 (0.8)	3 (0.5)
Patients with at least 1 thrombocytopenia event	0	0	0	0
Patients with at least 1 new or worsening congestive heart failure event	0	1 (0.3)	1 (0.2)	0
Patients with at least 1 demyelination event	0	0	0	0
Patients with at least 1 lupus-like reaction	0	0	0	0

N=number of patients in Safety Analysis Set; n=total number of patients with observation.
Percentages for Period I and Overall based on the number of patients in the Safety Analysis Set and percentages for Period II based on the number of patients in the Safety Analysis Set who entered Period II.
Each patient counted only once within each adverse event of interest.

During period I, there were slightly lower rates of infections on FKB327 than on Humira (22.2% vs. 28%, respectively) and serious infection (0.9% vs. 1.6%).

Comparing FKB327 to Humira, there were lower rates of events potentially indicative of hypersensitivity reaction or anaphylaxis to study drug (0.3% vs. 1.9%, respectively), injection site reactions (1.2% vs. 1.6%, respectively), and congestive heart failure events (0% vs. 0.3%, respectively), and slightly higher rates of malignancy (0.3% vs. 0%, respectively) and neutropenia (1.2% vs. 0.3%, respectively). Overall, these very low rates are considered comparable.

No patient had a pancytopenia/aplastic anaemia, thrombocytopaenia, demyelination event or a lupus-like reaction, although these are known risks with adalimumab.

Integrated Analysis of Phase 3 Studies

Table 41 Integrated Analysis of FKB327-002 and FKB327-003: Summary of Adverse Events of Special Interest: FKB327-002 Safety Analysis Set

	FKB327 N=664 837.26 patient-years		Humira N=470 336.01 patient-years		Total N=728 n (%)
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	
Patients with at least one infection	279 (42.0)	0.63 (0.58-0.69)	170 (36.2)	0.80 (0.71-0.91)	379 (52.1)
Patients with at least one serious infection (including tuberculosis)	20 (3.0)	0.03 (0.02-0.05)	10 (2.1)	0.03 (0.02-0.06)	30 (4.1)
Patients with at least one malignancy or lymphoproliferative disorder	6 (0.9)	0.01 (0.00-0.02)	2 (0.4)	0.01 (0.00-0.02)	8 (1.1)
Patients with at least one injection site reaction to study drug (related or possibly related)	15 (2.3)	0.06 (0.05-0.08)	18 (3.8)	0.10 (0.07-0.15)	31 (4.3)
Patients with at least one hypersensitivity reaction or anaphylaxis to study drug (related or possibly related)	19 (2.9)	0.03 (0.02-0.04)	13 (2.8)	0.05 (0.03-0.08)	31 (4.3)
Patients with at least one neutropenia event	7 (1.1)	0.01 (0.01-0.02)	1 (0.2)	0.00 (0.00-0.02)	8 (1.1)
Patients with at least one thrombocytopenia event	1 (0.2)	0.00 (0.00-0.01)	1 (0.2)	0.01 (0.00-0.03)	2 (0.3)
Patients with at least one new or worsening congestive heart failure event	2 (0.3)	0.00 (0.00-0.01)	1 (0.2)	0.01 (0.00-0.02)	3 (0.4)

CI=confidence interval; IR=incidence rate (events/patient-year); N=number of patients in Safety Analysis Set; n=total number of patients with observation. Percentages based on the number of patients ever receiving a treatment within a treatment group in the Safety Set of the FKB327-002 study. Switching patients (either at Week 24 or Week 54 or both) are included in the N count, and can be summarized, for both treatments.

No major differences were observed while comparing the following adverse events of special interest (AESI) between FKB327 and Humira: infections (most commonly nasopharyngitis, UTI, URTI, and bronchitis), serious infection (low incidence), injection site reactions (low incidence, most commonly injection site erythema and injection site reaction or pruritus), hypersensitivity reactions (low incidence, most commonly rash, allergic dermatitis and urticarial), neutropenia, malignancies, and congestive heart failure (low incidence). Although the overall number of cases of neutropenia was small, there was a slightly higher incidence on FKB327, with 5 patients receiving FKB327 with 7 events (IR of 0.01 events per patient-year), compared to 1 patient receiving Humira with 1 event (IR of 0.003 events per patient-year). Six patients on FKB327 (squamous cell carcinoma, plasma cell myeloma, squamous cell carcinoma of skin, basal cell carcinoma, breast cancer, cervix carcinoma) and 2 patients on Humira (squamous cell carcinoma, lymphoma) experienced a malignancy during this study, corresponding to an IR of 0.01 events per patient-year for both treatments. Since numbers are low, caution should be applied when interpreting these data.

Long-term (1-Year) Safety Comparison (FKB327-002 / FKB327-003 period I)

Treatment emergent adverse events (TEAEs) of special interest were similarly reported in both treatment sequences:

- Infections: TEAEs 36.4% FF vs. 43.3% HH (the most common being nasopharyngitis, bronchitis, URTI, and urinary tract infection); TESAEs 4.3% (11 patients) vs. 2.8% (7 patients), respectively. Despite more cases in the FF arm, there was no specific pattern of serious infection, and in particular, the number of active tuberculosis cases was 1 vs 3, in favour of FF.
- Injection site reaction to study drug: TEAEs (related or possibly related) 1.9% vs. 3.9%, respectively (the most common being injection site erythema, injection site reaction and injection site pruritus). Injection site pain was lower on FKB327 than Humira (VAS mean of 6.8 vs. 11.1 respectively), possibly due to the different excipients contained in the products.

- Potential Hypersensitivity Reactions or Anaphylaxis to Study Drug: TEAEs (related or possibly related) 4.7% vs. 3.1%, respectively (the most common being rash and allergic dermatitis).
- Neutropenia: TEAEs 1.2% vs. 0.4%, respectively
- Thrombocytopenia: TEAEs 0% vs. 0.4%, respectively
- Malignancies or lymphoproliferative disorder: TEAEs 1.2% vs. 0.8%, respectively
- Congestive heart failure: 1 patients in FF and no patient in HH

Other significant adverse events

Vital signs

- Phase I studies: There were no trends in changes from Baseline or any clinically meaningful findings for any of the vital signs parameters.
- Phase 3 Study FKB327-002: There were no trends in changes from Baseline for any of the vital signs parameters.
- Phase 3 Study FKB327-003: There were no trends in changes from Baseline/Week 0 for any of the vital signs parameters.

Electrocardiogram (ECG)

The studies included in this summary of safety were not designed to formally investigate a QT effect.

Physical examination

- Study phase 1 FKB327-001: One subject had a concomitant non-serious AE of sore throat that was considered to be moderate in intensity and related to study drug, and resolved after treatment with penicillin.
- Study phase 1 FKB327-005: Three subjects developed rashes after dosing that were considered to be clinically significant and were reported as drug-related TEAEs and resolved without treatment.
- Phase 3 Study FKB327-002: Several patients had an abnormal physical examination related to the patients' underlying RA and were recorded as AEs, as appropriate.
- Phase 3 Study FKB327-003: A minority of patients had abnormal findings, and the majority of these were musculoskeletal abnormalities and likely related to underlying RA.

Tuberculosis Testing

- Phase 1 Studies

All subjects in Study FKB327-001 had a negative TB result at Screening.

In Study FKB327-005, 1 subject had a false positive TB test.

- Phase 3 Study FKB327-002

At Screening, the majority of patients (89.0%) had negative test results. At Week 22, the proportion of patients with a negative result at Screening who had developed a positive or indeterminate test result was similar in both treatment groups.

One patient in the Humira treatment group developed a new TEAE of M. tuberculosis at Week 24. Details of the follow-up examination are not available but active TB was excluded in this case.

- Phase 3 Study FKB327-003

Based on Period I treatment, the proportion of patients with positive or indeterminate results at Week 24 was 9.4% with FKB327 and 9.1% with Humira. For FKB327, this proportion was slightly decreased from the Week 0 result (10.3%), and for Humira the proportion was similar to Week 0 (9.0%). At Week 76 the proportion of patients with positive or indeterminate results was 6.1% with FKB327 and 9.5% with Humira. For both FKB327 and Humira the proportion of positive/indeterminate results at Weeks 0 and 24 in this study were similar to those at Baseline of Study FKB327-002, however at Week 76 a lower proportion of patients were positive/indeterminate for FKB327. It should be noted that a number of patients with positive/indeterminate tests were discontinued from this study due to the protocol requirement for anti-TB prophylaxis. No important difference was seen between FKB327 and Humira in this respect.

Local tolerability

- Phase 1 Studies

Study FKB327-001: The majority of subjects did not experience any evidence of irritation at the injection site. Pain at the injection site was assessed using VAS. Immediately post dose, subjects in the FKB327 treatment group (vial) reported less injection pain than subjects in the Humira treatment groups.

Tolerability was not assessed in Study FKB327-005.

- Phase 3 Study FKB327-002

For the injection site reaction, at day 1, there were no important differences observed between the treatment groups, though the VAS assessed injection site pain was lower in the FKB327 group.

During the overall study, the incidence of injection site reactions reported as AEs was slightly lower with FKB327 (8 patients - 2.2%) than with Humira (14 patients - 3.9%), mostly due to a difference in reported injection site erythema and injection site reactions.

- Phase 3 Study FKB327-003

At Week 0, the majority of patients had no evidence of irritation (FKB327 94.4% and Humira 95.6%). For the small number of patients who did have an injection site reaction (18 patients with FKB327 and 14 with Humira), the majority had minimal erythema (barely visible) and only 1 patient in either group had definite erythema (readily visible)/minimal oedema or minimal popular response. Similar results were observed across the treatment sequences.

At Week 30, of the 554 patients with an injection site assessment (regardless of presentation), most (96.6%) had no evidence of irritation. Four patients experienced an injection site reaction that was graded at higher than 2 (erythema [readily visible]/minimal oedema or minimal popular response) at Week 30 (1 in each treatment sequence: F-F-F, F-H-F, H-F-F and H-H-F).

Of the 507 patients who switched to the AI presentation, 490 had an injection site assessment recorded at the time of switch (Week 30), and the majority (96.5%) had no evidence of irritation. There was no evidence of any difference in injection site reactions between presentations.

Likewise, the overall incidence of injection site reactions to study drug reported as TEAEs was similar between FKB327 and Humira (0.059 vs. 0.080 events per patient-year), and the most frequently

reported injection site reactions were injection site erythema and injection site reaction. No events were considered to be serious.

At Week 0, the mean VAS injection site pain score was twice as high on Humira as on FKB327 (12.9 vs. 6.2), possibly due to the different excipients in the 2 formulations; however a substantial number of scores were missing on both arms. At Week 30, for the 479 patients who had an injection site pain VAS recorded, regardless of presentation, overall mean VAS score (5.2) was lower than the values observed for either FKB327 or Humira at Week 0. Of the 507 patients who switched to the AI presentation, 425 had an injection site pain VAS score recorded at the time of switch, and the mean VAS score was 4.8.

In summary, the data indicate no tolerability concerns with the AI presentation compared with the PFS one.

- Integrated Analysis of Phase 3 Studies

An injection site assessment and an injection site VAS assessment was performed within 30 minutes of W0 dosing in FKB327-002 and FKB327-003 (Week 24 overall), and within 30 minutes of W30 dosing with FKB327 (PFS or AI) in FKB327-003 (Week 54 overall).

Table 42 Integrated Analysis of FKB327-002 and FKB327-003: Summary of Injection Site Reactions: FKB327-003 Safety Analysis Set

	F-F-F N=216 n (%)	F-H-F N=108 n (%)	H-F-F N=108 n (%)	H-H-F N=213 n (%)
FKB327-002 Week 0 (Baseline)				
Patients with injection site assessment[a]	214 (99.1)	108 (100.0)	106 (98.1)	211 (99.1)
Assessment result[b]				
0 (No evidence of irritation)	209 (97.7)	100 (92.6)	99 (93.4)	204 (96.7)
1 (Minimal erythema, barely visible)	5 (2.3)	3 (2.8)	5 (4.7)	7 (3.3)
2 (Definite erythema, readily visible; minimal oedema or minimal papular response)	0	4 (3.7)	1 (0.9)	()
3 (Erythema and papules)	0	1 (0.9)	1 (0.9)	0
FKB327-003 Week 0 (Week 24 overall)				
Patients with injection site assessment[a]	214 (99.1)	107 (99.1)	108 (100.0)	210 (98.6)
Assessment result[b]				
0 (No evidence of irritation)	201 (93.9)	103 (96.3)	103 (95.4)	200 (95.2)
1 (Minimal erythema, barely visible)	12 (5.6)	3 (2.8)	5 (4.6)	10 (4.8)
2 (Definite erythema, readily visible; minimal oedema or minimal papular response)	1 (0.5)	1 (0.9)	0	0
FKB327-003 Week 30 (Week 54 overall)				
Patients with injection site assessment[a]	180 (83.3)	98 (90.7)	91 (84.3)	185 (86.9)
Assessment result[b]				
0 (No evidence of irritation)	176 (97.8)	94 (95.9)	90 (98.9)	175 (94.6)
1 (Minimal erythema, barely visible)	3 (1.7)	3 (3.1)	0	9 (4.9)
2 (Definite erythema, readily visible; minimal oedema or minimal papular response)	1 (0.6)	1 (1.0)	1 (1.1)	1 (0.5)

F=FKB327; H=Humira; N=number of patients in Safety Analysis Set; n=total number of patients with observation.
[a] Percentages based on the number of patients in the FKB-003 Safety Analysis Set.
[b] Percentages based on the number of patients in the FKB-003 Safety Analysis Set with data at a given visit.
Note: No patients had assessment results of 3 (Erythema and papules), 4 (Definite oedema), 5 (Erythema, oedema and papules), 6 (Vesicular eruption), or 7 (Strong reaction spreading beyond test site).

No important differences were observed in injection site assessments between the FKB327 and Humira treatment groups or as a result of switching treatments. With respect to injection site pain, there was an improvement in pain scores from Baseline of Study FKB327-002 to Week 30 of Study FKB327-002 in all treatment sequences. At both Baseline and Week 0, the highest mean VAS scores were observed for patients receiving Humira compared to FKB327. When all patients received FKB327 in Period II, the greatest pain diminutions (from Week 0) were observed for patients who switched from Humira.

Table 43 Integrated Analysis of FKB327-002 and FKB327-003: Summary of Injection Site Pain VAS Scores: FKB327-003 Safety Analysis Set

	F-F-F N=216	F-H-F N=108	H-F-F N=108	H-H-F N=213
Treatment in FKB327-002 Week 0 (Baseline)	**FKB327**	**FKB327**	**Humira**	**Humira**
n	197	96	95	191
Mean (SD)	9.6 (14.37)	10.4 (17.36)	19.1 (22.08)	20.7 (23.27)
Min, Max	0, 84	0, 91	0, 88	0, 95
Treatment in FKB327-003 Week 0 (Week 24)	**FKB327**	**Humira**	**FKB327**	**Humira**
n	194	98	94	187
Mean (SD)	6.8 (10.61)	16.3 (22.67)	4.9 (7.38)	11.1 (16.18)
Min, Max	0, 67	0, 100	0, 44	0, 94
Treatment in FKB327-003 Week 30 (Week 54)	**FKB327**	**FKB327**	**FKB327**	**FKB327**
n	158	84	76	161
Mean (SD)	5.6 (9.80)	3.9 (7.79)	5.9 (10.01)	5.1 (10.65)
Min, Max	0, 57	0, 64	0, 70	0, 76

F=FKB327; H=Humira; N=number of patients in Safety Analysis Set; n=total number of patients with observation; SD=standard deviation; VAS=Visual Analogue Scale.
Note: '0' indicates 'No pain' and '100' indicates 'Intolerable pain' on the VAS scale

Laboratory findings

Phase 1 Study FKB327-001

There were several trends in change from baseline in mean values for the hematology, biochemistry and urinalysis parameters that followed the same pattern in all treatment groups.

In total, 9 subjects had clinically significant abnormal laboratory results, including low neutrophil counts, low platelet count, and increases in ALT and aspartate transaminase (AST).

Phase 1 Study FKB327-005

There were no notable trends in change from baseline in mean values for the hematology, biochemistry and urinalysis parameters for any treatment group.

Transient reductions were seen in leukocytes and neutrophils for multiple subjects but were not considered to be clinically significant by the Investigator.

Phase 3 Study FKB327-002

There were no clinically relevant changes from baseline in mean values for any of the haematology, biochemistry or urinalysis parameters, with the exception of ESR where a decrease was observed over time for both the FKB327 and Humira treatment groups.

Several patients experienced changes in laboratory parameters that were reported as non-serious TEAEs, the most common ones being hypercholesterolaemia, anaemia and dyslipidaemia.

Phase 3 Study FKB327-003

There were no clinically relevant changes from Baseline/Week 0 in mean values for any of the hematology, biochemistry or urinalysis parameters, and no patterns in the laboratory parameters could be discerned.

TEAEs related to changes in clinical laboratory parameters occurred in a number of patients during the study period. None of the most common laboratory-related TEAEs was considered serious and the majority were mild in intensity.

Positive M. tuberculosis complex test was a frequently observed event, occurring in 9 patients receiving FKB327 and 8 patients receiving Humira during Period I and by 4 patients receiving FKB327 in Period II, which was a result of protocol requirements.

In Period I, anaemia was reported as a TEAE for 5 patients receiving FKB327 PFS and 4 patients receiving Humira PFS. Hypochromic anaemia and normochromic normocytic anaemia were each reported by a single patient receiving Humira. Leukopenia and neutropenia were each reported by 3 patients receiving FKB327 and 1 patient receiving Humira. TEAEs related to liver function test abnormalities were reported by slightly more patients receiving FKB327 than Humira. A TEAE of abnormal urine analysis was reported for 3 patients receiving FKB327. TEAEs related to metabolism or nutrition disorders were experienced by similar numbers of patients receiving FKB327 and Humira. Haematuria was experienced by 3 patients on FKB327 and 2 patients on Humira. Leukocyturia was experienced by 1 patient on FKB327 and 2 patients on Humira. Other TEAEs related to changes in clinical laboratory parameters occurred in single patients.

In Period II, anaemia was reported as a TEAE by 11 patients; ALT increased by 10 patients; CRP increased and dyslipidaemia by 8 patients; AST increased by 7 patients; blood creatinine increased, GGT increased, transaminases increased, WBC count increased, and hyperglycaemia by 3 patients; leukopenia, neutropenia, hypothyroidism, blood cholesterol increased, blood urea increased, hepatic enzyme increased, neutrophil count increased, hypercholesterolaemia, hyponatraemia, and haematuria by 2 patients. Other TEAEs related to changes in clinical laboratory parameters occurred in single patients.

As FKB327 has been developed as a proposed biosimilar product to Humira, no comparison has been made between FKB327 and Humira in special patient sub-groups or situations. Patients with significant renal and/or hepatic impairment were excluded from the clinical studies.

Immunological events

Phase 1 Study FKB327-001

The comparative profiles for the detection of confirmed positive ADA samples and positive results in the nAb assay are summarized in the table and figure below.

Table 44 Detected ADA and nAb responses by treatment group (study FKB327-001; Safety Analysis Set) (ISI – table 34)

Category	Time-point (day)			
	1 (pre-dose)	16	30	65
FKB327 (n=60 treated)				
Number of samples	60	60	60	60
Number ADA positive	3	21	20	41
% ADA positive	5.0	35.0	33.9	69.5
Median titer[a]	0.0625	0.0625	0.0625	4
Maximum titer[a]	64	4096	65536	65536
Number nAb positive	0	0	2	35
% nAb positive	0	0	3.4[b]	59.3[b]
US-licensed Humira (n=60 treated)				
Number of samples	60	60	60	60
Number ADA positive	3	15	18	42
% ADA positive	5.0	25.0	30.0	70.0
Median titer	0.0625	0.0625	0.0625	4
Maximum titer	64	1024	1024	65536
Number nAb positive	0	0	6	34
% nAb positive	0	0	10	56.7
EU-licensed Humira (n=60 treated)				
Number of samples	60	60	60	60
Number ADA positive	3	19	19	44
% ADA positive	5.0	31.7	31.7	73.3
Median titer	0.0625	0.0625	0.0625	4
Maximum titer	16	256	256	4096
Number nAb positive	0	0	6	36
% nAb positive	0	0	10	60.0

a: If data a certain time point was missing, result carried forward from previous time point which data was available.
b: Denominator for percentages is n= 59 due to missing data.

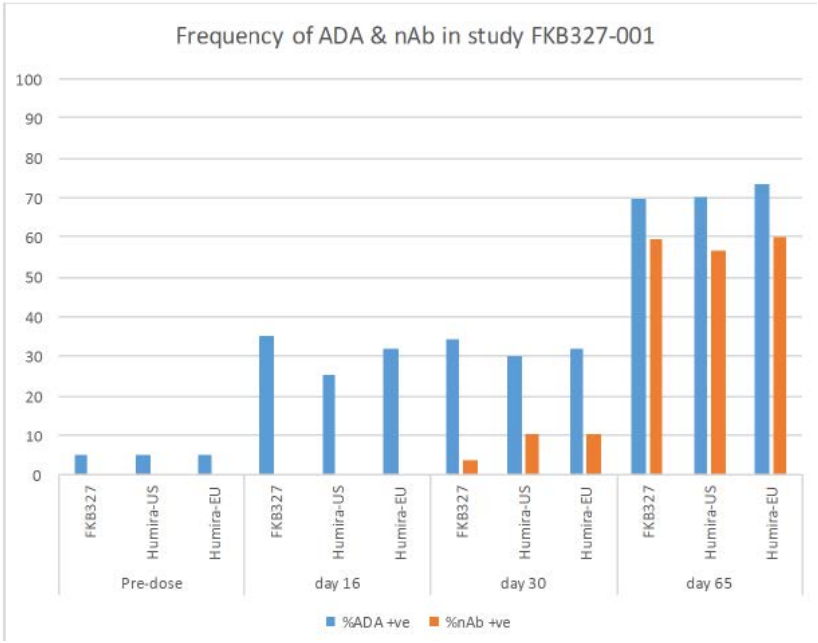


Figure 13 Detected ADA and nAb responses by treatment group (study FKB327-001; Safety Analysis Set)

ADA titre distribution at the last time point by treatment group is illustrated in the figure below.

Figure 14 ADA titer distribution at day 65 by treatment group

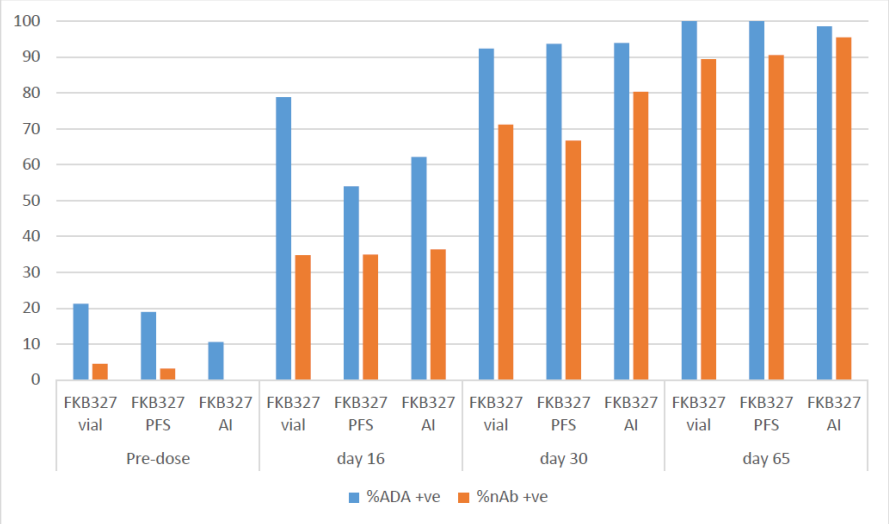
Injection site reactions were observed immediately post-dose in 10 of the 180 treated subjects: 1 subject treated with FKB327; 5 subjects treated with EU-approved Humira; 4 subjects treated with US-licensed Humira. No evidence of irritation was observed 12 hours after dose.

Phase 1 Study FKB327-005

The comparative profiles for the detection of confirmed positive ADA samples and positive results in the nAb assay are summarized in the table and figure below.

Table 45 Detected ADA and nAb responses by treatment group (study FKB327-005)

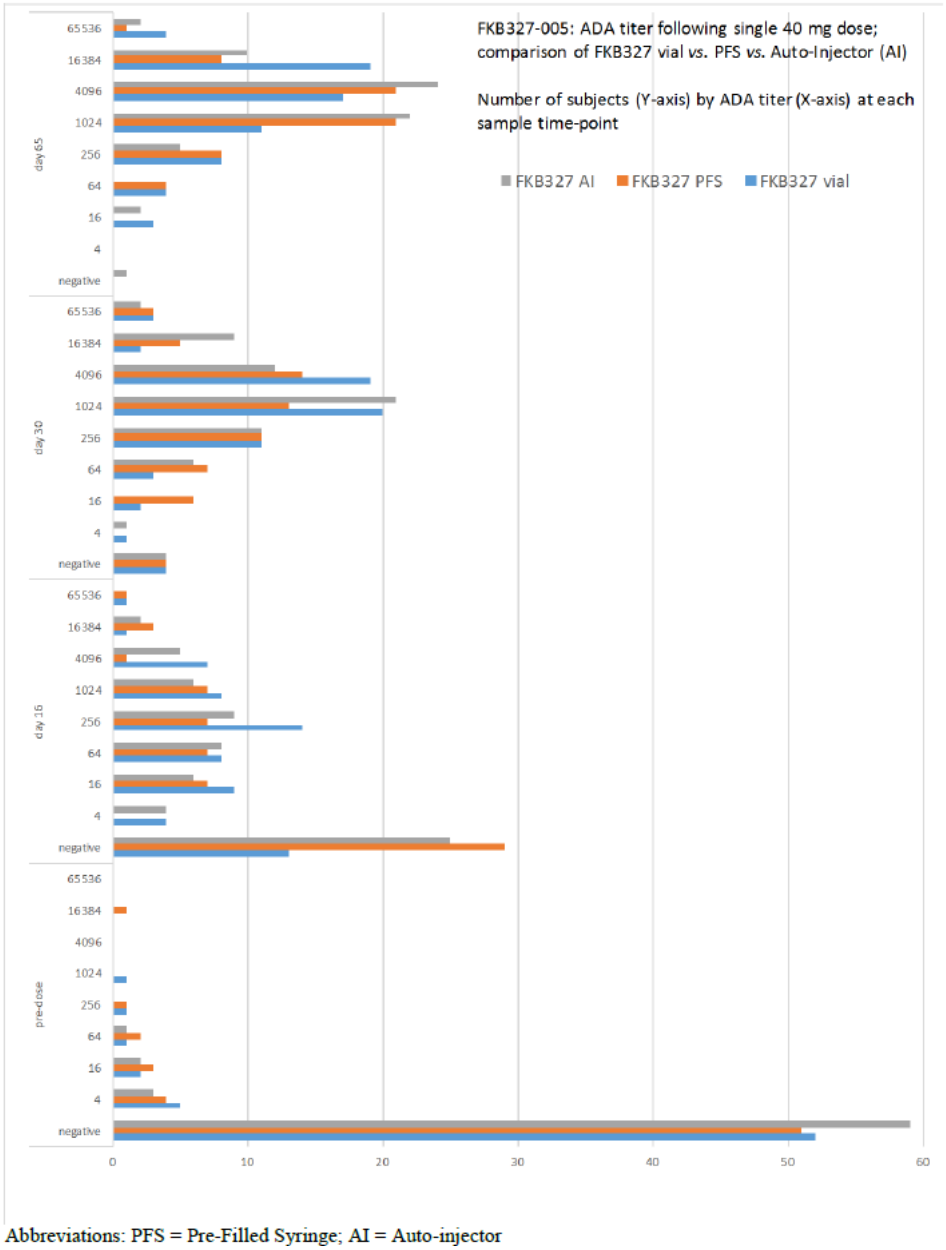
Category	Time-point (day)			
	1 (pre-dose)	16	30	65
FKB327 vial (n=66)				
Number ADA positive	14	52	61	66
% ADA positive	21.2	78.8	92.4	100.0
Median titer	0.1	64	640	2400
Mean titer	13.0	4465.1	7008.6	8052.9
Maximum titer	640	256000	256000	192000
Number nAb positive	3	23	47	59
% nAb positive	4.5	34.8	71.2	89.4
FKB327 Pre-Filled Syringe (n=63)				
Number ADA positive	12	34	59	63
% ADA positive	19.0	54.0	93.7	100
Median titer	0.1	8	500	800
Mean titer	106.6	2953.0	3034.2	2589.5
Maximum titer	6400	160000	56000	25600
Number nAb positive	2	22	42	57
% nAb positive	3.2	34.9	66.7	90.5
FKB327Auto-injector (n=66)				
Number ADA positive	7	41	62	65
% ADA positive	10.6	62.1	93.9	98.5
Median titer	0.1	8	640	1400
Mean titer	0.8	436.9	5380.6	4132.2
Maximum titer	24	9600	192000	64000
Number nAb positive	0	24	53	63
% nAb positive	0	36.4	80.3	95.5



Abbreviations: PFS = Pre-Filled Syringe; AI = Auto-injector

Figure 15 Detected ADA and nAb responses by treatment group (study FKB327-005; Safety Analysis Set)

ADA titre distribution at each time point by treatment group is illustrated in the figure below.



Abbreviations: PFS = Pre-Filled Syringe; AI = Auto-injector

Figure 16 Distribution of ADA titer category vs. time in Study FKB327-005

The overall incidence of TEAEs was similar for the vial and PFS groups (60.6% and 58.7% subjects, respectively), and higher in the AI group (72.7% of subjects). The higher incidence in the AI group was largely due to a greater incidence of nasopharyngitis, injection site rash, vessel puncture site pain and vessel puncture site bruise in this group. The majority of TEAEs in all 3 groups were mild in severity (94.6% of all TEAEs). No severe TEAEs or SAEs were reported by any subjects, and no subjects discontinued due to TEAEs.

All TEAEs related to the injection site were considered TEADRs and were mild in severity.

For the 3 subjects reporting TEAEs of injection site reaction, 2 subjects were noted to have high ADA titre and 1 subject had moderate ADA titre shortly after the event. An eventual relationship with TEHAEs was not been discussed.

Phase 3 Studies FKB327-002 and FKB327-003

Anti-drug antibody (ADA)

ADA development for the FKB327 presentations (vial, PFS, AI) was evaluated throughout Study FKB327-002 (24 weeks) and Periods I and II of Study FKB327-003 (+76 weeks in patients who proceeded to FKB327-003 study).

Table 46 Frequency of ADA Positive and Neutralizing ADA (Nab) in Studies FKB327-002 and FKB327-003 by Treatment Sequence

Study	FKB327-002 FKB327-vial or Humira					FKB327-003 Period I FKB327-PFS or Humira			FKB327-003 Period II FKB327-AI or PFS		
Wks from 002 start	0	2	4	12	24	(24)	(36)	(48)	(54)[b]	(78)	(100)
Wks from 003 start						0	12	24	30[b]	54	76
F-F-(F) Sequence[a]	**FKB327-vial**					**FKB327-PFS**			**FKB327 (AI/PFS)**		
No. of subjects	216	216	215	214	216	216	202	197	187	181	176
No. ADA positive	8	25	86	125	132	133	109	100	98	104	90
(%)	(3.7)	(11.6)	(40.0)	(58.4)	(61.1)	(61.6)	(54.0)	(50.8)	(52.4)	(57.5)	(51.1)
No. Nab positive	5	20	79	124	131	132	108	100	98	101	90
(%)	(2.3)	(9.3)	(36.7)	(57.9)	(60.6)	(61.1)	(53.5)	(50.8)	(52.4)	(55.8)	(51.1)
F-H-(F) Sequence [a]						**Humira**			**FKB327 (AI/PFS)**		
No. of subjects	108	108	107	106	108	108	103	100	100	93	90
No. ADA positive	4	7	39	58	69	69	60	58	61	49	49
(%)	(3.7)	(6.5)	(36.4)	(54.7)	(63.9)	(63.9)	(58.3)	(58.0)	(61.0)	(52.7)	(54.4)
No. Nab positive	3	7	38	57	67	67	60	57	60	49	49
(%)	(2.8)	(6.5)	(35.5)	(53.8)	(62.0)	(62.0)	(58.3)	(57.0)	(60.0)	(52.7)	(54.4)
H-F-(F) Sequence [a]	**Humira**					**FKB327-PFS**			**FKB327 (AI/PFS)**		
No. of subjects	108	108	107	107	108	108	103	96	93	89	81
No. ADA positive	7	10	38	59	67	67	54	47	42	41	39
(%)	(6.5)	(9.3)	(35.5)	(55.1)	(62.0)	(62.0)	(52.4)	(49.0)	(45.2)	(46.1)	(48.1)
No. Nab positive	6	6	36	59	67	67	53	47	42	41	38
(%)	(5.6)	(5.6)	(33.6)	(55.1)	(62.0)	(62.0)	(51.5)	(49.0)	(45.2)	(46.1)	(46.9)
H-H-(F) Sequence [a]						**Humira**			**FKB327 (AI/PFS)**		
No. of subjects	213	213	213	213	212	212	202	199	190	181	174
No. ADA positive	10	29	76	109	123	123	102	101	98	77	74
(%)	(4.7)	(13.6)	(35.7)	(51.2)	(58.0)	(58.0)	(50.5)	(50.8)	(51.6)	(42.5)	(42.5)
No. Nab positive	8	24	70	106	122	122	102	99	96	75	73
(%)	(3.8)	(11.3)	(32.9)	(49.8)	(57.5)	(57.5)	(50.5)	(49.7)	(50.5)	(41.4)	(42.0)
FKB327 Total	**FKB327-vial Total**					**FKB327-PFS Total**			**FKB327 (AI/PFS) Total**		
No. of subjects	324	324	322	320	324	324	305	293	569	544	521
No. ADA positive	12	32	125	183	201	200	163	147	299	271	252
(%)	(3.7)	(9.9)	(38.8)	(57.2)	(62.0)	(61.7)	(53.4)	(50.2)	(52.5)	(49.8)	(48.4)
No. Nab positive	8	27	117	181	198	199	161	147	296	266	250
(%)	(2.5)	(8.3)	(36.3)	(56.6)	(61.1)	(61.4)	(52.8)	(50.2)	(52.0)	(48.9)	(48.0)
FKB327-AI Total in Study 003 Period II									**FKB327-AI Total**		
No. of subjects	-	-	-	-	-	-	-	-	505	480	461
No. ADA positive									270	241	224
(%)									(53.5)	(50.2)	(48.6)
No. Nab positive									269	238	223
(%)									(53.3)	(49.6)	(48.4)
FKB327-PFS Total in Study 003 Period II									**FKB327-PFS Total**		
No. of subjects	-	-	-	-	-	-	-	-	64	64	60
No. ADA positive									29	30	28
(%)									(45.3)	(46.9)	(46.7)
No. Nab positive									27	28	27
(%)									(42.2)	(43.8)	(45.0)

Humira Total	**Humira Total**					**Humira Total**			**NA**		
No. of subjects	321	321	320	320	320	320	305	299	290	-	-
No. ADA positive	17	39	114	168	190	192	162	159	159		
(%)	(5.3)	(12.1)	(35.6)	(52.5)	(59.4)	(60.0)	(53.1)	(53.2)	(54.8)		
No. Nab positive	14	30	106	165	189	189	162	156	156		
(%)	(4.4)	(9.3)	(33.1)	(51.6)	(59.1)	(59.1)	(53.1)	(52.2)	(53.8)		

ADA=anti-drug antibody; AI=auto-injector; F=FKB327; H=Humira; PFS=pre-filled syringe; US=United States
[a] The first letter (F or H) in treatment sequence shows the treatment received in Study FKB327-002, the second letter (F or H) shows the treatment in Study FKB327-003 Period I. The third letter (F) in parentheses shows the treatment in Period II, in which all patients received FKB327.
[b] Last day of Period I of Study FKB327-003.

Overall ADA positive ratios in FKB327 and Humira treatment groups in the FKB327-002 study were 9.9% and 12.1% at Week 2, 38.8% and 35.6% at Week 4, 57.2% and 52.5% at Week 12, 62.0% and 59.4% at Week 24, respectively, showing that the frequency of ADA positive samples increased similarly between both treatment groups and reached plateau at Week 24 in both groups. At the end of this period, there was a 3% difference in favour of Humira.

During period I of the Study FKB327-003, the relevant population to compare immunogenicity consists of the patients who are maintained on the same product as in the previous study (216 patients on FKB327 and 212 patients on Humira). Similar rates were observed in these subgroups as in the whole population during Study FKB327-002, with rates at Week 24 of 61.6% and 58.0%, respectively. During period I, the rates tended to decrease in both subgroups and, at Week 48, the same rate of 50.8% was reported. In the smaller subgroups of patients that switched product at the start of period I, at Week 48, a decrease in positive rates was also observed (58.0% in F-H and 49.0% in H-F). This finding is reassuring.

With regard to ADA development by each FKB327 presentation (i.e., vial, PFS, AI), in the FKB327 treatment continuous group (i.e., F-F-F group), the ADA positive ratio increased during the course of FKB327-002 study, and reached a plateau at Week 24, being observed in 61.1% of patients treated by FKB327-vial. ADA did not increase in Period I in patients who were switched to FKB327-PFS (52.4%, FKB327-003 beginning of Period II Week 30) and in Period II in which the majority of patients who were switched to FKB327-AI (51.1% FKB327-003 Week 76). A similar pattern was observed for the other sequences (F-H-F, H-F-F and H-H-F). Therefore, the switch to FKB327-PFS and FKB327-AI did not increase ADA activity.

Table 47 Summary of Anti-Drug Antibody Titre Results, by Time in: FKB327-002 Safety Analysis Set

Study	FKB327-002				
Wks from -002 Start	0	2	4	12	24
Wks from -003 Start	-	-	-	-	-
F-F-F Sequence[b]					
n	216	216	211	210	215
Mean (SD)	48.5 (392.36)	3437.3 (34767.88)	5045.4 (44939.86)	3938.9 (12881.00)	10078.0 (40996.46)
Lower quartile	0.06250	0.06250	0.06250	0.06250	0.06250
Median	0.06250	0.06250	0.06250	400.00000	800.00000
Upper quartile	0.06250	0.06250	600.00000	2800.00000	5760.00000
F-H-F Sequence[b]					
n	108	106	107	103	108
Mean (SD)	32.7 (243.40)	1942.3 (19423.13)	1307.8 (5693.82)	2967.9 (6535.84)	5993.9 (11739.81)
Lower quartile	0.06250	0.06250	0.06250	0.06250	0.06250
Median	0.06250	0.06250	0.06250	400.00000	800.00000
Upper quartile	0.06250	0.06250	600.00000	2560.00000	5800.00000
H-F-F Sequence[b]					
n	108	106	104	103	108
Mean (SD)	774.7 (5416.62)	801.0 (5466.68)	1383.9 (4559.22)	4755.0 (17035.98)	8703.5 (27778.72)
Lower quartile	0.06250	0.06250	0.06250	0.06250	0.06250
Median	0.06250	0.06250	0.06250	240.00000	1080.00000
Upper quartile	0.06250	0.06250	400.00000	4000.00000	3200.00000
H-H-F Sequence[b]					
n	212	211	211	205	212
Mean (SD)	109.3 (1379.82)	3309.8 (44075.26)	4300.2 (26460.34)	2829.4 (12319.17)	6324.5 (26714.38)
Lower quartile	0.06250	0.06250	0.06250	0.06250	0.06250
Median	0.06250	0.06250	0.06250	120.00000	400.00000
Upper quartile	0.06250	0.06250	400.00000	1600.00000	3200.00000

Table 48 Summary of Anti-Drug Antibody Titre Results, by Time in: FKB327-003 Safety Analysis Set

Week	Summary statistics of ADA titre			
	F-F-F N = 216	F-H-F N = 108	H-F-F N = 108	H-H-F N = 213
Week 0				
n	216	108	108	211
Mean	10761.32031	6179.83738	8703.54225	6343.10664
SD	42154.620105	11805.157066	27778.720030	26776.534781
Median	800.00000	1040.00000	1080.00000	400.00000
Min, Max	0.0625, 400000.0000	0.0625, 64000.0000	0.0625, 160000.0000	0.0625, 320000.0000
Week 12				
n	202	103	103	202
Mean	84925.77135	13981.46299	9407.02002	16955.47649
SD	718895.639248	40854.985745	27428.178109	81566.106312
Median	540.00000	800.00000	480.00000	180.00000
Min, Max	0.0625, 9600000.0000	0.0625, 240000.0000	0.0625, 160000.0000	0.0625, 960000.0000
Week 24				
n	197	100	95	199
Mean	29515.25920	46375.42625	29862.13684	26097.81972
SD	156250.481215	322214.722541	113547.923953	233684.288169
Median	200.00000	760.00000	0.06250	150.00000
Min, Max	0.0625, 1600000.0000	0.0625, 3200000.0000	0.0625, 768000.0000	0.0625, 3200000.0000
Week 30				
n	187	100	93	190
Mean	46108. 69285	144074.42438	26373.79772	53556.97763
SD	357242.660523	1279530.806779	101617.601685	495457.413148
Median	600.00000	1600.00000	0.06250	150.00000
Min, Max	0.0625, 4800000.0000	0.0625, 12800000.0000	0.0625, 640000.0000	0.0625, 6400000.0000
Week 54				
n	181	93	89	181
Mean	28347.22548	22948.41667	15744.75281	58823.12983
SD	161231.775495	116676.231496	86602.929613	491308.333819
Median	640.00000	800.00000	0.06250	0.06250
Min, Max	0.0625, 1920000.0000	0.0625, 800000.0000	0.0625, 800000.0000	0.0625, 6400000.0000
Week 76				
n	176	90	81	174
Mean	28626.16690	7041.80625	11879.78549	6454.42672
SD	252657.835985	29134.746009	48479.254793	49318.590861
Median	200.00000	280.00000	0.06250	0.06250
Min, Max	0.0625, 3200000.0000	0.0625, 256000.0000	0.0625, 400000.0000	0.0625, 640000.0000

ADA: Anti-drug Antibody. SD: Standard Deviation.
Negative titre results presented as 0.0625, titre results <1 (including <LLOQ) presented as 0.25. Based on titre ADA results only (i.e. screening, confirmatory and neutralising results excluded).

Overall, mean ADA titre increased in all treatment sequences during Study FKB327-002. Mean ADA titre continued to increase during Period I of FKB327-003 (to the beginning of Period II – Week 30) in all treatment sequences with the exception of the F-F-F treatment sequence, where the mean ADA titre at Week 24 was lower than at Week 12 (mainly due to 2 patients who shown unusually high ADA titres without any specific clinical cause). Then, in Period II (full set of data to week 76), mean ADA titre decreased in all treatment sequences. In conclusion, overall ADA titre profiles across the treatment sequences are highly similar and numerical differences are considered to be not clinically significant.

Neutralising Antibody (nAb)

The frequency of neutralizing ADA (Nab) positive samples was almost equivalent to the frequency of ADA positive patients in the course of Studies FKB327-002 and FKB327-003.

With regard to Nab development by each FKB327 presentation (i.e., vial, PFS, AI), in the FKB327 treatment continuous group (i.e., F-F-F group), the Nab positive ratio increased during the course of FKB327-002 study, and reached a plateau at Week 24, being observed in 60.6% of patients treated by FKB327-vial. Nab did not increase in Period I in patients who were switched to FKB327-PFS (52.4%, FKB327-003 beginning of Period II Week 30) and in Period II in which the majority of patients who were switched to FKB327-AI (51.1% Week 76). A similar pattern was observed for the other sequences (F-H-F, H-F-F and H-H-F). Therefore, the switch to FKB327-PFS and FKB327-AI did not increase Nab activity.

- Treatment-emergent Hypersensitivity Adverse Events (TEHAE) by ADA Titre or neutralizing ADA (Nab)

1. *Comparison of TEHAE by ADA Titre and Nab between FKB327 and Humira*

Overall TEHAE were observed at a relatively low incidence across both treatment groups (0.03 events per patient-year (IR) for FKB327 and 0.05 IR for Humira) during the overall period from Study FKB327-002 to Period II of Study FKB327-003 (integrated analysis). There were no events of anaphylaxis reported and no cases of anaphylaxis.

By ADA status, the overall incidence rate of TEHAEs was slightly higher in patients who developed moderate and high ADA titre in both FKB327 and Humira treatment groups (0.011 and 0.020 in low ADA titre, 0.035 and 0.041 in moderate ADA titre, 0.047 and 0.091 in high ADA titre, respectively). This trend was observed especially in the system organ class (SOC) Skin and subcutaneous tissue disorders in both FKB327 and Humira group (0.005 and 0.010 in low ADA titre, 0.028 and 0.034 in moderate ADA titre, 0.036 and 0.080 in high ADA titre, respectively) and SOC Immune system disorders such as hypersensitivity in both FKB327 and Humira group (0.000 and 0.000 in low ADA titre, 0.003 and 0.000 in moderate ADA titre, 0.010 and 0.011 in high ADA titre, respectively).

By Nab status, higher incidence rate were observed in patients who detected positive for Nab in both FKB327 and Humira similarly (0.012 – 2 events and 0.011 – 1 event in negative Nab, 0.039 – 19 events and 0.062 – 15 events in positive Nab, respectively), especially in the SOC Skin and subcutaneous tissue disorders (0.006 and 0.000 in negative Nab, 0.030 and 0.053 in positive Nab) and SOC Immune system disorders (0.000 and 0.000 in negative Nab, 0.006 and 0.004 in positive Nab, respectively). However, the incidence rate was low for both the FKB327 and Humira treatment groups with very low numbers of events.

2. *Comparison of TEHAE by ADA Titre and Nab by FKB327 Presentation*

In FKB327003 period I and II, the overall incidence rates of TEHAEs for patients who received FKB327 AI (0.018 – 5 events) was slightly higher than with PFS (0.005 – 1 event). However, the incidence rate was low for both presentations with very low numbers of events.

The incidence rates of TEHAE by ADA status were slightly higher in high ADA titre with AI (0.056 – 4 events) compared to moderate (0.009 – 1 event) and low ADA titre (0), and compare to PFS (high ADA titre: 0.019 – 1 event, moderate and low ADA titres: 0). There were 3 skin and subcutaneous tissue disorders in high ADA titre with AI, and 1 event of hypersensibility in both AI and PFS high ADA titre. Finally, there was 1 event of eyelid oedema with AI in moderate ADA.

The incidence of TEHAEs in Nab positive patients was also slightly higher especially in patients who were administered the AI presentation (0.025 – 5 events with AI and 0.007 – 1 event with PFS in positive Nab, and 0.000 and 0.000 in negative Nab); same events as described above.

- *Incidence and Severity of Injection-Site Reactions by ADA Titre or neutralizing ADA (Nab)*

1. *Comparison of Injection-Site Reactions by ADA Titre and Nab between FKB327 and Humira*

The incidence of injection-site reactions at Week 0 of Study FKB327-002 was 13/332 patients (4.0%) for the FKB327-vial group, which was comparable with 14/317 patients (4.4%) for the Humira-PFS group. The incidence of injection-site reactions was 18/322 patients (5.6%) for the FKB327-PFS and 14/317 patients (4.4%) for the Humira-PFS at Week 0 in Period I of Study FKB327-003. The overall incidence of injection-site reactions in both the FKB327 and Humira treatment groups was relatively low (with low grade).

The incidence of injection-site reactions by ADA and Nab status for FKB327 and Humira was presented at FKB327-002 week 0, FKB327-003 week 0 (week 24 from the beginning) and FKB327-003 - week 30 (week 54 from the beginning). There was no clear increase in the grade of injection-site reaction for patients with a high ADA titre or a positive Nab for either treatment group.

2. *Comparison of Injection-site Reactions by ADA Titre and Nab by FKB327 Presentation*

At week 30 of FKB327-003 (day 1 of Period II), the applicant has compared the incidence of injection-site reactions in 487 patients who received FKB327 via the AI and 65 patients enrolled in the United States (US) who received FKB327 via the PFS. The incidence of injection-site reactions was not related to ADA titre or Nab in either presentation. However, the number of patients having received PFS was too low to allow a proper comparison.

Injection-site reactions including all PFB327 presentations (ie. Vial, PFS, AI) were overall also comparable in all Phase III studies by ADA and Nab status.

Comparative PK Study FKB327-004 (supportive study)

Study FKB327-004 was a Phase I, randomized, single-blind, parallel-group, single-dose study to compare pharmacokinetic characteristics and safety of FKB327 with those of US-licensed Humira in Japanese healthy male subjects. This study is considered as supportive for the immunogenicity assessment.

A relatively high frequency of ADA was detected in both treatment groups, attaining a level of >98% at day 65, with a relatively high frequency of nAb (although slightly lower than ADA), attaining a level of >80% of subjects were positive for nAb at Day 65.

Comparison across the treatment groups indicated similar frequencies of confirmed ADA positive and nAb positive samples at each time-point.

Although there was a higher apparent incidence of injection site reactions in the US-Humira treatment group, the numbers of events are too small to conclude that there was a real difference between the treatments.

Thus, these results are supportive of a conclusion of biosimilarity of FKB327 and Humira.

Discontinuation due to adverse events

Phase 1 Studies in Healthy Subjects

There were no AEs leading to treatment discontinuation in the Phase 1 studies. Two pregnancy-related discontinuations occurred, one in each study.

Phase 3 Study FKB327-002

Fourteen patients (3.8%) and 10 patients (2.8%) in the FKB327 vial and Humira PFS treatment groups, respectively, experienced a TEAE leading to treatment discontinuation. Most TEAEs leading to treatment discontinuation were reported only once, with the exception of latent tuberculosis, disseminated tuberculosis, pulmonary tuberculosis and Mycobacterium tuberculosis complex test positive.

Seven point four per cent (7.4%) of the patients in the FKB327 treatment group and 10.5% of patients in the Humira treatment group experienced a TEAE leading to temporary interruption. The most common TEAE leading to temporary treatment interruption was nasopharyngitis, which was reported for a similar proportion of patients in the FKB327 and Humira treatment groups.

Phase 3 Study FKB327-003 – period I

In period I of study FKB327-003:

- The proportion of patients with TEAEs leading to discontinuation was generally comparable for patients who remained on FKB327 (F-F, 4.6%) compared to those who remained on Humira (H-H, 5.2%). For patients who switched from Humira to FKB327, there was no increase compared to H-H reference (H-F, 3.7%).
- The proportion of patients with TEAEs leading to temporary treatment interruption was comparable for patients who remained on FKB327 (F-F, 8.8%) compared to those who remained on Humira (H-H, 9.4%). For patients who switched from Humira to FKB327, there was a small increase compared to H-H reference (H-F, 13.0%). The most common TEAEs leading to temporary treatment interruption were in the Infections and infestations SOC.

Integrated Analysis of Phase 3 Studies

The incidence of TEAEs leading to discontinuation was similar for FKB327 (0.09 events per patient-year) and Humira (0.07 events per patient-year). TEAEs leading to discontinuation were most frequently reported for the SOC Infections and infestations.

Long-term (1-Year) Safety Comparison (FKB327-002 / FKB327-003 period I)

The proportion of patients with at least 1 TEAE leading to discontinuation was similar for patients in F-F (9.3%) and H-H treatment sequence (8.3%); Infections and Infestations TEAE being the most frequent reason for discontinuation. Overall, the number of patients with a particular TEAE (PT) causing discontinuation was low, and the majority were reported for single patients.

2.6.1. Discussion on clinical safety

Patient exposure

The Safety Analysis Set in Study FKB327-002 comprised 366 patients treated with FKB327 and 362 patients treated with Humira. Of these patients, 216 patients on FKB327 and 213 on Humira proceeded to the FF and HH treatment sequences in Study FKB327-003, respectively, and 189 patients on FKB327 and

190 on Humira completed Period I (1-year data). For the 1-year safety comparison, the safety profile for 258 patients in the FF sequence (including 216 patients from FKB327-003 FF and 42 patients who received FKB327 in Study FKB327-002 but did not enter Study FKB327-003) has been compared to the safety profile for 254 patients in the HH sequence (including 213 patients from FKB327-003 HH and 41 patients who received Humira in Study FKB327-002 but did not enter Study FKB327-003).

The integrated analysis of Phase 3 Studies concerns all patients who received at least 1 dose of either FKB327 or Humira during the 2 Phase 3 studies. Patients who switched products are included in both treatment groups for the relevant duration of exposure. Overall, in FKB327-002 and FKB327-003, exposure was 837.26 patient-years for FKB327 and 336.01 patient-years for Humira. The lower exposure to Humira is due to all patients switching to FKB327 for Period II of the FKB327-003 study.

Adverse events

Overall, the safety profile was similar between FKB327 and the US-licensed and EU-approved Humira in the Phase I study FKB327-001, and was consistent with the known events associated with adalimumab treatment. However, the incidence of subjects with at least 1 TEAE is slightly lower with FKB327 (58.3%) compared to US-Humira (60%) which is slightly lower with EU-Humira (65%). Similar trend is seen for subjects with at least 1 treatment-related TEAE (50%, 53.3%, and 58.3%, respectively). However, the sample size was too small to draw any meaningful conclusions from these potential differences.

The most commonly reported TEAEs were headache, upper respiratory tract infection, nasopharyngitis, oropharyngeal pain and injection site hematoma. Overall, these TEAE were reported for similar numbers of subjects in each treatment group with some isolated differences. Similar observations were made for treatment-related TEAE.

Overall, FKB327 was comparable to Humira with regards to the overall safety profile following 24 weeks of exposure, with no major outstanding differences observed in the Phase 3 study FKB327-002. In both groups, the most common TEAEs occurred in the SOC Infections and infestations, Gastrointestinal disorders, and Musculoskeletal and connective tissue disorders with similar rate in both groups. However, with FKB327 compared with Humira, TEAEs (55.5% vs. 61.6%, respectively) and treatment-related TEAEs (20.2% vs. 23.2%, respectively) were slightly less reported. These differences could be chance findings given the small numbers of each type of event.

The incidence of subjects with at least 1 TEAE is slightly lower with the sequence F-F (47.7%) compared to the sequence H-H (54.9%) and a similar trend is seen for subjects with at least 1 treatment-related TEAE (18.1% vs. 23%, respectively) in the Phase 3 study FKB327-003 period I. Overall, review of the incidence of AEs showed that there was no major outstanding difference between switching and non-switching treatment sequences (H-F, F-H, F-F and H-H). Patient and event numbers per sequence are too low for the observed differences to be regarded as clinically relevant in the absence of a consistent trend.

There were no major differences between the safety profiles of the different treatment sequences (F-H-F, F-F-F, H-F-F and H-H-F) during period II and the whole study period in the Phase 3 study FKB327-003.

From the integrated analysis of phase 3 studies, the safety profiles of FKB327 and Humira, overall, are comparable with regards to the treatment-emergent adverse events (TEAEs), severe TEAE, treatment-emergent serious adverse events TEAE (TESAE), treatment-related TEAE, and discontinuation or interruption (due to TEAE or TESAE). However, the incidence was slightly lower with FKB327 compared to Humira for TEAE (2.00 vs. 2.69, respectively) and treatment-related TEAE (0.56 vs. 0.74). Treatment related TEAEs were most frequently reported for the SOC Infections and infestations. The most common

treatment related TEAEs were injection site erythema, nasopharyngitis, urinary tract infection, latent tuberculosis, upper respiratory tract infections, bronchitis, pharyngitis, pneumonia, sinusitis, Mycobacterium tuberculosis complex test positive, alanine aminotransferase increased, hypercholesterolaemia, and RA flare. The incidence rates of these treatment-related TEAEs were broadly comparable between treatments. Findings are compatible with the safety profile for Humira, per the Summary of Product Characteristics.

In the long-term (1-Year) Safety Comparison (FKB327-002 / FKB327-003 part I), the long-term (1-year) safety profile of FKB327 (F-F) was overall comparable to Humira (H-H), though the incidence of TEAEs and treatment-related TE was slightly lower for F-F patients compared to other treatment sequences (H-H, F-H & H-F).

Serious adverse events and deaths

There were no deaths during the Phase 1 studies. In the Phase 3 Studies in Rheumatoid Arthritis Patients, a total of 5 patients died (4 patients receiving FKB327 at the time of death and 1 patient receiving Humira, corresponding to death rates of 0.006 and 0.003 per patient-year, respectively).

In Phase 3 Study FKB327-002, no pertinent difference in TESAE was noted between FKB327 vial and Humira PFS presentations, with most TESAEs being experienced by only 1 patient.

In Phase 3 Study FKB327-003, generally, there was no significant difference in TESAEs reported by any of the treatment schedule groups. In period I, the incidence of TESAEs was generally comparable for patients who remained on FKB327 (F-F) compared to those who remained on Humira (H-H). For patients who switched from Humira to FKB327 (F-H), there was a slight increase compared to H-H reference in the incidence of TESAEs. Overall, the number of patients with TESAEs was low and the majority was reported for single patients, making it difficult to make comparisons across the treatment sequences.

In the integrated analysis of the Phase 3 studies, the incidence of TESAEs was similar for FKB327 compared to Humira. The most reported SOC were infections/infestations and Musculoskeletal & Connective Tissue disorders.

Adverse events of special interest

Overall, there were no major differences for AESI (infections, serious infections, injection site reactions, hypersensitivity reactions, neutropenia, thrombocytopenia, malignancies, and congestive heart failure) in study FKB327-0002 between FKB327 and Humira, in study FKB327-0003 period I between FKB327 and Humira, in the integrated analysis of the Phase 3 studies between FKB327 and Humira, or in the 1-year safety comparison between F-H and H-H. No patient had pancytopaenia or aplastic anaemia, demyelination, or a lupus-like event.

Other significant adverse events

The safety profile of FKB327 was similar to that for Humira, as assessed by vital signs, physical examination findings, and TB testing.

No important differences were observed in injection site assessments between the FKB327 and Humira treatment groups or as a result of switching treatments. In general, the trend seems to indicate that FKB327 has a better injection site pain profile compared to Humira.

Extensive patient data (n=507) from study FKB327-003 showed no evidence that the use of an AI was associated with worse local tolerance compared to PFS. On the contrary, spontaneous treatment-emergent reports as well as systematic injection site assessment suggested slightly less reactions and pain with the AI. Only 4 patients (0.7%) had a Grade 2 reaction (definite erythema [readily visible]/minimal oedema or minimal popular response) with the AI and the mean injection pain evaluated on a visual analogue scale was similar or lower when switching from the PFS to the AI.

Laboratory findings

There were no clinically important trends in any of the haematology, biochemistry or urinalysis parameters during the clinical development programme.

Safety in special populations

Concomitant anti-rheumatic drugs:

In phase 3 study FKB327-002, the FKB327 and Humira treatment groups were well matched with respect to concomitant, stable, background treatment for RA. A similar proportion of patients in the FKB327 and Humira treatment groups were receiving concomitant oral steroids for RA (most common being methylprednisolone and prednisone) and concomitant NSAIDs for RA (most common being meloxicam and diclofenac).

In phase 3 study FKB327-003 period I, the proportion of patients receiving concomitant oral steroids for RA and/or concomitant NSAIDs for RA was broadly similar for the 2 treatments with similar average concomitant MTX doses (same most common concomitant oral steroids and concomitant NSAIDs as in FKB327-002).

In the overall study FKB327-003, the proportion of patients receiving concomitant oral steroids and concomitant NSAIDs for RA was higher for the F-H-F treatment sequence and lower in the F-F-F treatment sequence compared to the other sequences

Medical history and concurrent medical condition

Overall, in phase 3 studies, past and concurrent medical history (excluding RA reported by all patients) were reported with similar proportions in both the FKB327 and Humira treatment groups and in each sequence treatments.

Immunological events

In the Phase I study FKB327-001, FKB327 seemed overall comparable to US-licensed Humira and EU-approved Humira in terms of the following parameters: ADA and nAb frequency at all time-points, ADA titer distribution at Day 65, and incidence and severity of injection site reactions. However, due to the uncertainties related to the numerous inconclusive samples in the assays, no conclusion can be drawn on the comparability of the immunogenicity profiles of FKB327 and EU-Humira and US-Humira for the healthy subjects included in this study (See section 2.4).

In the Phase 3 Studies FKB327-002 and FKB327-003, ADA development for the FKB327 presentations (vial, PFS, AI) was evaluated throughout Study FKB327-002 (24 weeks) and Periods I and II of Study FKB327-003 (+76 weeks in patients who proceeded to FKB327-003 study).

The frequency of neutralizing ADA (Nab) positive samples was almost equivalent to the frequency of ADA positive patients in the course of Studies FKB327-002 and FKB327-003.

In patients maintained on the same product (F-F or US H-H) for 48 weeks, the frequency of positive samples for binding and neutralising ADA increased up to Week 24 (around 60%), then started to decrease to plateau at about 50%. The same rate was reported at Week 48 with both products. It is reassuring that the ADA rates did not increase when patients were switched from one product to another (F-H and H-F) and that ADA rates similarly decreased in these patients.

There were no major differences in ADA frequency, Nab positive rate and ADA titre distribution among treatments via FKB327 presentations (ie. vial, PFS and AI), and these were not increased when switching during the course of Study FKB327-002 and Period I and Period II of Study FKB327-003.

During the overall period from Study FKB327-002 to Period II of Study FKB327-003 (integrated FKB327-002 Safety Analysis Set), TEHAE were observed at a relatively low incidence across both treatment groups (FKB327 and Humira). By ADA or Nab status, the overall incidence rate of TEHAEs was similar in both treatment groups.

The overall incidence of injection-site reactions was low and similar in the FKB327 and Humira treatment groups (with low grade). There was no clear increase in the grade of injection-site reaction for patients with a high ADA titre or a positive Nab for either treatment group. Injection-site reactions including all PFB327 presentations (ie. Vial, PFS, AI) were overall also comparable in all Phase III studies by ADA and Nab status.

The observed ADA level (50-60%) is much higher to what is established in the SmPC of Humira for the RA population (5%). This difference could be due to a much more sensitive assay. Moreover, for both products, although the safety profile seems quite similar, there is a decrease of the efficacy associated with an increase of ADA and Nab during time.

Discontinuation due to AES

There were no AEs leading to treatment discontinuation in the Phase 1 studies. Overall, 3.8% of FKB327 vial patients and 2.8% of Humira PFS patients experienced a TEAE leading to treatment discontinuation in Phase 3 Study FKB327-002. Additionally, 7.4% of FKB327 vial patients and 10.5% of Humira PFS patients experienced a TEAE leading to temporary interruption.

In Study FKB327-003 – Period I, the proportion of patients with TEAEs leading to discontinuation was generally comparable for patients who remained on FKB327 (F-F) compared to those who remained on Humira (H-H) and compared to patients who switched (H-F). The proportion of patients with TEAEs leading to temporary treatment interruption was comparable for patients who remained on FKB327 (F-F) compared to those who remained on Humira (H-H). For patients who switched (H-F), there was a small increase compared to H-H. The most common TEAEs leading to temporary treatment interruption were in the Infections and infestations SOC. Overall, the number of patients particular TEAE leading to discontinuation or temporary treatment interruption was low and the majority were reported for single patients, making it difficult to make comparisons across the treatment sequences.

In the integrated Analysis of Phase 3 Studies the incidence of TEAEs leading to discontinuation and to temporary treatment interruption was comparable for FKB327 and Humira. TEAEs leading to discontinuation were most frequently reported for the SOC Infections and infestations.

In the long-term (1-Year) Safety Comparison (FKB327-002 / FKB327-003 period I), the proportion of patients with at least 1 TEAE leading to discontinuation was similar for patients in F-F and H-H treatment sequence; Infections and Infestations TEAE being the most frequent reason for discontinuation. To complete the set of safety and immunogenicity data from study FKB327-003 CSR, the applicant has

committed to submit the final report of the pivotal Phase 3 study FKB327-003 by 31 October 2018 (see RMP section).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

In conclusion, up to 1-year, the descriptive comparison of safety, immunogenicity, and tolerability profile of FKB327 and Humira did not reveal any major differences between both treatments.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Serious infections including diverticulitis and opportunistic infections (e.g. invasive fungal infections, parasitic infections, legionellosis, and tuberculosis [TB]) • Reactivation of hepatitis B • Pancreatitis • Lymphoma • Hepatosplenic T-cell Lymphoma (HSTCL) • Leukaemia • Non-melanoma skin cancer (NMSC) • Melanoma • Merkel cell carcinoma (MCC) (neuroendocrine carcinoma of the skin) • Demyelinating disorders (including multiple sclerosis [MS], Guillain- Barré syndrome [GBS], and optic neuritis) • Immune reactions (including lupus-like reactions and allergic reactions) • Sarcoidosis • Congestive heart failure (CHF) • Myocardial infarction (MI) • Cerebrovascular accident (CVA) • Interstitial lung disease (ILD) • Pulmonary embolism (PE) • Cutaneous vasculitis • Stevens-Johnson syndrome (SJS) • Erythema multiforme (EM)

	• Worsening and new onset of psoriasis (Ps) • Haematologic disorders • Intestinal perforation • Intestinal stricture in Crohn's disease (CD) • Liver failure and other liver events • Elevated alanine transaminase (ALT) levels • Autoimmune hepatitis • Medication errors and maladministration
Important potential risks	• Other malignancies (except lymphoma, hepatosplenic T-cell lymphoma [HSTCL], leukaemia, non-melanoma skin cancer [NMSC], and melanoma) • Vasculitis (non-cutaneous) • Progressive multifocal leukoencephalopathy (PML) • Reversible posterior leukoencephalopathy syndrome (RPLS) • Amyotrophic lateral sclerosis (ALS) • Colon cancer in ulcerative colitis (UC) patients • Infections in infants exposed to Hulio® in utero • Medication errors with paediatric vial • Off-label use
Missing information	• Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications • Long-term safety information in the treatment of children aged from 6 to <18 years with Crohn's disease (CD) and paediatric enthesitis-related arthritis (pedERA) • Pregnant and lactating women • Remission-withdrawal-retreatment data for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (nr-axSpA) and episodic treatment in psoriasis, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis (Ps, CD, UC, and JIA) • Long-term safety information in the treatment of adults with hidradenitis suppurativa (HS) • Long-term safety information in the treatment of adults and children with uveitis

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
FKB327-003 study: An Open-label Extension Study to Compare the Long term Efficacy, Safety, Immunogenicity and Pharmacokinetics of FKB327 and Humira® in Patients with Rheumatoid Arthritis on Concomitant Methotrexate (ARABESC-OLE). Ongoing	To compare the safety of long term treatment with FKB327 and Humira® in patients with RA and also to evaluate safety, and changes in efficacy, in patients who were switched from FKB327 in the preceding FKB327-002 double blind study to Humira® in the FKB327-003 OLE study, and then switched back to FKB327 in the second part of the FKB327-003 OLE study.	Long-term safety in RA.	Protocol finalised	Q1 2015
			Study start	Q3 2015
			Study finish	Q1 2018
			Final report available	31 October 2018
British Society for Rheumatology Biologics Register- Rheumatoid Arthritis (**BSRBR-RA**): A longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies (UK). Planned	To evaluate the long term safety and confirm the assumption that Hulio® therapy in patients with RA is associated with similar risks compared to patients with similar disease activity receiving established anti-TNF medications.	Long-term safety in RA with emphasis on TB/other serious infection, malignancies, elevated ALT levels, autoimmune hepatitis, and CHF/MI.	Protocol finalised	Q1 2019
			Study start	Q1 2019
			Study finish	Q4 2031
			Final report available	Q4 2032

Risk minimisation measures

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk 1: **Serious infections including diverticulitis and opportunistic infection, e.g., invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB)**	Routine risk minimisation measures: *SmPC section 4.3 where patients with active tuberculosis or other severe infections are contraindicated* *SmPC section 4.4 where a warning is given not to initiate treatment in patients with active infections, to closely monitor patients for infections, and to discontinue Hulio® if a patient develops a new serious infection or sepsis* *SmPC section 4.8 where a description of serious infections observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed as adverse reactions* *PL section 2 where patients with active tuberculosis or other severe infections are contraindicated* *PL section 2 where a warning is given for the patient not to use if they have a severe infection, and that they will be monitored closely for infections and TB* *PL section 4 listed as side effects* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*
Important Identified Risk 2: **Reactivation of Hepatitis B**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given to test patients for HBV infection before initiating treatment with Hulio®, to closely monitor patients who are carriers of HBV, and to stop treatment if HBV reactivation develops*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities:

	SmPC section 4.8 listed as an adverse reaction *PL section 2 where a warning is given that the doctor will test them for HBV* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	*None*
Important Identified Risk 3: **Pancreatitis**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Identified Risk 4: **Lymphoma**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of lymphomas in patients (including children) treated with a TNF antagonist* *SmPC section 4.8 where a description of lymphomas observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*
Important Identified Risk 5: **Hepatosplenic T-cell Lymphoma (HSTCL)**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of HSTCL in patients treated with adalimumab and that the combination*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

	adalimumab and that the combination of azathioprine or 6-mercaptopurine and Hulio® should be carefully considered *SmPC section 4.8 where a description of HSTCL observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*	*None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*
Important Identified Risk 6: **Leukaemia**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of leukaemia in patients treated with a TNF antagonist* *SmPC section 4.8 where a description of leukaemia observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can increase the risk of getting leukaemia* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*

Important Identified Risk 7: **Non-melanoma skin cancer (NMSC)**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of other malignancies in patients treated*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None*
	with a TNF antagonist *SmPC section 4.8 listed as an adverse reaction* *SmPC section 4.8 where a description of NMSC observed in adalimumab clinical trials is provided* *PL section 2 where a warning is given that Hulio® can increase the risk of getting non-melanoma skin cancer* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*	Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*
Important Identified Risk 8: **Melanoma**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about possible development of other malignancies in patients treated with a TNF antagonist* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer* *PL section 2 where a warning is given for the patient to talk to their doctor if new skin lesions appear during or after treatment* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*

Important Identified Risk 9: **Merkel cell carcinoma (MCC)**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about the possible development of other malignancies in patients treated with a TNF antagonist* *SmPC section 4.8 listed as an adverse reaction*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance
	reaction *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*	activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*

Important Identified Risk 10: **Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS], and optic neuritis)**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disease* *SmPC section 4.4 where a warning is given to exercise caution in considering the use of Hulio® in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders, and to consider discontinuation if these disorders develop* *SmPC section 4.4 where guidance is given to perform neurologic evaluation in patients with non-infectious intermediate uveitis prior to and during treatment* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given for the patient to talk to their doctor if experiencing symptoms such as weakness, numbness or tingling of the limbs* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
	HCP Educational Material	

Important Identified Risk 11: **Immune reactions (including lupus-like reactions and allergic reactions)**	Routine risk minimisation measures: *SmPC section 4.3 where patients with hypersensitivity to the active substance or to any of the excipients are contraindicated* *PL section 2 where patients with allergies to adalimumab or any of the other ingredients are contraindicated* *SmPC section 4.4 where instruction is given to discontinue treatment immediately and initiate appropriate therapy if an anaphylactic reaction or other serious allergic reaction occurs* *SmPC section 4.4 where a warning is given to stop further treatment with Hulio® if a patient develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA* *SmPC section 4.8 listed as an adverse reaction* *PL sections 2 and 4 where warnings are given for the patient not to further use Hulio® if they experience allergic reactions and to seek urgent medical attention* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Identified Risk 12: **Sarcoidosis**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Identified Risk 13:	Routine risk minimisation measures: *SmPC section 4.3 where patients with*	Routine pharmacovigilance activities beyond adverse reactions reporting and

Congestive heart failure (CHF)	*moderate to severe heart failure (NYHA class III/IV) are contraindicated* *SmPC section 4.4 where a warning is given to discontinue treatment with Hulio® in patients who develop new or worsening symptoms of congestive heart failure* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given for the patient not to use if they have moderate or severe heart failure* *PL section 2 where a warning is given for the patient to talk to their doctor if they have mild heart failure or have, or have previously had, a serious heart condition before starting treatment, or if they develop new or worsening symptoms of heart failure* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*	signal detection: *None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*
Important Identified Risk 14: **Myocardial infarction (MI)**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*
Important Identified Risk 15: **Cerebrovascular accident (CVA)**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None*

	Legal status (prescription only medicine) Additional risk minimisation measures: *None*	Additional pharmacovigilance activities: *None*
Important Identified Risk 16: **Interstitial lung disease (ILD)**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Identified Risk 17: **Pulmonary embolism (PE)**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Identified Risk 18: **Cutaneous vasculitis**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Important Identified Risk 19: **Stevens-Johnson syndrome (SJS)**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Important Identified Risk 20: **Erythema multiforme (EM)**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Identified Risk 21: **Worsening and new onset of psoriasis (Ps)**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Important Identified Risk 22: **Haematologic disorders**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that adverse events of the haematologic system have been reported in patients treated with adalimumab* *SmPC section 4.4 where a warning is given to consider discontinuation of Hulio® therapy in patients with confirmed significant haematologic abnormalities* *SmPC section 4.8 listed as an adverse reaction* *PL section 2 where a warning is given that Hulio® can cause low blood-cell counts* *PL section 2 where a warning is given for the patient to seek urgent medical attention if they develop pale complexion, dizziness, persistent fever, bruise or bleed very easily* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

	None	
Important Identified Risk 23: **Intestinal perforation**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Important Identified Risk 24: **Intestinal stricture in Crohn's disease (CD)**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that failure to respond to treatment for CD may indicate the presence of fixed fibrotic stricture, although available data suggest that adalimumab does not worsen or cause strictures* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Identified Risk 25: **Liver failure and other liver events**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 2 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Identified Risk 26: **Elevated alanine transaminase (ALT) levels**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 2 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)*
		British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)

Important Identified Risk 27: **Autoimmune hepatitis**	Routine risk minimisation measures: *SmPC section 4.8 listed as an adverse reaction* *PL section 2 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*
Important Identified Risk 28: **Medication errors and maladministration**	Routine risk minimisation measures: *SmPC section 4.2 where guidance is given that Hulio® treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Hulio® is indicated* *SmPC section 4.2 where guidance is given on the recommended posology and method of administration* *SmPC section 6.4 where guidance is given on the special precautions for storage* *PL section 3 where instructions are given on how to use Hulio®* *PL section 3 where instruction is given for the patient to tell their doctor or pharmacist if they have accidentally injected more or less Hulio® than recommended or forgotten a scheduled dose* *PL section 5 where guidance is given on the storage conditions for Hulio®* *PL section 7 where instructions for preparing and giving an injection of Hulio® are detailed* *Legal status (prescription only*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

	medicine) Additional risk minimisation measures: *None*	
Important Potential Risk 1: **Other malignancies (except lymphoma, hepatosplenic T-cell lymphoma [HSTCL], leukaemia, non-melanoma skin cancer [NMSC], and melanoma)**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about the possible development of other malignancies in patients (including children and adolescents) treated with a TNF antagonist* *SmPC section 4.8 listed as adverse reactions* *PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer especially if the patient has COPD or is a heavy smoker* *PL section 2 where a warning is given for the patient to talk to their doctor if they have COPD or are a heavy smoker and to discuss whether treatment with Hulio® is appropriate* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Alert Card* *HCP Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Further monitoring and characterisation of long-term treatment in patients with RA in the ongoing FKB327-003 clinical trial (ARABESC- OLE)* *British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) (UK)*
Important Potential Risk 2: **Vasculitis (non-cutaneous)**	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Potential Risk 3: **Progressive multifocal leukoencephalopathy (PML)**	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Important Potential Risk 4:	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and
Reversible posterior leukoencephalopathy syndrome (RPLS)	*Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	signal detection: *None* Additional pharmacovigilance activities: *None*
Important Potential Risk 5: **Amyotrophic lateral sclerosis (ALS)**	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Potential Risk 6: **Colon cancer in ulcerative colitis (UC) patients**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that the risk for developing dysplasia or colon cancer in UC patients is unknown* *SmPC section 4.4 where instruction is given to screen UC patients for dysplasia at regular intervals before therapy and throughout their disease course (including use of colonoscopy and biopsies) if they are at increased risk or have a prior history of dysplasia or colon carcinoma* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Potential Risk 7: **Infections in infants exposed to Hulio® in utero**	Routine risk minimisation measures: *SmPC section 4.6 where a recommendation is given not to administer live vaccines to infants exposed to adalimumab in utero for 5 months following the mother's last adalimumab injection during pregnancy* *PL section 2 where instruction is given for the patient to tell their baby's doctors and/or other HCPs about their Hulio® use during pregnancy before the baby receives any vaccinations* *Legal status (prescription only*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

	medicine) Additional risk minimisation measures: *None*	
Important Potential Risk 8: **Medication errors with paediatric vial**	Routine risk minimisation measures: *SmPC section 4.2 where guidance is given that Hulio® treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Hulio® is indicated* *SmPC section 4.2 where guidance is given on the recommended posology and method of administration* *SmPC section 6.4 where guidance is given on the special precautions for storage* *PL section 3 where instructions are given on how to use Hulio®* *PL section 5 where guidance is given on the storage conditions for Hulio®* *PL section 7 where instructions are detailed for preparing and giving an injection of Hulio®* *PL section 3 where instructions are given for the patient carer to tell the doctor or pharmacist if they have accidentally injected the child with more or less Hulio® than recommended or forgotten a scheduled dose* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Important Potential Risk 9: **Off-label use**	Routine risk minimisation measures: *SmPC sections 4.1 and 4.2 where clear specifications of authorised indications and posology, respectively, are provided* *PL sections 1 and 3where clear specifications of authorised indications and posology, respectively are provided* *Legal status (prescription only medicine)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

	Additional risk minimisation measures: *None*	
Missing Information 1: **Subjects with immune-compromised conditions may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications**	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given for physicians to exercise caution when considering the use of Hulio® in patients with underlying conditions which may predispose them to infections, including the use of concomitant immunosuppressive medications* *PL section 2 where a warning is given for the patient to tell their doctor before using Hulio® if they are suffering from another condition which makes them more susceptible to getting infections* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Missing Information 2: **Long-term safety information in the treatment of children aged from 6 to <18 years with Crohn's disease (CD) and paediatric enthesitis- related arthritis (pedERA)**	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Missing Information 3: **Pregnant and lactating women**	Routine risk minimisation measures: *SmPC section 4.6 where women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and not to breast-feed for at least five months after the last Hulio® treatment* *PL section 2 where advice is given for the patient to use adequate contraception and not to breast-feed while using Hulio® and for at least 5 months after the last Hulio® dose* *Legal status (prescription only medicine)* Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
	None	

Missing Information 4: **Remission-withdrawal-retreatment data for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (nr-axSpA) and episodic treatment in psoriasis, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis (Ps, CD, UC, and JIA)**	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Missing Information 5: **Long-term safety information in the treatment of adults with hidradenitis suppurativa (HS)**	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Missing Information 6: **Long-term safety information in the treatment of adults and children with uveitis**	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. 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.

2.9. Product information

2.9.1. 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.>*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Hulio (adalimumab) is included in the additional monitoring list as new 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. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed biosimilar FKB327 is intended for all of the therapeutic indications approved for Humira in the EU: rheumatoid arthritis, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), axial spondyloarthritis (ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa (HS), Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis and paediatric uveitis.

Three pharmaceutical forms are proposed, which are similar to three of the pharmaceutical forms of Humira and contain a 40 mg/0.8 mL solution for injection: a vial (for paediatric use), a pre-filled syringe and a pre-filled pen (all of a volume of 0.8 mL).

3.1.2. Available therapies and unmet medical need

This is a biosimilar application to Humira.

3.1.3. Main clinical studies

The claim of biosimilarity is based on the totality of the evidence including analytical, nonclinical and clinical data. The comparability exercise is mainly based on the following studies:

- Analytical studies: primary structure, glycosylation, higher order structure, size heterogeneity, charge heterogeneity, hydrophobic heterogeneity, amino acid modifications, process-related impurities, visible and sub-visible particles, strength;
- Functional studies: binding to target antigen (soluble rhTNFα, tmTNFα); binding to FC receptors FcγR (I, IIa, IIb, IIIa (V and F), IIIb (NA1 and NA2) and FcRn; binding to C1q; Fab-associated functions (cytotoxicity neutralisation, apoptosis); Fc-associated functions (ADCC, CDC);
- FKB327-001: A single-dose (40 mg sc) three-arm parallel PK trial in healthy volunteers comparing FKB327, EU- and US-sourced reference products;
- FKB327-002: A phase III Randomised, Blinded, Active-Controlled Study to Compare FKB327 Efficacy and Safety with the US-sourced Humira in Rheumatoid Arthritis Patients Inadequately Controlled on Methotrexate

In addition, the Applicant conducted Study FKB327-003 which was an Open-label Extension Study to Compare the Long term Efficacy, Safety, Immunogenicity and Pharmacokinetics of FKB327 and Humira in Patients with Rheumatoid Arthritis on Concomitant Methotrexate (ARABESC-OLE).

3.2. Favourable effects

From a quality and non-clinical point of view, the biological function parameters such as neutralization of soluble TNF-α induced cytotoxicity in L929 cells, induction of apoptosis in mTNF-α expressing cells, binding to Fcγ receptors and FcRn; binding to C1q; ADCC activity and CDC activity in mTNF-α cells were found to be similar between FKB327 and the reference product Humira.

With respect to the clinical pharmacokinetics, the development program to demonstrate the similarity between Hulio and Humira is adequate and was performed according to the guidance on similar biological products and the recommendations given in the CHMP Scientific Advices. The comparability exercise was performed between EU/US sourced reference products and the formulation intended to be marketed in the European Union. Using ANCOVA, biosimilarity is demonstrated as the 90% CI for PK parameters are in the acceptance range of 80-125%. The introduction of covariates in the statistical analysis (ANCOVA) helps to reduce the variability introduced by using patients with possibly different baseline characteristics on each treatment arm and is used instead of ANOVA. ANCOVA was pre-specified in the SAP and deemed justified for a parallel design of a monoclonal antibody with the aim to increase precision.

A statistical comparison for the C_{trough} pre-dose concentrations (at weeks 4, 12, 20 and 24 and at weeks 12, 24 and 30 in the phase III studies FKB327-002 and 003 respectively) has been carried out by the Applicant. The small differences in mean trough serum drug concentrations observed in the clinical studies are not expected to result in clinically meaningful differences in efficacy and safety.

From an efficacy perspective, equivalence between FKB327 and Humira was demonstrated through assessment of the ACR20 RR at week 24 in the pivotal equivalence trial FKB327-002. The ACR20 RR difference (FKB327 vs Humira- measured in the FAS with RCI for missing data) was -1.3% (95% CI -7.6,5.0), of which the 95% CI lies within the prespecified +/- 13% equivalence range. Similarly, equivalence was demonstrated when the ACR20 RR difference was analysed in the PPAS (difference FKB327 vs Humira -0.4, 95% CI -6.7,5.9). DAS28-CRP difference at week 24 was 0.01 (95% CI -0.17,0.18) in the FAS and -0.03 (95% CI -0.21,0.15) in the PPAS with both 95% CI narrower than the predefined +/- 0.6 margin. Equivalence was confirmed in a sensitivity analysis with variable imputations for missing data. ACR20, ACR50 and ACR70 RR for FKB327 and Humira did not differ significantly at different time points from week 0 to week 24 in study FKB327-002.

Maintenance of efficacy up to 1 year of treatment, both in patients that continued on their initial treatment and in patients that switched between adalimumab presentations, was demonstrated in the long term follow up safety and efficacy study FKB327-003.

3.3. Uncertainties and limitations about favourable effects

From a quality perspective, discrepancies were seen between the N-glycan patterns of Hulio and EU-approved Humira, including differences in high mannose content, a quality attribute which was formerly reported to affect pharmacokinetic properties. At the CHMP request, the applicant further investigated potential reasons for the observed PK differences discussing all the attributes known to have an impact on the PKs of mAbs (drug presentations, ethnic factors...). A special attention has been paid to the physicochemical and functional characteristics of FKB327 (glycan patterns, LMWS) and evidence has been provided that the relative difference in high mannose content (and/or other physicochemical/biological parameters) between test and reference products has negligible impact on pharmacokinetics.

A sensitivity analysis (ANOVA) failed to show equivalence of Cmax and the truncated AUC0-360h, with higher values for FKB327 than for EU-Humira. However, given the parallel design, the use of an ANCOVA is considered more appropriate (see discussion above).

3.4. Unfavourable effects

The main data relevant for comparability exercise in terms of safety comes from the study FKB327-002 and the open label extension study FKB327-003 in RA patients. The applicant has re-randomized patients between FKB327-002 and FKB327-003 to either FKB327 or Humira in order to address potential consequences of switching between the originator and the biosimilar.

At the end of FKB327-003 Period I (Week 52 overall), the safety profiles are similar for FF and HH treatment sequences (although it might be slightly better for FF). There was no outstanding difference, and FF is comparable to HH with regard to TEAEs, treatment-related TEAEs, TESAEs, prematurely discontinuation due to TEAEs, prematurely discontinuation due to TESAEs, and deaths.

For both treatment sequences, TEAEs were most frequently reported in the Infections and Infestations SOC (mostly nasopharyngitis, bronchitis, URTI, UTI), musculoskeletal and connective tissue disorders (mostly RA flare), investigations (mostly Mycobacterium tuberculosis complex test positive) and gastrointestinal disorders (diarrhoea and nausea).

For both treatment sequences, treatment-related TEAEs were most frequently reported in the Infections and Infestations SOC (bronchitis), General disorders and administration site conditions (injection site reaction), and Blood and lymphatic system disorders (anaemia).

The most frequently reported TESAEs were also in the Infections and Infestations SOC. Finally, Infections and Infestations TEAE were also the most frequent reason for treatment discontinuation. TEAEs of special interest were similarly reported in both treatment sequences.

In Study FKB327-003 Period I, there was no outstanding difference between patients who remained on Humira (H-H) compared to patients who switched to FKB327 (H-F). And, although the safety profile was slightly better with F-F treatment sequence compared to the others, the incidence of severe TEAEs, treatment-related TEAEs, TESAEs, discontinuations due to TEAEs, and treatment interruptions due to TEAEs was generally comparable between treatment sequences (with switch or not). Patient and event numbers per sequence are too low for the observed differences to be regarded as clinically relevant in the absence of a consistent trend.

Overall, the immunogenicity profiles were comparable in terms of overall ADA incidences (and titers) and neutralising antibodies between the FKB327 and Humira treatment groups in RA patients up to 100 weeks (24 wk FKB327-002 + 76 wk end of FKB327-003). Approximatively 50-60% of the patients treated with FKB327 or Humira develop ADAs. The frequency of nAb positive patients was almost equivalent to the frequency of ADA positive patients for both products. The incidence of TEHAEs and injection site reactions was low and well-balanced between the 2 products.

3.5. Uncertainties and limitations about unfavourable effects

With regard to the ADA and Nab assays used in the study FKB327-001, no conclusion can be drawn on the comparability of the immunogenicity profiles of FKB327 and EU-Humira and US-Humira for the healthy subjects included in this study due to the uncertainties related to the numerous inconclusive samples in the assays. However, because the deficient ADA and NAb assays were only used in the study FKB327-001 and because ADA or NAb are not included as a covariate of the ANCOVA model used to conclude the bioequivalence between all 3 treatments in the study FKB327-001, this issue was not pursued by the CHMP.

In the integrated analysis of FKB327-002 and FKB327-003, while comparing the 3 different presentations (vial, PFS and AI), although the safety profile was overall similar, slight differences were observed: better safety profile observed with AI compared to PFS safety profile which was better to vial safety profile. These differences may have been related to the fact that the presentations were used in series (rather than in parallel): the exposure to the vial presentation represents the initiation of anti-TNF therapy (for the first time in most patients), whereas exposure to the PFS mostly represents the continuation of the treatment, and AI represents long-term maintenance therapy. There were no clinically meaningful differences and caution should be applied when interpreting these data due to the relatively small number of events for some categories.

The observed ADA level (50-60%) is much higher to what is established in the SmPC of Humira for the RA population (5%). This difference could be due to a much more sensitive assay. Moreover, for both products, although the safety profile seems quite similar, there is a decrease of the efficacy associated with an increase of ADA and Nab during time.

To complete the set of safety and immunogenicity data from study FKB327-003 CSR, the applicant has committed to submit the final report of the pivotal Phase 3 study FKB327-003 by 31 October 2018 (see RMP section).

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

A single pivotal equivalence trial comparing the test and reference product is considered adequate to support this biosimilar application. The choice of the indication (rheumatoid arthritis), the clinical setting (patients not adequately controlled with methotrexate, including previous anti-TNF responders), the primary and key secondary endpoints (ACR20 and DAS28-CRP at week 24) and the equivalence margin (± 13%) are in line with the CHMP guidance and were endorsed in CHMP Scientific Advice. This clinical model is considered sufficiently sensitive to enable the detection of differences between the two products.

Whilst US-licensed Humira was used as the reference product in these 2 Phase 3 studies, the pharmacokinetics (PK) of US-licensed and EU-approved Humira have been shown to be equivalent in the preceding Phase 1 study, FKB327-001. There is also now more than 10 years of post-marketing

experience with US-licensed and EU-approved Humira which has not resulted in substantially different safety findings for the 2 products. Thus, the safety results relating to US-licensed Humira are considered to be extrapolable to EU-approved Humira.

Supportive data are provided from the Phase 1 studies in healthy subjects. Comparative safety data between FKB327 and US-Humira were collected in RA patients in the pivotal Phase 3 studies at the recommended clinical dose.

Three presentations of FKB327 were used in the clinical program (while only Humira PFS was used): vials, PFS (FKB327-003 Period I only) and the auto-injector (FKB327-003 Period II only).

3.6.2. Balance of benefits and risks

From a quality and non-clinical point of view, the biological functionality parameters such as neutralization of soluble TNF-α induced cytotoxicity in L929 cells, induction of apoptosis in mTNF-α expressing cells, binding to Fcγ receptor I, IIa(R), IIa(H), IIb, IIIa(F), IIIa(V), IIIbNA1 and IIIbNA2 and FcRn; binding to C1q; ADCC activity and CDC activity in mTNF-α were found to be similar between FKB327 and the reference product Humira. The applicant has shown that the biological assays supporting their conclusions on biosimilarity were sufficiently sensitive.

From a PK perspective, using ANCOVA, the 90% CIs around the ratio of geometric LSMs are well within the pre-specified bioequivalence limits of 0.80 to 1.25 for all treatment comparisons for the primary PK endpoints, thus PK similarity was concluded between all 3 treatments (FKB327, EU-Humira and US-Humira).

Equivalence of efficacy was demonstrated through robust assessment of the ACR20 RR and DAS28-CRP values of FKB327 vs Humira (adalimumab) treated RA patients, which are considered clinically relevant endpoints. Efficacy was comparable up to one year of treatment.

The safety profiles of FKB327 and Humira are similar (and similar to the safety profile for Humira as described in the Summary of Product Characteristics) without clinically important difference in safety between the proposed biosimilar and the reference product.

The CHMP therefore concluded that the similarity of FKB327 and Humira have been demonstrated in terms of structural and functional characteristics, PK, immunogenicity profiles, efficacy and safety.

3.6.3. Additional considerations on the benefit-risk balance

The selection of RA as the indication in which to conduct the comparative efficacy clinical studies is considered appropriate for the justification of extrapolation of indications based on the fact that RA patients are a sensitive population with adalimumab exerting a good effect size, and where the efficacy endpoints used in RA clinical trials are validated and extensively used. In addition, the disease pathology and the role of TNF-α inhibition in RA are known.

The known safety profile of adalimumab is consistent across all approved indications of Humira.

The incidence rate of ADA against adalimumab was observed to be generally similar in studies of RA, AS, Ps, CD and JIA, and considering the use of immunosuppressants, with only small differences reported between the different populations.

Given the consistent findings from Hulio development program and on the basis of the current understanding of the mechanisms of action of adalimumab, the data from studies of FKB327 in RA has been regarded by the CHMP as predictive of the effectiveness and safety of the product in all of the approved indications for Humira.

In addition, given the observed similarity of FKB327 and Humira, the CHMP has concluded that the benefit risk profiles of FKB327 and Humira will be similar in all the indications approved for Humira.

3.7. Conclusions

The overall B/R of Hulio is positive.

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 Hulio is favourable in the following indication:

Rheumatoid arthritis

Hulio 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.

Hulio 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

Hulio 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). Hulio 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

Hulio 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)

Hulio 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

Hulio 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

Hulio 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

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

Paediatric plaque psoriasis

Hulio 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)

Hulio 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

Hulio 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

Hulio 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

Hulio 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.

Uveitis

Hulio 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

Hulio 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 Hulio 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 MAH shall ensure that in each Member State where Hulio is marketed, all healthcare professionals who are expected to prescribe Hulio are provided with the following educational package:

- Physician educational material
- Patient information

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient alert card

The Guide for healthcare professionals shall contain the following key elements:

- Relevant information on the safety concerns of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies to be addressed by the additional risk minimisation measures (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable).

The patient alert card shall contain the following key messages:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Hulio.

- That Hulio treatment may increase the potential risks of serious infections, sepsis, tuberculosis and opportunistic infections; congestive heart failure; demyelinating disorders; malignancies.

- Signs or symptoms of the safety concern and when to seek attention from a HCP

- Contact details of the prescriber

The patient information pack should contain:

- Patient information leaflet