31 January 2019
EMA/214726/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Kromeya

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/005158/0000

Note

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

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List of abbreviations

2AB	2-aminobenzamide
ADA	Anti-drug antibody
ADCC	Antibody Dependent Cellular Cytotoxicity
AE	Adverse event
a.o.	among others
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	Analytical ultracentrifugation
AUC0-∞	Area under the concentration-time curve from time 0 extrapolated to infinity
AUC0-last	Area under the concentration-time curve from time 0 to the last quantifiable concentration
BMI	Body mass index
Cmax	Maximum serum concentration
C1Q	Complement component C1q
CAP	Capture
CE-SDS	Capillary Electrophoresis Sodium Dodecyl Sulfate
CD	Circular dichroism
CDC	Complement-dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CMC	Chemistry, manufacturing and control
CPP	Critical Process Parameter
CQAs	critical quality attributes
CV	Coefficient of variation
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug Substance
DSP	Downstream Process
EC_{50}	Concentration of active ingredient producing the 50% of maximal activity
ELISA	Enzyme-Linked Immunosorbent Assay
E_{Max}	Maximal activity
eow	Every other week
EQ-5D	EuroQoL 5-dimensions questionnaire
ETP	Extended Treatment Period
ExCB	Extended Cell Bank
Fab	Fragment antigen-binding
FACS	Fluorescence-activated cell sorting
Fc	Fragment crystallizable
FcγRs	Fc gamma receptors
FcRn	Neonatal Fc receptor
FLS	Fibroblast-like synoviocytes
FT-IR	Fourier-transform infrared spectroscopy
GCP	Good Clinical Practice

GLP	Good laboratory practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCP	Host Cell Protein
HC	Heavy chain
HILIC	Hydrophilic-Interaction Liquid Chromatography
HMW	High Molecular Weight
HRQoL	Health-related quality of life
HUVEC	Human umbilical vein endothelial cell
IBD	Inflammatory bowel disease
ICAM-1	Intercellular adhesion molecule 1
ICH	International Council for Harmonisation
icIEF	Imaged Capillary Isoelectric Focusing
IgG	Immunoglobulin G
IKK	IκB kinase
IPC	In process Control
ITT	Intent-to-treat
K_D	Equilibrium dissociation constant
LAL	Limulus Amebocyte Lysate
LC	Light chain
LC	Liquid chromatography
LMW	Low Molecular Weight
LOD	Limit of Detection
LOQ	Limit of Quantitation
LTBI	Latent Tuberculosis Infection
mAbs	Monoclonal antibodies
MAPK	Mitogen-activated protein kinase
MAR	Missing at random
MCB	Master Cell Bank
MLR	Mixed lymphocyte reaction
MoA	Mechanism of action
MS	Mass Spectroscopy
MSB11022	Company code for adalimumab biosimilar product
NF-κB	Nuclear factor kappa light-chain-enhancer of activated B cells
NGHC	Non Glycosylated Heavy Chain
NHK	Normal human keratinocytes
NK	Natural killer
NLT	Not Less Than
NMT	Not More Than
NOR	Normal Operating Range
NR	Non reduced
NSD	Needle Safety Device
PAR	Proven Acceptable Range
PA-HPLC	Polar Advantage High Performance Liquid Chromatography
PBMC	Peripheral blood mononuclear cell
PAR	Proven Acceptable Range
PASI	Psoriasis Area and Severity Index
PASI 50	Psoriasis Area and Severity Index score reduction of ≥ 50% from Baseline
PASI 75	Psoriasis Area and Severity Index score reduction of ≥ 75% from Baseline

PASI 90	Psoriasis Area and Severity Index score reduction of ≥ 90% from Baseline
PASI 100	Psoriasis Area and Severity Index score reduction of 100% from Baseline
PD	Pharmacodynamic
PGA	Physician's Global Assessment
PJA-VAS	Patient Global Assessment for Joints on a Visual Analog Scale
PK	Pharmacokinetic
PFP	Pre Filled Pen
PFS	Pre Filled Syringe
Ph. Eur.	European Pharmacopoeia
PMN	Peripheral blood mononuclear cell
PP	Per Protocol
PPQ	Process Performance Qualification
qPCR	Quantitative Polymerase Chain Reaction
QC	Quality control
RMP	Reference medicinal product (EU-approved)
RoW	Rest of the World
rVLP	retrovirus-like particles
RP	Reference product (US-licensed)
SAF	Safety Analysis Set
SAE	Serious adverse event
SCX-HPLC	Strong Cation Exchange High Performance Liquid Chromatography
SD	Standard Deviation
SE-HPLC	Size Exclusion-High Performance Liquid Chromatography
SmPC	Summary of Product Characteristics
SPR	Surface plasmon resonance
sTNF	Soluble TNF
t1/2	Half-life
TAMC	Total Aerobic Microbial Count
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
tmax	Time to Cmax
TNBS	2,4,6-Trinitrobenzenesulfonic acid
TNF	Tumor necrosis factor alpha
tmTNF	Transmembrane tumor necrosis factor
TNFR	Tumor necrosis factor receptor
TOC	Total Organic Carbon
TFF	Tangential Flow Filtration
TNF	Tumour Necrosis Factor
USP	Upstream Process
UPLC	Ultra-performance liquid chromatography
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Deutschland GmbH submitted on 25 October 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Kromeya, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2016.

The applicant applied for the following indication for Kromeya 40 mg solution for injection:

Rheumatoid arthritis

Kromeya 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.

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

Kromeya reduces the rate of progression of joint damage as measured by X-ray and improves physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Kromeya 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). Kromeya 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

Kromeya 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)

Kromeya 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

Kromeya 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

Kromeya 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. Kromeya reduces 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 improves physical function.

Psoriasis

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

Paediatric plaque psoriasis

Kromeya 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.

Crohn's disease

Kromeya 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

Kromeya 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

Kromeya 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

Kromeya 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 corticosteroidsparing, or in whom corticosteroid treatment is inappropriate.

Paediatric Uveitis

Kromeya 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.

For the paediatric use formulation, Kromeya 40 mg/0.8 ml solution for injection, the indications applied for are Juvenile idiopathic arthritis, Paediatric plaque psoriasis, Paediatric Crohn's disease and Paediatric Uveitis.

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.1)
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/256/001-006

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.1)
- Date of authorisation: 08-09-2003, 07-11-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/256/001-010

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

- Product name, strength, pharmaceutical form: Humira 40 mg solution for injection
- Marketing authorisation holder: AbbVie Ltd.1)
- Date of authorisation: 08-09-2003
- Marketing authorisation granted by:
  - Union
- (Union) Marketing authorisation number(s):EU/1/03/256/003, EU/1/03/256/005

1) MAH changed durning the procedure to Abbvie Deutschland GmbH & Co. KG

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on:

Scientific advice	date	Area
EMEA/H/SA/3159/1/2015/III	24 September 2015	Quality, non-clinical, clinical
EMEA/H/SA/3159/1/FU/1/2016/II	01 April 2016	Clinical

The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:
Quality: Analytical Methods Panel to use in support of the demonstration of analytical similarity and use of statistical approach to evaluate analytical attributes.
Non-Clinical: Completeness and adequacy of the data package of *in vitro* and *in vivo* studies to demonstrate biosimilarity.
The main clinical aspects under consideration were:

- The design of the PK trial in healthy volunteers with attention to dose and safety.
- The design of the efficacy and safety trial in Psoriasis Patients including: population selected and the primary endpoint, proposed margins and statistical assumptions, duration and safety database.
- The bioequivalence PK bridging study in healthy volunteers for an alternative formulation.
- The design of the efficacy and safety trial in Crohn's Disease patients to be conducted with the alternative formulation including: population selected and the primary endpoint, proposed margins, duration and safety database.
- Extrapolation of the clinical results in Psoriasis to support registration in the other indications approved for the Reference Medicinal Product.
- Proposed pharmacovigilance activities in the early post-marketing period

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Romaldas Mačiulaitis

The application was received by the EMA on	25 October 2017
The procedure started on	23 November 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	13 February 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 February 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 March 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 September 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 request was adopted for Merck Serono S.p.a. Via delle Magnolie 15, Loc. frazione Zona Industriale, 70026, Modugno, Italy between 18-22 June 2018 due to information received from a third party.	01 Aug 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	23 October 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2018
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	08 November 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 November 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 December 2018
The Rapporteurs circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 January 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kromeya on	31 January 2019

2. Scientific discussion

2.1. Problem statement

Kromeya (MSB11022) has been developed as a biosimilar to Humira and the applicant claims all the indications of the reference product for Kromeya 40 mg solution for injection

For the paediatric formulation (40 mg/0.8 ml solution for injection), only the paediatric indications are applied for.

Disease or condition

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), Non-infectious Uveitis (UV) and paediatric uveitis in the European Union.

About the product

The proposed product, Kromeya, has been developed as a biosimilar to Humira (adalimumab). Adalimumab belongs to the pharmacotherapeutic group 'immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors' (ATC code: L04AB04). The mechanism of action of adalimumab is binding

specifically to TNF-α and neutralising its biological function by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Three pharmaceutical forms are proposed, which are the same as three of the pharmaceutical forms of the reference product and contain a 40 mg/0.8 ml solution for injection: a vial (for paediatric use), a pre-filled syringe (PFS) and a pre-filled pen (all of a volume of 0.8 ml). For the reference product, Humira, there is also a 20mg/0.2 ml strength available in a pre-filled syringe.

Type of Application and aspects on development

The various CHMP guidelines for similar biological medicinal products as well as indication-specific guidelines and guidelines relevant for the PK trial design and efficacy trial design were considered in the design of the clinical programme, in particular the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and the Guideline on Similar Biological Medicinal Products (CHMP/437/04 rev 1, 2014).

CHMP scientific advice was given on 24 September 2015, 16 October 2016 and 1 April 2016.

The main clinical aspects agreed by the CHMP concerning the pivotal efficacy trial were as follows:

- The proposed psoriasis population selected is appropriate and should be sensitive to detect differences between the test and Reference Medicinal Product (RMP) adalimumab.
- As it is more sensitive, mean PASI change was preferred over PASI75 as primary outcome. Efficacy assessments over various time points to plateau effect would be needed to ensure similarity.
- The 18% equivalence margin would need to be further justified using a meta-analysis and clinical justification.
- Predefined equivalence margins for the key secondary endpoint (percentage PASI change) should be provided in addition to the chosen primary endpoint (PASI75).
- Follow-up efficacy and safety assessments of patients taken off treatment are needed until week 16, unless patients withdraw their consent.
- The planned safety database could be adequate in terms of the number of subjects and duration of exposure. However 1 year of safety data and immunogenicity would need to be submitted early in the assessment.
- For indications where neutralising the soluble TNF -α appears to be mainly involved e.g. psoriasis, ankylosing spondylitis and RA, the extrapolation from psoriasis could be acceptable.
- Extrapolation to Crohn's disease would require convincing evidence from the preclinical studies related to these other potential mechanisms, e.g. the binding and effector functions in the setting of membrane bound TNF-α.

2.2. Quality aspects

2.2.1. Introduction

The finished product is a solution for injection in three different presentations: a PFS, a pre-filled pen and a vial (for paediatric use), all nominally containing 0.8 ml of the solution equivalent to 40 mg (50 mg/ml) of adalimumab as active substance.

Other ingredients are: sodium dihydrogen phosphate dihydrate; disodium phosphate dihydrate; mannitol; sodium chloride; citric acid monohydrate; sodium citrate; polysorbate 80; sodium hydroxide (for pH adjustment) and water for injections.

The product is available in three presentations: a pre-filled syringe, a pre-filled pen containing a pre-filled syringe, a vial with a rubber stopper. The adult posology foresees the administration of the full content of the syringe/pen. The paediatric posology requires administering partial doses from the vial; appropriate materials for administering the dose are supplied with the vial (1 sterile injection syringe, 1 sterile needle, 1 vial adaptor).

2.2.2. Active Substance

General information

Adalimumab is a recombinant human IgG1 monoclonal antibody composed of two kappa light chains each with a molecular weight of approximately 24 kilo Daltons (kDa) and two IgG1 heavy chains each with a molecular weight of approximately 49 kDa based on the amino acid sequence. The total molecular weight of adalimumab with post-translational modifications is approximately 148 kDa. Each light chain consists of 214 amino acid residues and each heavy chain consists of 451 amino acid residues resulting in a total of 1330 amino acids for the entire IgG1 molecule; one glycosylation site (N301) is present. The primary amino-acid sequence of the heavy and light chains is reported.

The internal company code of this preparation is MSB11022.

Manufacture, process controls and characterisation

The active substance manufacturing and quality control (QC) release and stability testing take place at Merck Serono SA, Corsier-sur-Vevey, Switzerland. The active substance QC release and stability testing can also be performed at Merck Serono S.p.A, Guidonia Montecelio, Italy.

Description of manufacturing process and process controls

Adalimumab active substance manufacturing process has been adequately described. The main steps are fermentation, recovery and purification as well as virus removal and inactivation steps.

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. All media used in cell culture processes are chemically-defined media. These media are free from substances of animal origin and free of proteins, except for the presence of insulin. The insulin used is recombinant human insulin produced and has compendial grade (European Pharmacopoeia (Ph. Eur.)). No other raw materials

from animal origin are used in the cell culture process or purification process. Acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate. All raw materials used in this process are received, quarantined and released according to approved specifications and written procedures as required under current GMP.

Adalimumab is produced by batch suspension culture of Chinese hamster ovary (CHO) cells that have been transfected with an expression vector containing coding sequences for the heavy and light chains of adalimumab.

A two-tiered cell banking system is used, consisting of a Master Cell Bank (MCB) from which WCBs are derived. The origin, source, history of cells and generation of the cell substrate as well as the cell banking system has been sufficiently documented. An extended cell bank (ExCB) was also produced, representing cells cultured till the maximum production limit during the cell expansion phase and an additional four population doubling levels after harvesting at the end of production. MCB-1, WCB-1.1 and ExCB underwent phenotypic and genotypic characterisation to confirm identity, purity and stability of the cell line, according current ICH guidance. Overall, the results support the stability of the production cell line. All future Working Cell Banks will be established in a dedicated cGMP cell banking area according to a protocol based on that used for the preparation of the WCB-1.1.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the adalimumab active substance manufacturing process is given. Acceptable information has been provided on the control system 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.

For each process step, critical process parameters were identified based on a risk assessment, using information coming from process development. Whenever necessary, experiments were conducted at small-scale to confirm the criticality of the process parameters and to define acceptable ranges. Appropriate controls have been included to detect possible deviations from the acceptable ranges for the critical process parameters. In-process controls (IPCs) have been defined to ensure appropriate performance of the manufacturing process. IPCs for the upstream process are mainly targeted on controlling cell viability and adventitious agents and for down-stream processing on bioburden, endotoxin and yield. During the procedure a number of concerns were identified, which has been adequately addressed by the applicant.

Process validation

The adalimumab active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial batches including process performance qualification batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the manufacturing process consistently produces adalimumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria. As part of the large scale process performance qualification a cumulated hold time study on process intermediates has been performed. The study aimed to confirm the absence of impact of the hold times on the quality of the active substance and to demonstrate that the microbiological level of process intermediates is appropriately controlled.

The life time of the resins used in the chromatographic purification operations have been properly validated. The provided data are satisfactory and support the proposed lifetimes. Clear protocols for confirmation of the proposed lifetimes at production scale have been provided. Cleaning performance and

monitoring of microbial charge has also been properly addressed. The approach of the company to validate the lifetime of the tangential flow filtration membrane is considered adequate as well.

Adequate shipping validation data have been provided.

Manufacturing process development

The manufacturing process for the nonclinical and Phase I material was developed at commercial scale. A second clinical campaign resulted in GMP batches used for the Phase III clinical studies. PPQ studies were conducted subsequent to the clinical campaign. No substantial changes were introduced in the upstream and downstream processes during the course of development of the active substance. A limited number of minor changes were implemented between phase I and phase III studies. The applicant provided an integrated (active substance and finished product) comparability exercises as discussed under the pharmaceutical development of the finished product.

Characterisation

The adalimumab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG1-type antibody. Edman chemistry, peptide mapping and liquid chromatography (LC) with mass spectrometry (MS) (LC-MS) were used to for the characterisation of the primary structure and post-translational modifications; peptide mapping by LC-MS/MS (non-reducing), circular dichroism (CD) and nano-differential scanning calorimetry (DSC) were used for the characterisation of higher order structure; charged isoforms were characterised by imaged capillary isoelectric focusing (icIEF), glycosylation by 2-aminobenzamide HILIC-UPLC (2-AB HILIC-UPLC). The biological characterisation was performed measuring the inhibition of TNF induced cytotoxicity as bioassay, further described under analytical methods; determination of biological activity (potency), binding to TNF by surface plasmon resonance (SPR) and binding to the fragment crystallisable (Fc) receptors and C1q, antibody dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) assays.

The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. Biological characterization of adalimumab indicates that this antibody has the ability to bind TNF with high affinity and to specifically bind to Fc Receptor as expected of an IgG1. In summary, the characterization is considered appropriate for this type of molecule.

Specification

The adalimumab active substance specification include physicochemical tests (appearance, clarity and degree of opalescence, degree of coloration, pH, osmolality), biological activity and protein content, product related substances, impurities, process related impurities and microbiological tests as per Ph.Eur.

The specification has been prepared in line with the requirements of applicable ICH and EMA guidelines and Ph.Eur. monograph on monoclonal antibodies. The specification takes into account the critical quality attributes (CQAs) of the active substance that can affect the safety and efficacy of the product, and defines the acceptable range for the physicochemical and biological characteristics of the active substance within the context of the wider control strategy. The justification of specifications is based on data from available active substance batches.

Analytical methods

The non-compendial methods that are in common with the specification of the finished product are either identical or present small variations. Upon request, the description of the analytical methods was expanded. The analytical methods used are now adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

The adalimumab bioassay is based on the ability of adalimumab to inhibit cytotoxicity induced by recombinant-human TNF in a dose dependent manner. The method description has been updated during the review to a sufficient and unequivocal level of detail.

Batch analysis

Batch analysis data on full scale batches of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

An interim reference standard has been employed in the analysis of the active substance and finished product for release and stability testing during development and was replaced by the current reference standard used for the active substance and finished product release and stability testing. Both reference standards are appropriately identified and characterised. An appropriate policy for replacement of the reference standard is provided.

Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life at the indicated conditions with the possibility of freeze-thaw cycles in the proposed container.

Real time, real condition stability data of active substance for stored in a representative container closure system were provided. Data under accelerated conditions according to the ICH guidelines were provided.

Results on stress conditions were also provided. In addition, a freeze-thaw study has been performed.

Stability indicating parameters were tested.

Stability study results generated at the long-term stability testing meet the proposed commercial acceptance criteria and demonstrate stability throughout the proposed shelf-life. Most parameters do not change over time; which is to be expected during frozen storage. Where common trends can be discerned statistically, they are considered too small to be relevant, and may actually reflect chance findings.

In accordance with EU GMP guidelines 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the EU), 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 is supplied as a sterile, clear, colourless solution for subcutaneous administration injection containing adalimumab (50 mg/mL) as active substance, citric acid monohydrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate (as buffering agents); mannitol (tonicity and stabilising agent); polysorbate 80 (stabilising agent), sodium chloride (tonicity agent), sodium citrate (buffering agent); sodium hydroxide (for pH adjustment) and water for injections (solvent). All excipients

are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

The product is available in three presentations: a pre-filled syringe (type I glass) with a 29G Thin-Wall, ½ inch needle with a latex free needle cap, a plunger stopper (synthetic rubber), extended finger flanges and a passive needle shield; in a pre-filled single use, disposable, handheld, mechanical Physioject pen containing a pre-filled syringe (type I glass) with a 29G Thin-Wall, ½ inch needle with latex free needle cap and a plunger stopper (synthetic rubber); and in a glass (type I glass) vial with a rubber stopper (synthetic rubber) and aluminium crimp seal.

The adult posology foresees the administration of the full content of the syringe/pen. The paediatric posology requires administering partial doses from the vial; appropriate materials for administering the dose are supplied with the vial (1 sterile injection syringe, 1 sterile needle, 1 vial adaptor).

The material of the primary packaging of each presentation complies 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. Each presentation contains an overfill to compensate for dead volume and to assure a nominal amount of 40 mg adalimumab in 0.8 ml is delivered.

Pharmaceutical development

Pharmaceutical development was aimed at establishing a medicinal product which is biosimilar to the originator, matching its composition. The pH (5.2) is the same pH as the reference product and provides appropriate stability of the active substance against aggregation and degradation, as supported by the stability results.

The manufacturing development has been evaluated through the use of risk assessment to identify the CQAs and critical process parameters (CPPs). The CQAs have also been investigated in the biosimilarity assessment and they are listed in**Table 4** below. A risk analysis was performed in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge, process development experience and information gathered from process pre-characterisation and characterisation studies. On request, the applicant provided additional details and satisfactorily justified why some process parameters were identified as non-critical. For selected process steps and their potential critical process parameters, the impact on CQAs was further studied by using design of experiments and/or one-factor-at-a-time experimental designs. The studies were performed at laboratory scale. The outcome of these studies was to confirm the criticality of potential CPPs and to define proposed operational limits for the confirmed CPPs that ensure process consistency and delivery of a product complying with quality specifications. For a selection of CPPs the operational limits were confirmed in CPP range confirmation studies. The approach of the company is state-of-the-art. The CPPs have been adequately identified.

Comparability during development

The Applicant provided comparability exercises with associated data to substantiate comparability of Phase I vs. Phase III; Phase III PFS vs. commercial PFS; and Phase III PFS vs. commercial Vial. The complete and integrated data, related to both the active substance and the finished product, are presented in Module 3.2.S.2.6. The comparability exercises comprise a detailed description of the changes to the finished product (mainly limited to differences between vial and PFS and different stoppers manufacturing process), QC/batch release data, comparative real time and accelerated stability data and an extensive characterisation data. These data indicate that no meaningful difference exists; all results are within expected batch to batch variability.

Manufacture of the product and process controls

The finished product manufacturing and QC release and stability testing take place at Merck Serono S.p.A, Modugno, Bari, Italy. The finished product QC release and stability testing can also be performed at Merck Serono S.p.A., Guidonia Montecelio, Italy.

The manufacturing method has been satisfactorily described.

Upon request, a more elaborate description of the assembly of auto-injector or safety device, including appropriate CPPs and controls, has been included in the submission; in addition, appropriate validation data were provided.

The general outline of the manufacturing process for vials is similar to the description for PFS; except that after sterile filtration the solution is filled into vials, with different target fill volume, and no forward manufacturing takes place.

The manufacturing process has been adequately validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of the intended quality in a reproducible manner.

CPPs and Critical IPCs for PFS and Vials are equal, except for fill weight checks and hold times. CPPs and IPCs are sufficiently justified by manufacturing process development studies. The in-process controls are adequate.

Product specification

The adalimumab finished product specification include physicochemical tests (appearance, clarity and degree of opalescence, degree of coloration, pH, osmolality, particulate contamination and extractable volume), identity, biological activity and protein content, product related substances, impurities and microbiological tests as per Ph.Eur.

The stated impurities have been studied in nonclinical and clinical studies, as relevant.

The acceptance criteria are applicable from release to end of shelf-life..
The specifications for vial and PFS are identical.

Analytical methods and reference materials

Cross reference is made to the active substance section regarding analytical procedures and the reference standard; the non-compendial methods for active substance and finished product are identical and have been updated in parallel during the procedure. Compendial methods are sufficiently described and validated by reference to Ph. Eur.

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

Batch analysis

Batch analysis data together with batch genealogy and batch disposition data of the finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Stability of the product

Based on available stability data, the proposed shelf-life of 2 year and storage conditions (store in a refrigerator, 2°C – 8°C, do not freeze) as stated in the SmPC are acceptable. The product should be stored in the outer carton in order to protect from light.

The finished product may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The finished product must be kept in its outer carton in order to be protected from light, and discarded if not used within the 14-day period.

For the PFS, real time, real condition stability data and under accelerated conditions finished product manufactured using the commercial manufacturing process according to the ICH guidelines, were provided. The batches of adalimumab finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Additional stability data on representative batches packed in the proposed container, at real time at real condition and accelerated were provided. Real time, real condition and accelerated stability data stability data according to the ICH guidelines have also been provided. Stability data on batches stored under stress conditions were also provided. Stability indicating parameters were tested.

To support temporary storage of the finished product out of the refrigerator, stability data at room temperature has been provided for two batches. The results demonstrate that the product has suitable stability profile for several weeks at room temperature therefore the product can be stored for at least 2 weeks at room temperature as an alternative storage condition for convenience of the patient, in line with the in use storage recommendations of the reference product.

Furthermore, forced degradation testing has been performed side-by-side with the test product and the reference product sourced from EU and US to support the analytical similarity assessment. Samples were evaluated for thermal, mechanical, oxidative stress as well as low and high pH and light exposure. The results demonstrate that there are no substantial differences between all products tested, thus fully supporting the proposed storage conditions and the 3-way analytical similarity (see biosimilarity section below).

For the vial, the stability data stored under long real time, real conditions, accelerated and stressed are aligned with the results obtained for the vial and support the applicability of the same shelf-life conditions for both the PFS and the vial. Additionally, compatibility of the finished product upon in-use administration with the ancillaries (i.e. vial adapter + needle, 1ml plastic syringe) has been demonstrated through an in-use stability study.

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.

Adventitious agents

The approach for adventitious agents testing is described. The only material of animal origin used in the manufacture of Kromeya is insulin as discussed under control of materials for the active substance.

During the cell line development and establishment of the cell banks, animal derived component free media were used during all steps, with the only exception of the initial clone picking step. Its origin is from a country with negligible risk of TSE/BSE and is therefore acceptable.

All raw materials used in manufacture of the finished product are certified to be free of animal derived components based on supplier certificates. Therefore, the raw materials are not a concern from a viral safety or TSE risk-minimization perspective.

The risk of adventitious viral contamination of active substance through the manufacturing process is low. Tests of the MCB, WCB and ExCB for adventitious viral contaminants *in vivo* and *in vitro* were negative for replication competent viruses. Adventitious viruses were not detected *in vitro* for the unprocessed bulk harvests using up to seven detector cell lines. The purification process includes various virus reduction and inactivation steps. Spiking experiments were performed on chromatography and filtration scaled-down models, to assess the viral reduction capacity of all the relevant steps for different model viruses. While the unprocessed bulk harvest is known to contain non-infectious retrovirus-like particles (rVLP) originating from the CHO cell line, the downstream process has been validated to remove or inactivate retroviruses in excess of known levels of rVLP contamination.

In summary, the implemented measures ensure high safety with respect to adventitious agents.

GMO

N/A

2.2.4. Biosimilarity

The applicant has performed an extensive comparability analysis to demonstrate biosimilarity to the reference product (Humira). The approach chosen is in line with current guidance and a scientific advice received by EMA-CHMP on 24 September 2015 (EMA/CHMP/SAWP/593876/2015).

Batches included

The applicant analysed batches from the EU; US; and rest of the world (RoW) markets ; with various expiry dates . Individual (raw) batch data from each batch are provided and traceability is ensured.

Comparability criteria

The presented analysis falls into two broad categories; a comparison of all the finished product batches to the QTPP of the originator (with separate QTPP analyses for EU batches and aggregated EU/US/RoW batches); and specific side-by-side analytical exercises, performed at separate points in time during different stages of development. Where a quantitative analysis was possible, Min-Max ranges for the finished product were established and compared to Mean$\pm$3SD intervals calculated for the originator (with Min-Max ranges presented for comparison; it is noted that the 3SD interval is sometimes more restrictive than the Min-Max interval due to the relatively high number of data points); age at the time of testing is appropriately taken into account; the data are presented both in tabular and graphical format.

Method qualification

Descriptions of analytical methods and summary qualification data have been provided and considered acceptable. The qualification data comprise specificity, intra – and inter-assay precision (repeatability and intermediate precision), accuracy, linearity and range.

The biosimilarity results are summarised in the below.

Table 1. Biosimilarity results

Molecular Parameter	Attribute	Key findings
Primary Structure	Amino Acid Sequence	Identical to Reference

	Glycation	Similar to Reference
	N/C terminal modifications	Similar to Reference
Higher Order Structure	Free cystein	Similar levels observed
	Disulfide Bridges	Same disulphide bridges observed
Purity and Impurities	Monomer	Similar Purity levels
	LMW and HMW species	Similar levels to the Reference
Product Variants	Oxidized and Deamidated species	Closely overlapping levels with the Reference
	Isoforms	Similar levels observed
	Sialic acids	Slightly different but overall very low levels
	Glycan profiles	Qualitatively the same as the Reference
	Total galactosylated species	Overlapping ranges with the Reference
	Total High Mannose species	Slightly lower than the Reference
Protein Content	Protein Content	Similar
FAB binding and Purity	TNF Inhibition	Similar TNF inhibition
	TNF Binding (sTNF, tmTNF)	Similar binding and affinity as the Reference
FcRn binding	FcRn binding	Similar affinity to the Reference
Fc gamma binding	Fc gamma binding	Similar affinity as the Reference
	C1q binding	Similar binding potency
Fc effector activity	ADCC	Overlapping ranges with the Reference
	CDC	Similar CDC activity

Critical evaluation of analytical biosimilarity

High similarity between the biosimilar and the originator can be considered demonstrated with regard to the following attributes: primary structure, higher order structure; including disulphide bonds, dimers, aggregates and fragments, oxidation and related microheterogeneity; glycosylation, with the exception of total afucosylation/mannosylation/galactosylation; it is noted that sialylation is different but the levels are so low that this is not considered relevant; TNF-alfa binding (both soluble and membrane bound; binding to Fc-receptors, except FcγRIIIa-binding (by a.o. SPR, where limited sensitivity should be noted); C1q-binding (ELISA) and CDC

For the following interrelated attributes, the analytical comparability exercise results in the identification of differences: mannosylation/total afucosylation, FcγRIIIa 158F binding and ADCC. Data from several ADCC-type assays have been presented. Depending on the assay format, measurable ADCC is either absent in both the biosimilar and the reference product (ADCC with natural killer effector cells (NK) and activated monocyte target cells, i.e. peripheral blood mononuclear cell (PBMC)), or that ADCC is similar (whole blood ADCC, FcγRIIIa ADCC reporter) or lower than (NK-PBMC ADCC) the originator. In the latter case, during the procedure it was questioned whether the differences were linked to assay variability and, as explained under the clinical section, it was concluded that they were not clinically meaningful. These results are consistent with the noted lower total afucosylation and results of Fc-receptor binding: the

KD-ranges (as determined by SPR) for FcγRIIIa F158 binding overlap but are not 'within range'. In view of the comprehensive functional assay dataset provided, which supports biosimilarity for the mechanisms of action related to the extrapolation of indication for inflammatory bowel disease (IBD), namely, induction of apoptosis, inhibition of adhesion molecules, chemokines and cytokines as well as inhibition of T cell proliferation; the relevance of the difference in mannosylation/total afucosylation, FcγRIIIa 158F binding and ADCC was raised as multidisciplinary MO (non-clinical/clinical) and subsequently resolved, as outlined in the non-clinical part of the report.

A summary of the demonstration of similarity for those functionality tests linked to the extrapolation of indication for inflammatory bowel disease, is provided in Table 5 below.

Table 2. *In Vitro* Pharmacodynamic conclusion for Extrapolation of Indications

Activity	Analytical Procedure	Summary of Results and Impact assessment	Similarity Confirmed (Yes/No)
TNFR-dependent forward signaling activity	TNF-induced NF-κB signaling by luminescence reporter	MSB11022 and Humira® showed similar inhibition of TNF-induced NF-κB signaling.	**Yes**
	TNF-induced apoptosis of monocytic cells by luminescence	MSB11022 and Humira® showed similar Inhibition of TNF-induced monocytic apoptosis.	**Yes**
tmTNF-dependent reverse signaling activity	Apoptosis oftmTNF cells by luminescence	MSB11022 and Humira® showed similar Induction oftmTNF cell apoptosis.	**Yes**
***In vitro* activity relevant across all indications**	TNF-induced ICAM-1 in vascular endothelial cells by immunofluorescence	MSB11022 and Humira® showed similar inhibition of TNF-induced ICAM-1 expression.	**Yes**
	TNF-induced IL-8 in vascular endothelial cells by ELISA	MSB11022 and Humira® showed similar inhibition of TNF-induced IL-8 secretion in vascular endothelial cells.	**Yes**
	TNF-induced IL-8 in peripheral blood polymorphonuclear leukocytes by ELISA	MSB11022 and Humira® showed similar inhibition of TNF-induced IL-8 secretion in polymorphonuclear leukocytes.	**Yes**
***In vitro* activity relevant to rheumatoid arthritis**	TNF-induced IL-6 in fibroblast-like synoviocytes from RA patients by ELISA	MSB11022 and Humira® showed similar inhibition of TNF-induced IL-6 secretion in FLS.	**Yes**
***In vitro* activity relevant to psoriasis**	TNF-induced IL-8 in keratinocytes by ELISA	MSB11022 and Humira® showed similar inhibition of TNF-induced IL-8 secretion.	**Yes**
***In vitro* activity relevant to inflammatory bowel disease**	TNF-induced apoptosis of colon cancer cell line cells by luminescence	MSB11022 and Humira® showed similar inhibition of TNF-induced colon cancer cell line apoptosis.	**Yes**
	TNF-induced IL-8 in colon cancer cell line cells by ELISA	MSB11022 and Humira® showed similar inhibition of TNF-induced IL-8 secretion in colon cancer cell line.	**Yes**
	Apoptosis oftmTNF cells by luminescence	MSB11022 and Humira® showed similar induction oftmTNF cell apoptosis.	**Yes**
	T cell proliferation in allogeneic MLR by ^{3}H-thymidine incorporation	MSB11022 and Humira® showed similar inhibition of T cell proliferation in allogeneic MLR.	**Yes**
	Regulatory macrophage induction in allogeneic MLR by flow cytometry	MSB11022 and Humira® showed similar stimulatory activity of regulatory macrophage induction in allogeneic MLR.	**Yes**

Discussion on chemical and pharmaceutical aspects

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

Similarity between the biosimilar and the reference product, EU-Humira, has been addressed in an extensive comparability exercise and similarity can be confirmed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance

of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the applicant to take due account of technical and scientific progress, the CHMP recommends three points for investigation.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Adalimumab is a recombinant, fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) targeted against human TNFα. Both binding and functional assays were used to demonstrate that MSB11022 is comparable to Humira EU (RMP and Humira-US (RP) (3-way comparison) with respect to fragment antigen-binding (Fab) and fragment crystallizable (Fc) domain properties. Data on potency and binding properties included a TNFα inhibition bioassay (inhibition of TNFα induced cytotoxicity); binding to soluble TNFα (sTNFα) by SPR; binding to transmembrane TNFα (tmTNFα) by flow cytometry; FcRn, FcγRI, FcγRIIa (R131 & H131), FcγRIIb, FcγRIIIa (V158 & F158) and FcγRIIIb binding by SPR; and C1q binding by ELISA. The data on binding and on potency, demonstrating adalimumabs ability to bind to either sTNFα or tmTNFα and to neutralise the activity of TNFα, confirmed similarity.

The applicant provided the results from ADCC assays using varying formats. When using LPS-activated human primary monocytes as target cells and NK effector cells of V/V158 genotype as effector cells, no ADCC activity could be measured. Using whole blood cells and CHO cells overexpressing non-cleavable tmTNF as target cells, the %EC_{50} values for MSB11022 overlap with the range observed for the EU RMP using healthy or patient blood cells. In a FcγRIIIa ADCC Reporter Assay, %EC_{50} values for MSB11022 and EU RMP were slightly lower but overlapping or similar, when using the V158-reporter or the F158-reporter assay, respectively. When using a more sensitive assay format the ADCC activity of MSB11022 compared to EU RMP is reduced. In the ADCC assay of NK-cell-enriched PBMC, applied at high ratio versus target cells overexpressing non-cleavable tmTNF, the ADCC E_{Max} ranges using healthy donors were 84-92% vs 95-104% (at F/F genotype) and 88-99% vs 94-104% (at V/F genotype) for MSB11022 and EU RMP, respectively. In this assay the %EC_{50} values were 41-56% vs 79-162% (at F/F genotype) and 26-37% vs 70-174% (at V/F genotype) for MSB11022 and EU RMP, respectively. Comparable effects were found using patients blood but the difference was less pronounced in UC/CD patients (lower but overlapping) than with RA/PsO patient blood. The Applicant also provided data from the ADCC reporter assay showing that the ADCC activity induced by adalimumab was already greatly reduced in presence of 50% human serum and a difference was no longer observed between MSB11022 and RP, while ADCC reporter activity of both was not quantifiable in presence of 100% human serum. In addition, using the assay with the NK-enriched PBMC effector cells, the Applicant showed that addition of IgG diminishes the ADCC activity, and argues that in vivo it appears likely that endogenous IgG will compete with adalimumab for FcγRIIIa, making it less likely that ADCC would contribute to adalimumab's efficacy. A reduction of ADCC activity in this assay was also shown by addition of serum from either healthy donors or CD patients.

The applicant provided comparative functional in vitro data related to Fab-related functionalities of adalimumab. The Fab-related functionality concerns the binding of sTNFα measured by subsequent effects on cellular processes mediated by binding of sTNFα to its receptor TNFR and the binding to tmTNFα measured by subsequent effects on cellular processes mediated by reverse signalling.

Functional sequelae of sTNFα-binding was shown by measuring sTNFα-induced NF-kB signalling in the reporter cell line; by sTNFα-induced apoptosis of (monocytic) cells by measuring caspase 3/7 activity; by sTNFα-induced ICAM-1 expression in vascular endothelial cells cells; and by sTNFα-induced IL-8 release in peripheral blood polymorphonuclear leukocytes. These assays show the immunological consequence of lower sTNFα levels and thus reflect in a functional way the capacity of adalimumab to bind sTNFα. This mode of action is considered relevant for all indications. In addition, functional effects of sTNFα-binding was shown by measuring sTNFα-induced IL-6 release in synoviocytes; by sTNFα-induced IL-8 release in keratinocytes or in colorectal adenocarcinoma-derived cells, or by measuring sTNFα-induced apoptosis (caspase 3/7 activity) in colorectal adenocarcinoma-derived cells. The latter three cell types were considered by the applicant as models for RA, psoriasis and IBD, respectively. The production of pro-inflammatory cytokines - IL-6 or IL-8, in synoviocytes or keratinocytes is considered plausibly to reflect sTNFα activity in tissues where RA and psoriasis are active. However, to consider IL-8 release in adenocarcinoma-derived cells as a model of IBD would seem a bit far-fetched. Nevertheless all of these assays show comparable results for both products, reflecting comparable efficacy in binding of sTNFα by both products.

Functional sequelae of tmTNFα-binding was investigated by measuring apoptosis of turkat tmTNF cells. Comparable caspase 3/7 activity (biomarker for apoptosis) was shown.

In addition, inhibition of T-cell proliferation and induction of regulatory macrophages in a two-way allogenic Mixed Lymphocyte Reaction (MLR) assay, supposed to involve both tmTNFα-binding (on activated T-cells) and binding to Fc-receptors (on macrophages), was shown to be similar, which lends support to a comparable activity of Kromeya and Humira in IBD indications.

The human TNF transgenic Tg197 mouse model is an established model to study the effects of immunomodulatory agents on arthritis. The applicant compared MSB11022 and Humira in this model and measured the effect on body weight, arthritic score and histopathological score. The results show that both compounds have a dose-related effect on these parameters, demonstrating their efficacy in this model and using statistical analysis, similarity was found on body weight change, total arthritic score and total histopathological score at week 12.

The applicant provided data obtained in a mouse human TNF transgenic Tg197 TNBS colitis model. Body weight change and TNFα release in colon thick organ cultures were affected by both compounds, without a dose-response relationship.

2.3.2. Pharmacokinetics

The applicant provided toxicokinetic data that were gathered in a repeated dose toxicology study in cynomolgus monkeys. Generally, these data show similar pharmacokinetic behaviour of both products. Considering the low number of subjects in this study, these data do not significantly contribute to the establishment of biosimilarity of both products. Bioequivalence should be concluded from human data.

2.3.3. Toxicology

In a repeated dose toxicity study, 3 male and 3 female cynomolgus monkeys per group received weekly subcutaneous (SC) injections of either vehicle control, MSB11022 (32 mg/kg) or Humira-US (32 mg/kg) for a total of 5 injections. The results indicate a comparable exposure and immunogenicity profile and a similar toxicity profile without adverse findings for both Kromeya and Humira-US.

2.3.4. Ecotoxicity / environmental risk assessment

According to the CHMP Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2) for products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting specific ERA studies.

According to Directive 2001/83/EC, applicants are required to submit an ERA also for applications under Art 10(4) similar biological applications.

The active substance is a protein composed of natural amino acids, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, adalimumab is not expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

Comparable potency was shown for both products (see quality section). With regard to data on binding, comparability is generally observed. Although, for the low affinity variant of FcγRIIa (F158), the range of observed K_D values for MSB110022 (6.2 to 10.1 nM) was exceeding the range for the RMP (3.8 to 8.0 nM). These results are consistent with the lower total afucosylation of MSB11022.

Using the MLR assay, the effect on induction of regulatory macrophage and the associated inhibition of T cell proliferation was studied. MSB11022 and RMP/RP showed similar effects on both inhibition of T cell proliferation as well as on stimulation of regulatory macrophage induction in the MLR assay, which lends support to a comparable activity of Kromeya and Humira in IBD indications. However, as this method is only semi-quantitative, its applicability to establish biosimilarity is limited.

The ADCC assays measuring cytotoxic activity were run with freshly collected blood cells from healthy donors carrying the both alleles (V158 & F158) of the FcγRIIIA receptor, either from heterozygotes (V/F) or homozygotes (F/F, V/V). In addition, blood from RA, PsO, CD and UC patient with this F/F and/or V/F genetic constitution were used in the NK-cell enriched PBMC ADCC and in the whole blood ADCC assay. In the whole blood ADCC assay a similar effect was found for MSB11022 versus RMP/RP using both healthy and patient blood cells. In the NK-cell enriched PBMC ADCC assay using healthy donors, a lower non-overlapping %EC_{50} was found with MSB11022 as compared to RMP/RP. The difference was less pronounced in UC/CD patient blood (lower but overlapping) than with RA/PsO patient blood.

In addition, based on data on ADCC activity obtained with different assay formats using both healthy and patient blood cells, the applicant concludes that ADCC activity induced by adalimumab can only be detected under amplified artificial conditions and is even abrogated in the presence of physiological levels of human serum (healthy donors and CD patients) or IgG; and that no significant difference in ADCC is observed between MSB11022 and RMP/RP under more physiologically representative conditions such as when using whole blood effector cells or monocytes expressing physiological levels of tmTNF. In the most sensitive (NK-PBMC) ADCC assay the lower and not overlapping activities of MSB11022 were only found on the %EC_{50} parameter and not on Emax. In addition, given that the NK PBMC assay Emax occurs at or near Ctrough levels found at steady state in humans, the clinical relevance of the observed differences may be low.

It may be considered that the lower ADCC activity in some assays may be associated with the observed lower high mannose content of MSB11022 as compared with the RMP. The applicant showed that over the %afucosylation range present in the RMP, there was a high correlation with the NK-enriched PBMC ADCC assay activity but only moderate to low correlation for the ADCC reporter assay and the whole blood ADCC assay with a goodness of fit of 0.22 – 0.36 for the latter two assays.

In the literature, it is argued that efficacy of anti-TNFα compounds in IBD varies, depending on the type of compound. The presence of an active Fc part is considered crucial for efficacy in IBD and different responses in patients depending the allotype of FcγIIIa receptor in a patient (low affinity 158F or high affinity 158V) suggest that FcγIIIa is involved in the mode of action. ADCC depends on this receptor and thus could be considered potentially relevant for efficacy in IBD. The applicant argues that the literature provides conflicting evidence in this respect. In addition, the applicant showed that the high affinity (2 – 4 nM) allotype of FcγIIIa receptor 158V did not correlate with % afucosylation nor with any of the ADCC assays. To address uncertainties, upon request of the CHMP, the applicant provided additional data which showed the correlation between total afucosylation and ADCC activity in the whole blood ADCC, the NK PBMC ADCC and the ADCC reporter assays and also a correlation with FcγRIIIa low affinity (158F) but not with the high affinity (158V) activating receptor.

To further clarify the potential clinical relevance of the observed differences in ADCC activity, the Applicant provided data obtained with blood cells from healthy and patient donors, homozygous and/or heterozygous for the low affinity allele (F/F, V/F) and data with an ADCC reporter assay expressing the FcγRIIIA low affinity (158F) activating receptor. For the majority of assays, the data show similar or lower but overlapping data of MSB11022 and RMP with the exception of the NK-enriched PBMC ADCC assay %EC_{50}, for which the relevance of translation to the clinic is considered low given the abrogation of the difference when more physiological assay conditions or assay formats are used and when also the much higher plasma Ctrough steady state levels are considered. Furthermore, other anti-TNF biosimilars, which displayed similar differences in glycosylation, FcRIIIa-binding and/or ADCC levels *in vitro*, did not show signs of differences on clinical efficacy. Finally, although the MLR assay has its limitations for establishing biosimilarity, similar effects of MSB11022 and RMP/RP were shown on both inhibition of T-cell proliferation and on stimulation of regulatory macrophage induction, which lends support to comparable activity of MSB11022 and Humira in IBD indications.

The Applicant provided comparative functional in vitro data related to Fab-related functionalities of adalimumab. The Fab-related functionality concerns the binding of sTNFα as measured by subsequent effects on cellular processes mediated by binding of sTNFα to its receptor TNFR. This has been demonstrated in a wide range of assays. Effects on cellular processes mediated by reverse signalling subsequent to the binding to tmTNFα was measured as apoptosis induction in Jurkat:tmTNF cells.

In Tg197 mouse model for RA, the applicant used statistical tests to show similarity for the effect of both MSB11022 and RP on body weight change from baseline, total arthritic score and total histopathological score.

The applicant provided data obtained in a mouse Tg197/TNBS colitis model. TNBS induced colitis is a well-known method to investigate the effects of anti-inflammatory products on this disease. The design of these models vary, which affects the outcome of the study (te Velde et al, 2006). The applicant used Tg197 mice, expressing higher levels of soluble and cleavable tmTNFα. This transgenic mouse is created in a C57B1/6 strain. According to te Velde and co-workers (2006), this strain is insensitive to TNBS induced colitis. Although the transgene may have affected the sensitivity, it remains uncertain whether this mouse is the appropriate model to study colitis. Lack of sensitivity is reflected by absence of lethality, also in the vehicle controls. Lack of a dose-response relationship for body weight change and TNFα release in colon thick organ cultures diminishes the suitability of this model to establish biosimilarity. The applicant only evaluated TNFα release in colon thick organ cultures. No other cytokines were studied. No effects on colon draining lymph node were studied. Due to these omissions the applicant may have missed the measurement of more sensitive endpoints. The endpoints measured by the applicant (besides TNFα release in colon TOC), were body temperature and body weight. As evident from the presented results, an effect could be observed, but the sensitivity to detect a difference between both products

appears minimal. The applicant did not make a statistical comparison of the results for the chosen endpoints between both products. Only statistical tests were used to show that an effect occurred (by comparison with the vehicle control). In conclusion, this study does not contribute to the establishment of biosimilarity of Kromeya and Humira.

Considering the low number of subjects in the cynomolgus monkey repeated dose toxicity study, the safety and toxicokinetic and immunogenicity data do not fully contribute to the establishment of biosimilarity of both products. The available quality and in vitro data did not indicate a need to perform a study in this species. Consequently, according to current guidelines, this study was not required. The study should not have been performed.

2.3.6. Conclusion on the non-clinical aspects

Comparative *in vitro* data were presented on:

- Binding of MSB11022 and Humira (EU/US/RoW) to the target, TNFα (soluble and transmembrane).
- Binding to relevant Fc receptors (FcRn, FcγRI, FcγRIIa (R131 & H131), FcγRIIb, FcγRIIIa (V158 & F158) and FcγRIIIb.
- Binding to Complement component 1q (C1q).
- Effects on Fab-related functionality due to the binding of sTNFα. This was evaluated in a wide range of assays.
- Effects on Fab-related functionality due to the binding to tmTNFα. Apoptosis of Jurkat:tmTNF cells.

The *in vitro* data were presented by the applicant in Module 3, however, functional data were assessed in the non-clinical AR in line with EMA presubmission advice.

Comparative *in vivo* data were presented on:

- Activity of MSB11022 and Humira (US) in Tg197 mice, a model for RA.
- Activity of MSB11022 and Humira (US) in a Tg197/TNBS mouse model, proposed as a model for IBD.
- Toxicokinetics, safety and immunogenicity in cynomolgus monkeys.

It can be concluded that Kromeya can be expected to be biosimilar in all applied indications including also Crohn and UC indications.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development program consisted of two studies: a single-dose PK study in healthy volunteers (EMR200588-001) and an equivalence trial in patients with moderate to severe plaque psoriasis (EMR200588-002). An overview is provided in the tabular overview of clinical studies below.

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

Study ID	No. of centres/ locations	Design	Study Posology	Study Objectives	Subjs by arm entered/ compl.	Duration	Diagnosis Incl. criteria	Main Endpoints
EMR200588 -001	2 centres in 1 country	Phase I, randomized double-blind single-dose study with 3 parallel treatment groups: MSB11022, EU-approved Humira, US-licensed Humira.	MSB11022 EU-approved Humira, US-licensed Humira 40 mg sc single dose	To compare the PK, safety, immunogenicity and tolerability of MSB11022 with US-licensed Humira and EU-approved Humira.	Randomized: MSB11022: 79 EU-Humira: 79 US-Humira: 79 Completed: MSB11022: 78 EU-Humira: 78 US-Humira: 77	70 days	Male and female healthy volunteers	PK: AUC0-∞, Cmax, and AUC0-last Safety, tolerability, and immunogenicity data
EMR200588 -002 (AURIEL-PsO)	69 centers in 12 countries	Phase III, randomized, double-blind, multiple-dose active comparator study with 2 parallel treatment groups: MSB11022 versus EU-approved Humira Extension with re-randomisation: EU-Humira to MSB11022 versus EU-Humira to EU-Humira	MSB11022 EU-approved Humira 40 mg sc biweekly	Primary: equivalence in efficacy of MSB11022 compared with EU-approved Humira Secondary: similarity in pharmacokinetics, efficacy, safety and immunogenicity of MSB11022 compared with EU-approved Humira.	Randomized: MSB11022: 222 EU-Humira: 221 Treated in Core Treatment Period: MSB11022: 221 EU-Humira: 220 Re-randomized: MSB11022 to MSB11022: 214 EU-Humira to EU-Humira: 101 EU-Humira to MSB11022: 101 Treated in Extended Treatment Period: MSB11022 to MSB11022: 213 EU-Humira to EU-Humira: 101	Core Treatment Period: 15+1 weeks Extended Treatment Period: 37 weeks + 4 months safety evaluation	Patients with moderate to severe chronic plaque psoriasis	Primary: PASI75 at week 16 Main secondary: Percentage change in PASI at week 16 PK, safety, and immunogenicity data

		versus MSB11022 to MSB11022			EU-Humira to MSB11022: 101 Completed 24 weeks: MSB11022 to MSB11022: 210 EU-Humira to EU-Humira: 96 EU-Humira to MSB11022: 99			

2.4.2. Pharmacokinetics

To support this biosimilar application, the PK-profile of MSB11022 was investigated and compared to EU-Humira in the following two studies

(Pivotal) Phase I Study EMR200588-001 in healthy volunteers: double-blind, 3-arm parallel-group comparing the pharmacokinetics, safety, tolerability, and immunogenicity of MSB11022, US-Humira, and EU-Humira

(Supportive) Phase 3 Study EMR200588-002 in psoriasis patients: double-blind, confirmatory study to evaluate the efficacy, safety and immunogenicity of MSB11022 compared with EU-Humira

Analytical methods

The same analytical method was used for the determination of adalimumab in the serum from healthy volunteers and patients with psoriasis.

The following analytical methods were used: a. ELISA for the determination of adalimumab concentrations in human serum
b. Electrochemiluminescence (ECL) immunogenicity assay for detection of antibodies against adalimumab (ADA) in human serum
c. Meso-Scale Discovery (MSD)-ECL immunogenicity assay for the detection of neutralizing antibodies (NAB) against adalimumab in human serum.

The ELISA method. In general, the analytical methods were validated in line with the EMA bioanalytical guideline.

The adalimumab concentrations in the serum were determined by a validated ELISA method. In this assay, adalimumab (or its biosimilar) is captured by a recombinant human TNFα and an HRP-conjugated goat anti-human IgG antibody is used to detect the bound analyte. The same analytical method was used for the determination of adalimumab in the serum from healthy volunteers and patients with psoriasis.

A qualitative, single assay approach to detect anti-adalimumab in human serum from healthy individuals and patients with psoriasis was used.

For the NAB assay, a non-cell-based competitive ligand binding was used to determine the neutralizing capacity of the antibodies. The NAB assay used Sulfo-TAG-labeled TNFα (Ru-TNFα) to form a complex with biotinylated adalimumab. An affinity purified goat polyclonal anti-adalimumab was used as a positive control.

Pharmacokinetics of adalimumab in healthy subjects

PK similarity of adalimumab between MSB11022, EU-Humira and US-Humira was investigated in the pivotal study (EMR200588-001) in healthy subjects following administration of a 40 mg SC dose. For the primary parameters $AUC_{0-\infty}$ AUC_{0-t} and C_{max}, the 90% CI for the ratio of the test and reference products fell within the acceptance range of 80.00-125.00% when comparing MSB11022 to the reference product from EU as well as from US, and also when comparing the US versus the EU reference products. The concentration-time profiles, descriptive statistics of the PK-parameters, statistical comparison of the PK-parameters between MSB11022, EU-Humira and US-Humira are shown in Figure 3, Table 6 and 7 below.

Figure 1: PK-Figure : Arithmetic mean (SD) serum concentration-time profiles of profiles of MSB11022, EU-Humira and US-Humira (Study EMR200588-001)

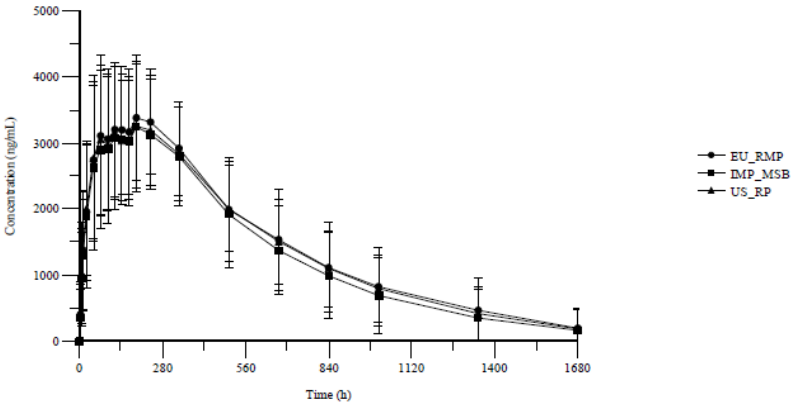


Table 3: Descriptive statistics for the PK parameters of of MSB11022, EU-Humira and US-Humira (Study EMR200588-001)

Parameter (units)	Statistic	Treatment		
		IMP-MSB 40 mg	US-RP 40 mg	EU-RMP 40 mg
C_{max}	n	78	79	79
(ng/mL)	Geometric Mean	3434.7	3532.8	3601.1
	GeoCV%	36.5	32.7	30.3
t_{max}	n	78	79	79
(h)	Median	191.41	191.07	190.75
	Range	24.00 – 506.00	48.00 - 339.90	48.00 - 503.80
$AUC_{(0\text{-last})}$	n	78	79	79
(h*ng/mL)	Geometric Mean	1983898.1	2065993.1	2167383.7
	GeoCV%	43.5	42.6	45.2
$AUC_{(0\text{-inf})}$	n	76	75	77
(h*ng/mL)	Geometric Mean	2276053.7	2515978.5	2553892.6
	GeoCV%	44.5	37.5	41.9
$t_{1/2}$	n	76	75	77
(h)	Geometric Mean	295.46	352.50	348.61
	GeoCV%	63.2	49.3	51.9
CL/F	n	76	75	77
(L/h)	Geometric Mean	0.0176	0.0159	0.0157
	GeoCV%	44.5	37.5	41.9
V_z/F	n	76	75	77
(L)	Geometric Mean	7.491	8.085	7.877
	GeoCV%	40.6	32.9	31.3

Table 4: Statistical analyses of primary PK parameters of of MSB11022, EU-Humira and US-Humira (Study EMR200588-001)

Parameter (unit)	Treatment	n	Geometric LS Mean	Comparison	Ratio (%)	90% CI of Ratio
$AUC_{(0\text{-}inf)}$ (h*ng/mL)	IMP-MSB	76	2276053.7	IMP-MSB/US-RP	90.46	(81.29, 100.67)
	US-RP	75	2515978.5	IMP-MSB/EU-RMP	89.12	(80.14, 99.10)
	EU-RMP	77	2553892.6	US-RP/EU-RMP	98.52	(88.56, 109.59)
$AUC_{(0\text{-}last)}$ (h*ng/mL)	IMP-MSB	78	1983898.1	IMP-MSB/US-RP	96.03	(85.32, 108.08)
	US-RP	79	2065993.1	IMP-MSB/EU-RMP	91.53	(81.33, 103.02)
	EU-RMP	79	2167383.7	US-RP/EU-RMP	95.32	(84.72, 107.25)
C_{max} (ng/mL)	IMP-MSB	78	3434.7	IMP-MSB/US-RP	97.22	(89.27, 105.88)
	US-RP	79	3532.8	IMP-MSB/EU-RMP	95.38	(87.58, 103.87)
	EU-RMP	79	3601.1	US-RP/EU-RMP	98.10	(90.11, 106.81)

EU-RMP=EU Reference Medicinal Product (Humira) 40 mg,

IMP-MSB=IMP-MSB11022 40 mg, LS=least-squares; US-RP=US Reference Product (Humira) 40 mg

Across the three treatment arms, 64 of 78 (82.1%), 66 of 79 (83.5%), and 65 of 80 (81.3%) subjects tested ADA positive for MSB11022, EU-Humira, and US-Humira, respectively. The effect of ADAs and NABs on the pharmacokinetics parameters of the three adalimumab products by ADA grouping are summarised below.

Table 5: Descriptive statistics for the PK parameters of adalimumab ADA-positive subjects for the three adalimumab products (Study EMR200588-001)

Parameter (units)	Statistic	Treatment		
		IMP-MSB 40 mg	US-RP 40 mg	EU-RMP 40 mg
C_{max}	n	64	65	66
(ng/mL)	Geometric Mean	3338.2	3371.7	3520.4
	GeoCV%	38.5	32.1	31.3
t_{max}	n	64	65	66
(h)	Median	191.48	191.52	189.13
	Range	24.00 - 502.90	48.00 - 339.90	48.00 - 336.60
$AUC_{(0\text{-}last)}$	n	64	65	66
(h*ng/mL)	Geometric Mean	1807070.0	1903087.1	1992034.9
	GeoCV%	40.8	53.8	43.8
$AUC_{(0\text{-}inf)}$	n	62	61	64
(h*ng/mL)	Geometric Mean	2037489.4	2330670.9	2331754.2
	GeoCV%	38.9	36.5	38.9
$t_{1/2}$	n	62	61	64
(h)	Geometric Mean	254.21	317.52	314.44
	GeoCV%	55.3	46.7	48.4
CL/F	n	62	61	64
(L/h)	Geometric Mean	0.0196	0.0172	0.0172
	GeoCV%	38.9	36.5	38.9
V_z/F	n	62	61	64
(L)	Geometric Mean	7.200	7.862	7.782
	GeoCV%	42.9	34.5	33.1

Table 6: Descriptive statistics for the PK parameters of adalimumab ADA-negative for the three adalimumab products (Study EMR200588-001)

Parameter (units)	Statistic	Treatment		
		IMP-MSB 40 mg	US-RP 40 mg	EU-RMP 40 mg
C_{max}	n	14	14	13
(ng/mL)	Geometric Mean	3912.6	4387.8	4040.4
	GeoCV%	21.9	26.4	21.6
t_{max}	n	14	14	13
(h)	Median	179.54	108.09	192.00
	Range	96.00 - 506.00	48.00 - 241.80	72.00 - 503.80
$AUC_{(0\text{-last})}$	n	14	14	13
(h*ng/mL)	Geometric Mean	3039940.9	3025105.0	3326201.4
	GeoCV%	20.8	14.6	13.1
$AUC_{(0\text{-inf})}$	n	14	14	13
(h*ng/mL)	Geometric Mean	3716548.9	3511374.7	3997255.9
	GeoCV%	25.7	15.6	15.7
$t_{1/2}$	n	14	14	13
(h)	Geometric Mean	575.07	555.84	579.31
	GeoCV%	32.3	23.5	27.1
CL/F	n	14	14	13
(L/h)	Geometric Mean	0.0108	0.0114	0.0100
	GeoCV%	25.7	15.6	15.7
V_z/F	n	14	14	13
(L)	Geometric Mean	8.929	9.135	8.363
	GeoCV%	21.1	21.9	20.8

The pharmacokinetics in ADA-negative subjects are of particular interest as this allows direct evaluation of elimination of the substances without interference of ADAs. Therefore, the agency requested additional analyses in ADA negative subjects. Inferential statistical analyses for ADA negative subjects is shown in Table 10; the 90% CIs for all comparisons between MSB11022 and EU-Humira fell between 80.00 and 125.00%. There was no difference in elimination half-life between MSB11022 and EU-Humira. Most subjects became ADA positive after day 43, at day 43 on average 42% of the subjects was ADA positive while on day 71 on average 82% of the subjects was ADA positive. Analysis of comparison of PK by ADA onset showed that there were no differences in both the mean as well as the variability at different time points for the 3 products in ADA negative subjects. When subjects converted ADA positive, adalimumab exposure decreased but was also comparable for the 3 products.

Table 7 Statistical Comparison of Pharmacokinetic Parameters between Treatment Groups - PK Analysis Set: ADA Negative subjects study (Study EMR200588-001)

					Pairwise Comparison of Geometric LS Means		
Parameter (Units)	Treatment	n	Geo-LS Mean	95% CI	Ratio	Ratio Estimate (%)	90% CI of Ratio
AUC(0-inf) (h*ng/mL)	IMP-MSB1102	214	3716548.9	(3345464.7, 4128794.4)	IMP-MSB11022/ US-RP	105.84	(93.51, 119.80)
	US-RP	14	3511374.7	(3160776.4, 3900861.9)	IMP-MSB11022/ EU-RMP	92.98	(81.95, 105.49)
	EU-RMP	13	3997255.9	(3583884.8, 4458305.9)	US-RP/EU-RMP	87.84	(77.43, 99.67)
AUC(0-last) (h*ng/mL)	IMP-MSB1102	214	3039940.9	(2780946.7, 3323055.8)	IMP-MSB11022/ US-RP	100.49	(90.49, 111.60)
	US-RP	14	3025105.0	(2767374.7, 3306838.2)	IMP-MSB11022/ EU-RMP	91.39	(82.13, 101.70)
	EU-RMP	13	3326201.4	(3032607.5, 3648218.8)	US-RP/EU-RMP	90.95	(81.73, 101.21)
Cmax (ng/mL)	IMP-MSB1102	214	3912.6	(3452.7, 4433.8)	IMP-MSB11022/ US-RP	89.17	(76.96, 103.32)
	US-RP	14	4387.8	(3872.0, 4972.3)	IMP-MSB11022/ EU-RMP	96.84	(83.34, 112.52)
	EU-RMP	13	4040.4	(3548.7, 4600.3)	US-RP/EU-RMP	108.60	(93.46, 126.18)

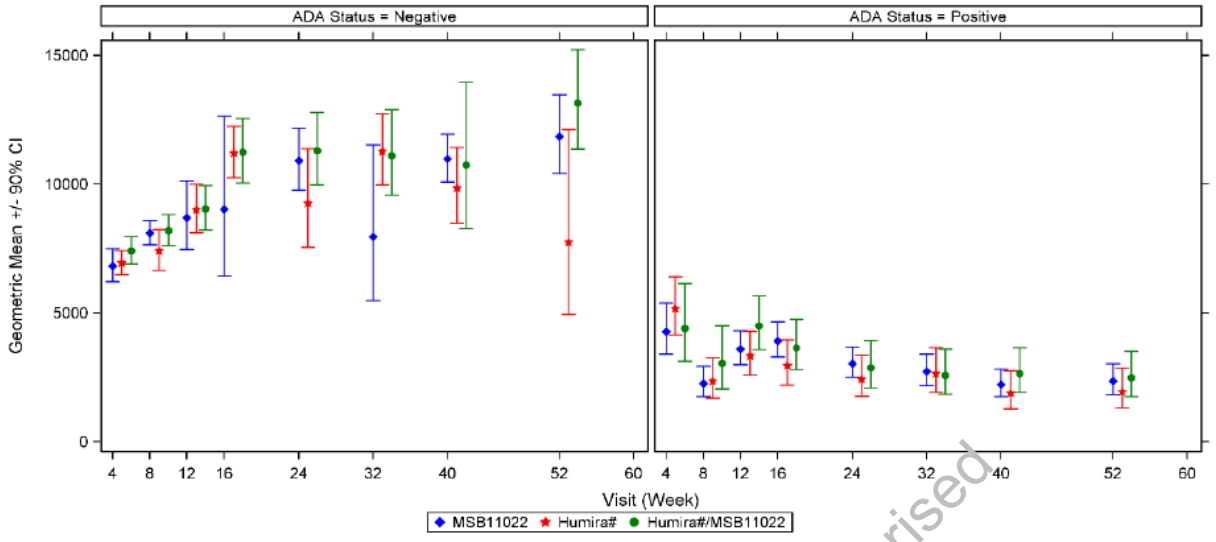
					Pairwise Comparison of Geometric LS Means		
Parameter (Units)	Treatment	n	Geo-LS Mean	95% CI	Ratio	Ratio Estimate (%)	90% CI of Ratio
Half-Life Lambda z (h)	IMP-MSB1102	214	575.1	(496.1, 666.7)	IMP-MSB11022/ US-RP	103.46	(86.93, 123.13)
	US-RP	14	555.8	(479.5, 644.4)	IMP-MSB11022/ EU-RMP	99.27	(83.13, 118.53)
	EU-RMP	13	579.3	(496.9, 675.3)	US-RP/EU-RMP	95.95	(80.35, 114.57)
Total CL Obs by F (L/h)	IMP-MSB1102	214	0.0108	(0.0097, 0.0120)	IMP-MSB11022/ US-RP	94.48	(83.47, 106.94)
	US-RP	14	0.0114	(0.0103, 0.0127)	IMP-MSB11022/ EU-RMP	107.57	(94.81, 122.04)
	EU-RMP	13	0.0100	(0.0090, 0.0112)	US-RP/EU-RMP	113.86	(100.35, 129.18)

Source: Q088-001.15
CI = confidence interval; Geo = geometric; LS = least-squares.
Results based on a one-way ANOVA model for log-transformed PK parameters with treatment as a fixed effect.

Pharmacokinetics of adalimumab in patients with psoriasis

In the supportive phase 3 study in psoriasis patients (EMR200588-002), MSB11022 or EU-Humira was administered with a pre-filled syringe as an initial subcutaneous dose of 80 mg on Day 1, followed by 40 mg subcutaneously every other week starting 1 week after the initial dose.
The Ctrough concentrations of MSB11022 and EU-Humira appear to be comparable as illustrated Figure 4. Similarity of Ctrough adalimumab concentrations was shown for the Core Treatment Period (0-16 weeks) (Table 11). More variability was observed for the Extended Treatment Period especially in the ADA negative group due to the low number of ADA negative subjects. In the cross-over comparison, that included subjects who were in the EU-Humira arm before Week 16 and were switched later to MSB11022, mean concentrations before and after the switch differed by less than 3%.

Figure 2 Adalimumab Ctrough concentrations (geometric Mean concentration and 90% CI) per Visit by ADA status in subjects with psoriasis (study EMR200588-002)



Source: Figure Q092-002.23 and Table Q092-002.19

Humira# = EU-approved Humira

Number of subjects included:

	ADA Status =negative								ADA Status = Positive							
Week	4	8	12	16	24	32	40	52	4	8	12	16	24	32	40	52
MSB11022	134	126	58	23	17	28	36	25	56	62	131	169	167	153	143	136
EU-Humira	68	56	17	8	7	12	15	7	34	39	76	76	79	70	61	59
EU-Humira/ MSB11022	62	55	26	11	7	10	10	10	28	34	62	75	78	71	70	62

Table 8 Statistical Comparison of Trough Adalimumab Concentrations in subjects with psoriasis - 90% CI (Core Treatment Period) - PP Analysis Set (study EMR200588-002)

				Pairwise Comparison of Geometric LS Means			
Treatment	n	Geo-LS Mean	90% CI	Ratio	Ratio Estimate (%)	90% CI of Ratio	p-value
MSB11022	725	4892.7	(4399.3, 5441.5)	MSB11022-Humira	104.68	(90.35, 121.27)	0.6091
EU-Humira	680	4674.1	(4183.0, 5222.7)				

Source: Table Q092-002.13

Note: Estimates are based on linear mixed model for each treatment with log adalimumab concentration as the dependent variable, ADA status at visit as fixed effect, and subject as a random effect. Subject-level body weight, age and sex are included in the model as covariates.

BLQ concentrations (<300 ng/mL) were set to BLQ/2 for these analyses.

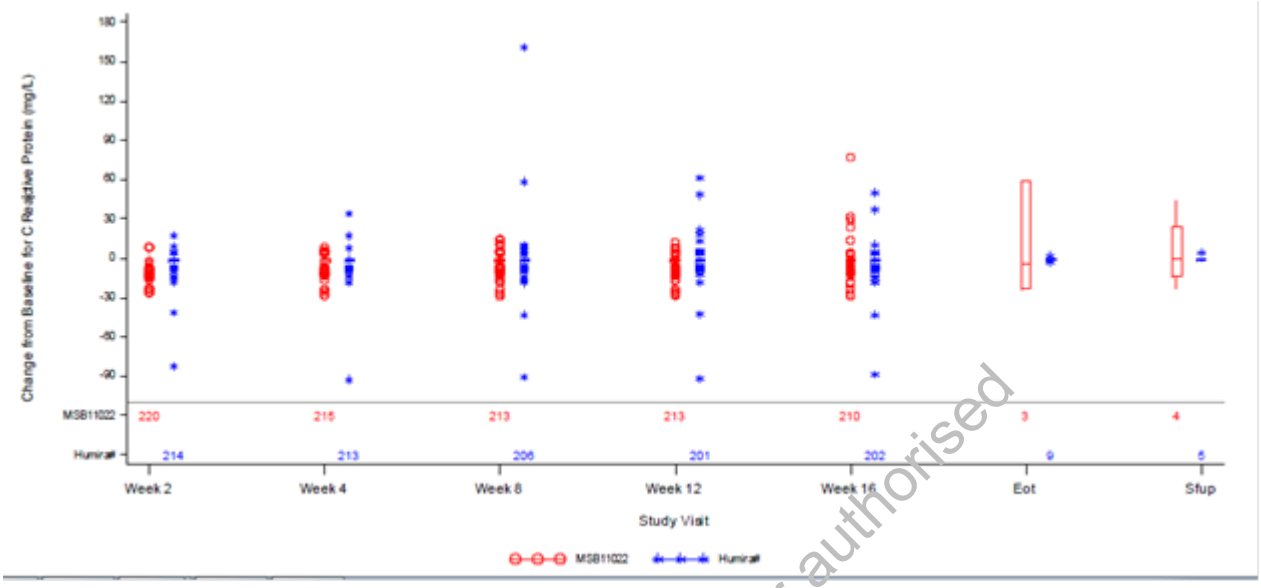
2.4.3. Pharmacodynamics

No clinical comparative PD study was submitted by the applicant. No accepted specific pharmacodynamic (PD) markers exist, being predictive of efficacy of adalimumab in patients. PD similarity of MSB11022 and Humira in terms of TNF-α inhibition has been investigated in non-clinical studies.

CRP (C-reactive protein) was among the biochemistry parameters investigated in study EMR200588-002.

Figure 5 shows a similar pattern of decline in CRP levels was observed between the MSB11022 and EU-Humira groups over the first 16 weeks (Core Treatment Period) of study EMR200588-002. A formal between-group comparison of CRP results was not performed.

Figure 3 Boxplots of change from baseline of CRP.



2.4.4. Discussion on clinical pharmacology

To support this biosimilar application, the PK-profile of MSB11022 was investigated and compared to EU-Humira in Phase I Study EMR200588-001 in healthy volunteers. The study design of the pharmacokinetic study EMR200588-001 is satisfactory; a parallel design is acceptable considering the long half-life of adalimumab (approximately 2 weeks) and the potential influence of immunogenicity. The use of healthy volunteers is agreed in line with the *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*. Supportive comparative PK data were collected in the Phase 3 Study EMR200588-002 in psoriasis patients, which is also in line with guideline recommendations. The 40 mg SC dose is the normally recommended dose.

Humira is presented in three formulations: vial, pre-filled syringe and pre-filled pen (auto-injector) formulations. The Applicant is applying for all these three formulations. However, only the pre-filled syringe has been used in the clinical studies and no PK study was done to show the equivalence of the pre-filled syringe and pre-filled pen formulations. Considering that the pre-filled syringe is assembled directly with the pen, this was considered acceptable to the CHMP since the quality of the medical device ensures comparable release of the solution (see Quality AR).

Analytical methods

The same analytical method was used for the determination of adalimumab in the serum from healthy volunteers and patients with psoriasis. This is acceptable as functional interchangeability between each version of adalimumab in the assay was demonstrated. Hence, use of MSB11022 as a calibration standard and for quality control samples during study sample analysis is agreed. The performance of the analytical method used for assessment of MSB11022 and adalimumab in serum seems acceptable and validation is in line with EMA Guideline on bioanalytical method validation. No relevant interference of ADA with the quantitation of adalimumab was observed when the concentration of anti-drug antibody was ≤ one third of adalimumab concentration in serum, at higher ADA concentrations interference occurs. The effect of ADAs on the quantitation of adalimumab was similar for the MSB11022 as for Humira. During validation it was discovered that anti-TNF-biologics might interfere with the adalimumab concentration

measurement. Therefore, subjects with anti-TNF-α therapies without an adequate wash-out period were excluded from the PK and patients studies. Absence of interference was confirmed by predose adalimumab concentrations <LLOQ at day 1.The immune response after adalimumab administration was evaluated by a three-step procedure comprising a screening (Tier 1) and confirmatory (Tier 2) electrochemoluminescence (ECL) assay for detecting anti-adalimumab antibodies (ADAs) and a neutralization antibody (Nab) ECL assay (Tier 3). In addition, titer of the ADAs was determined.

A one assay approach was used to detect anti-adalimumab in human serum from healthy individuals and patients with psoriasis. This was chosen to minimize the potentially confounding influence of higher inter-assay variability associated with labelling of both MSB11022 and EU-and US-Humira. This approach was agreed upon in one of the scientific advices sought by the applicant.

The tested drug tolerance of the ADA assay differs slightly among the 3 adalimumab products. For MSB11022, the high PCs 10000 and 250 ng/ml tolerated 500 µg/ml and the low PCsm 129.6 and 86.4 ng/ml tolerated 250 µg/ml; for EU-Humira, all the 4 PCs tolerated 500 µg/ml concentration; and for US-Humira, PCs 10000, 250 and 129.6 ng/ml tolerated 500 µg/ml and PC 86.4 ng/ml tolerated 250 µg/ml. The reported differences are likely to be the results of the variability of the assay observed. Despite this difference, this can be considered acceptable for the healthy human serum study samples considering that the highest Cmax concentration measured in these samples was about 7 µg/ml. This covers also the highest trough concentration of about 25 µg/ml in psoriasis patients.

For the NAB assay, a non-cell based competitive ligand binding was used to determine the neutralizing capacity of the antibodies. Some of the actions of adalimumab appear to be mediated through the induction of several cellular responses, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and apoptosis, in particular in patients with inflammatory bowel diseases. Cell-based assays are recommended for monoclonal antibody therapeutics with cellular effector functions for clinical efficacy as the mechanism of action may not be adequately reflected in a non-cell-based CLB assay (EMEA/CHMP/BMWP/14327/2006 Rev 1). ADAs induced by adalimumab have been shown neutralizing potential by competition with TNF for binding to the CDRs (Harding, 2010, van Schouwenburg, 2013, van Schouwenburg, 2014; van Schie, 2014). Therefore, it is considered unlikely that a cell-based assay would be able to detect Fc-mediated effector response inhibition on top of neutralising competitive inhibition. For adalimumab, the competitive ligand binding assay is acceptable to detect neutralizing anti-bodies though the assay is expected to underestimate the % of NAB positive patients because of drug interference but this is inherent to competitive binding ADAs. As adalimumab exposure is higher in patients than in the healthy subjects due to the longer wash-out period, underestimation of NAB incidence is mainly expected to occur in patients.

Overall, the analytical methods were validated in line with the relevant guidelines.

Pharmacokinetic studies

For the study in healthy subjects (EMR200588-001), the primary parameters $AUC_{0-\infty}$ AUC_{0-t} and $C_{max,}$ the 90% CI for the ratio of the test and reference products fell within the acceptance range of 80.00-125.00% when comparing MSB11022 to the reference product from EU as well as from US, and also when comparing the US versus the EU reference products (see Figure 3, Table 6 and Table 7). Further support for similarity between MSB11022 and EU-Humira was obtained in the study in psoriasis patients (study EMR200588-002). The Ctrough concentrations of MSB11022 and EU-Humira were comparable (Table 11). In addition, in patients who were switched from Humira to MSB11022 at week 16, mean adalimumab concentrations remained the same. In the cross-over comparison, that included subjects who were in the EU-Humira arm before Week 16 and were switched later to MSB11022, mean concentrations before and after the switch differed by less than 3%.

Immunogenicity was high: in the healthy subjects, ADA and NAB incidence approximately 80% and 70%, respectively, was high but comparable in all the three groups. In psoriasis patients, ADA and NAB incidence approximately 90% and 45%, respectively, was also high but comparable between the MSB11022 and EU-Humira group. Moreover, the incidence and the distribution of ADA titers over time was similar between MSB11022 and Humira. These results indicate comparable immunogenicity between the products. The new generation of ADA detection methods have an improved sensitivity compared to older ADA detection methods, resulting in a higher incidence of ADA positivity. Therefore, incidence of ADA for Humira reported in the EPAR is considerably lower than recently reported ADA incidences for Humira in biosimilar applications including this application.

Variability in the PK parameters was higher in subjects positive for ADA compared to ADA negative subjects. Elimination half-life and adalimumab exposure were lower in subjects positive for antidrug antibodies compared to subjects negative for antidrug antibodies as shown in **Table 8** and Table 9. This is already known for Humira.

Although the 90% CI for the ratio of MSB11022 and EU-Humira fell within the acceptance range of 80.00-125.00%, some issues were clarified. The upper limit of 90%CI for AUC_{inf} excludes 1 (i.e. 90% CI 80.14 – 99.10) and this statistical difference in AUCinf might indicate a difference in clearance. Sensitivity analyses for protein content and ADA status were conducted. Difference in protein content between MSB11022 and Humira-EU was slightly more than 5%, a sensitivity analysis was conducted correcting for protein amount administered. When correction for protein content, similarity was demonstrated for AUCinf, AUCt, and Cmax with 90% CI within 80-125% similarity margin including unity for all parameters. Also the results for ADA negative subjects were similar between MSB11022 and Humira supporting the conclusion for biosimilarity between MSB11022 and Humira based on the overall study population. The pharmacokinetics in ADA-negative subjects are of particular interest as this allows direct evaluation of elimination of the substances without interference of ADAs. No difference in elimination half-life was observed between MSB11022 and Humira in ADA negative patients. The elimination of adalimumab seemed somewhat faster for MSB11022 than for Humira in the ADA positive subjects but sensitivity analysis of elimination half-life by consideration of the time at which subjects became ADA positive indicated that there was no consistent pattern that elimination half-life of adalimumab was shorter for MSB11022 than for Humira. In addition, in psoriasis patients, the adalimumab concentrations of MSB11022 were comparable or slightly higher at all time points compared to EU-Humira. Overall, the PK results for ADA negative subjects and the Ctrough values in patients with psoriasis support the conclusion for biosimilarity between MSB11022 and Humira.

Pharmacodynamics

The relevance of the PD data on CRP in study EMR200588-002 in patients with psoriasis is considered to be limited. The results are supportive to compare the effects of MSB11022 and EU-Humira on disease activity data, but in psoriasis CRP levels are not sufficiently representative of disease activity. For that purpose, outcome measures of skin involvement (e.g. PASI, PGA) were used in the phase 3 studies.

2.4.5. Conclusions on clinical pharmacology

PK similarity has been demonstrated between MSB11022 and EU-Humira following administration of a 40 mg SC dose to healthy subjects in study EMR200588-001 and has been supported by PK data in psoriasis patients in study EMR200588-002.

2.5. Clinical efficacy

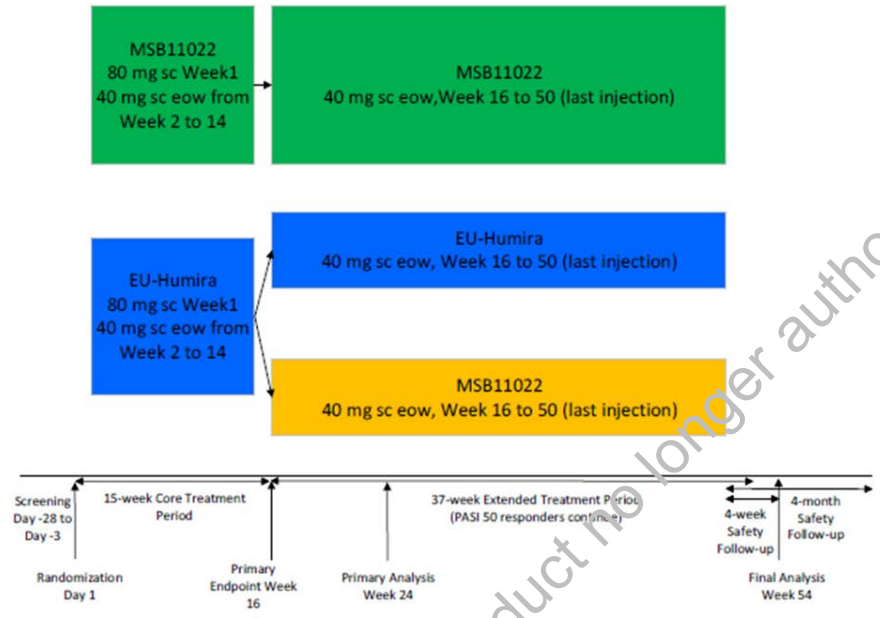
This application includes one main clinical study (**EMR200588-002).**

2.5.1. Main study

Study **EMR200588-002**

The primary objective of the study was to demonstrate equivalence in efficacy of MSB11022, a proposed biosimilar to adalimumab, compared to EU-approved Humira, both administered subcutaneously, in subjects with moderate to severe chronic plaque psoriasis. Immunogenicity and safety (and PK parameters) were also assessed. Study EMR200588-002 was a 52-week randomized, double-blind, Phase III study, consisting of a 15-week Core Treatment Period followed by a 37-week Extended Treatment Period and a 4-month safety follow-up (Figure 1).

Figure 1 **Schematic Study Design of EMR200588-002**



Source: CSR EMR200588-002 Week 24

eow= every other week; PASI= Psoriasis Area and Severity Index; sc=subcutaneous

Methods

Design

For the **Core Treatment Period**, patients with moderate to severe plaque psoriasis were randomized to receive MSB11022 or EU-sourced Humira for 16 weeks in a double-blind fashion (Figure 1). Patients were given an initial dose of 80 mg subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose. The primary outcome was 75% response (yes/no) in the Psoriasis Area severity Index (PASI75) at 16 weeks. Main secondary outcome was the percentage change in PASI. Safety and immunogenicity outcomes were also assessed. Study visits were scheduled at week 1, 2, 4, 8, 12 and 16.

For the **Extended Treatment Period** starting at week 16, patients with at least 50% PASI response were eligible. The Period lasted 37 weeks (Figure 1). Double-blinding was maintained in the Extended Treatment Period. Patients who had received EU-Humira in the Core Treatment Period were re-randomized to a switch to MSB11022 or to continue EU-Humira. Patients on MSB11022 continued to receive MSB11022. Study visits were scheduled at week 16, and every 8 weeks thereafter up to week 52 (Figure 1).

The study was performed in 50 centres in Europe and 19 centres in Northern America.

Study participants

Patients with moderate to severe plaque psoriasis who had received, or are candidate for, systemic therapy or phototherapy were eligible to enter the study. Patients having Psoriatic Arthritis could also be included, if they had a documented diagnosis by a rheumatologist, earlier than 6 months before baseline. Moderate to severe chronic plaque psoriasis was defined by: ≥ 10% body surface area affected, Psoriasis Area and Severity Index score of ≥ 12, and Physicians Global Assessment score of ≥ 3, at screening and baseline. Previous use of not more than 1 prior biological therapy with either etanercept or infliximab was allowed.

Randomisation and blinding

Eligible patients were randomized 1:1 to receive MSB11022 or EU-sourced Humira, stratified (block size of 4) according to three levels of pre-treatment: treatment-naïve, non-biological use, biological use. There were no other stratification factors. At week 16, all eligible patients took part in the re-randomization procedure. Patients who initially had been randomized to EU-Humira were re-randomization 1:1 to MSB11022 or EU-Humira. Patients who initially had been randomized to MSB11022 were re-randomized to MSB11022 again. Each study centre had received a blinded supply of study medication with individually numbered study kits, allocated to patients using a web based response system.

Study treatments

MSB1102 and EU-sourced Humira were delivered in blinded prefilled syringes for subcutaneous administration. In agreement with the Humira SmPC, the initial 'baseline' dose was 80 mg, followed by 40 mg every other week starting 1 week after the initial dose. The study product of MSB11022 was representative for the to-be-marketed product. At Weeks 1, 2 and 4 the study medication was administered at the study site, and the patient or the care giver was trained for self-administration. Subsequent administrations of study medication were performed every other week, at home or on the study site at the scheduled study visits. Compliance with study medication was checked using a patient diary and by counting all used and unused study medication, which the patient had to bring at each study visit.

Outcomes

The primary endpoint of study EMR200588-002 was the percentage of subjects meeting the PASI 75 (Psoriasis Area and Severity Index score reduction of ≥75% from baseline) response criteria at Week 16. The main secondary endpoint was percent change from baseline in Psoriasis Area and Severity Index (PASI) at Week 16. Continuous absolute PASI scores over all time points were also presented.

Further secondary efficacy endpoints included:

- Percentage of subjects achieving PASI 50/90/100 at Week 16 and Week 24
- Percent change from baseline in PASI at Week 24
- Percentage of subjects achieving a static Physician's Global Assessment (PGA) score of "clear" or "almost clear" at Week 16 and Week 24 compared to Baseline
- Change in PGA at Week 16 and Week 24 compared to Baseline
- Percent of body surface affected (BSA)

Sample size

It was calculated that approximately 382 subjects (191 evaluable subjects per arm) would be required for the analysis of the primary endpoint (PASI 75 at Week 16) to provide a power close to 90% for an equivalence margin of 18% and a Type I error of 2.5% (1-sided). The sample size was based on:

- An estimated response rate of 59% for the primary endpoint (based on an anticipated PASI 75 response rate of 72% in anti-TNF-naïve- subjects (1-3) and 30% in anti-TNF-experienced subjects (4-8), in subjects with normal weight [below 90 kg]; and an anticipated PASI 75 response rate of 61% in anti-TNF-naïve subjects (9-10) and 15% in anti-TNF-experienced subjects, in overweight subjects [weight between 90 kg and 120 kg]. The subject population is composed of 18% of anti-TNF-experienced patients and 82% of anti-TNF-naïve patients, as well as a maximum of 40% of overweight subjects and 60% of normal weight subjects). This was calculated as a weighted mean of the response rates observed in the above mentioned studies (1-10).
- An expected difference between EU-Humira and MSB11022 of 0 following a single 80 mg dose of EU-Humira at Week 1 and a 40 mg dose every other week from Week 2 up to Week 16 (1-8, 11).

Approximately 426 subjects (213 per arm) were planned to be randomised, to account for an estimated 10% of subjects excluded from the per protocol primary endpoint analysis population up to Week 16. This will also provide a power close to 90% for the key secondary endpoint.

Statistical methods

The Per Protocol (PP) data set was used for the analysis of primary and main secondary outcome (Table below). Additional analyses were performed using the Intent-To-Treat (ITT) data set.

Table 9 Overview of statistical methods planned

Analysis Set	Definition
PP	All randomized and treated subjects (hence a subgroup of the ITT Analysis Set) who do not have any clinically important protocol deviations during the Core Treatment Period with respect to factors likely to affect the efficacy of treatment. Subjects' data were analyzed according to their randomized and received treatment in the Core Treatment Period, as receipt of a different treatment from that assigned was a clinically important protocol deviation and hence would have resulted in exclusion from the PP analysis set. Subjects who discontinued from study medication prior to Week 16 were removed from the PP Analysis Set and were not included in the primary analysis. The PP Analysis Set was used for the primary efficacy analyses, for HRQoL, and for analyses exploring the impact of immunogenicity on efficacy.
ITT	All subjects randomized prior to the start of the Core Treatment Period. Subjects were analyzed according to the treatment they were randomized to at this time. The primary and secondary efficacy analyses were repeated using the ITT analysis set.
ETP-PP	All subjects who are in the PP Analysis Set and were re-randomized and received treatment in the Extended Treatment Period (hence a subgroup of the PP analysis set). Subjects were not be excluded from the ETP-PP Analysis Set if they experience a protocol deviation during the Extended Treatment Period.
ETP-ITT	All subjects re-randomized to Extended Treatment Period. Subjects were analyzed according to their re-randomized treatment.
PK	The PK Analysis Set includes all subjects in the SAF who also have at least 1 measurable postdose concentration.
SAF	The Safety Analysis Set includes all randomized subjects who receive at least 1 dose of MSB11022 or EU-approved Humira in the Core Treatment Period, up to Week 16.

Source: CSR EMR200588-002 Week 24, Appendix 16.1.9

ETP=Extended Treatment Period; HRQoL=health-related quality of life; ITT=Intent-To-Treat; PP=Per Protocol; PK=pharmacokinetics; SAF=Safety Analysis Set

Therapeutic equivalence of MSB11022 and EU-approved Humira was assessed based on the primary endpoint of PASI 75 at Week 16. The 2 treatment groups were compared using the 2-sided 95% Newcombe confidence interval (CI) (using Cochran-Mantel-Haenzel weights) for the treatment difference (MSB11022 – EU-approved Humira) in PASI 75 response rate stratified by previous systemic therapy (treatment-naive, prior exposure to a biological agent, prior exposure to a non-biological agent). To

declare equivalence, the 95% CI for the treatment difference in PASI 75 response rates at Week 16 had to be entirely contained in the predefined equivalence margins [-18%,18%].

Sensitivity analyses were carried out using 1) imputation missing-at-random (MAR), 2) a more conservative imputation assuming MAR where imputed responders in the MSB11022 group only were categorized as non-responders with a probability corresponding to the equivalence margin, and 3) a tipping point analysis. In the tipping point analysis, data were re-analysed for all possible combinations of the number of responders/non-responders imputed for drop-outs in each treatment arm.

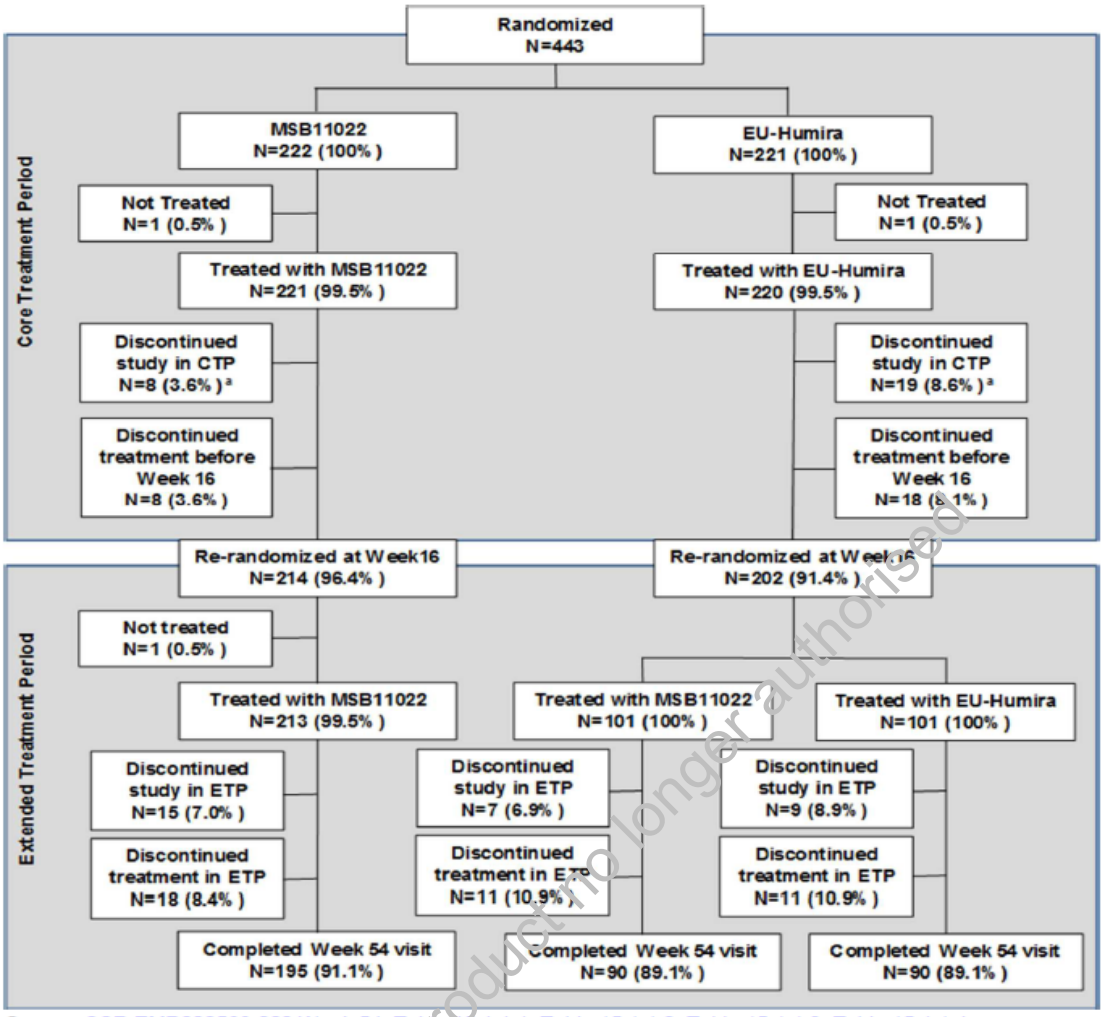
The key secondary endpoint was percent change from baseline in PASI at Week 16. The analysis of the key secondary endpoint was based on an analysis of covariance (ANCOVA) model with treatment group, previous systemic therapy use, gender, and body mass index (BMI) as fixed factors and baseline PASI score as a covariate. The analysis was performed primarily on the PP Analysis Set and was repeated on the ITT analysis set, using baseline-observation-carried-forward (BOCF)-like multiple imputation approach. In a BOCF-like multiple imputation approach it is assumed that that after drop-out, a subject's outcome reverts to a distribution similar to baseline values (i.e. of the PASI score) of the population.

Results

Participant flow

In total 649 patients were screened and 443 (68%) were randomised (Figure 2). The most common reasons for discontinuation in the **Core Treatment Period** were adverse events (MSB11022 n=1 and EU-Humira (n=9) and withdrawal of informed consent (MSB11022 n=1 and EU-Humira n=4) and protocol non-compliance (MSB11022 n=3 and EU-Humira n=1). Discontinuation due to lack of efficacy occurred infrequently. In the **Extended Treatment Period**, in total 41 patients discontinued after re-randomization (Figure 2), most commonly due to adverse events (n=18) or lack of efficacy (n=8) or withdrawal of consent (n=7), equally divided over all three treatment groups.

Figure 2 **Disposition of Subjects**



Source: CSR EMR200588-002 Week 54, Table 15.1.1.1, Table 15.1.1.2, Table 15.1.1.3, Table 15.1.1.4

CTP = core treatment period, ETP = extended treatment period, N = number of subjects.

a Includes the 1 subject who was randomized but not treated.

One subject in the MSB11022 group had several treatment interruptions due to adverse events during the Core Treatment Period. Because treatment was considered temporarily interrupted at the time of the Week 16 Visit, the subject was not included in the count of "treatment ongoing" (n=213), but was included in the count of re-randomized subjects (n=214).

Numbers analysed

In the Core Treatment Period, the proportion of patients remaining in the PP set was 91% in the MSB11022 group and 85% in the EU-Humira group (Table 6). Nearly all patients remained in the Safety Analysis (SAF) set.

In the Extended Treatment Period, the proportion of patients remaining in the ETP-PP set was 95% in the MSB11022 group, 94% in the EU-Humira group and 95% in the EU-Humira to MSB1102 group (Table 7). Nearly all patients remained in the SAF set.

Table 6 Analysis Sets - Core Treatment Period (Screening Analysis Set)

	MSB11022 n (%)	EU-Humira n (%)	Overall n (%)
Number of subjects in Screened Analysis Set [a]			649
Number of subjects in ITT Analysis Set [b]	222 (100.0)	221 (100.0)	443 (100.0)
Number of subjects in PP Analysis Set [c]	203 (91.4)	191 (86.4)	394 (88.9)
Number of subjects in SAF Analysis Set [d]	221 (99.5)	220 (99.5)	441 (99.5)
Number of subjects in PK Analysis Set [e]	217 (97.7)	215 (97.3)	432 (97.5)

Source: Table 15.1.1.3

EU-Humira = EU-approved Humira; ITT = Intent-to-Treat; PK = pharmacokinetic; PP = Per-protocol, SAF = Safety.

a All subjects who provided informed consent.

b All subjects who were randomized.

c All ITT subjects without any major protocol violations during the Core Treatment Period.

d All randomized subjects who received at least 1 dose of MSB11022 or EU-Humira.

e All subjects in the SAF Analysis Set who also had at least 1 measurable postdose concentration.

Table 7 Analysis Sets - Extended Treatment Period (ETP Analysis Set)

	MSB11022 n (%)	EU-Humira n (%)	EU-Humira/ MSB11022 n (%)	Overall n (%)
Number of subjects in ETP-ITT Analysis Set [a]	214 (100.0)	101 (100.0)	101 (100.0)	416 (100.0)
Number of subjects in ETP-PP Analysis Set [b]	203 (94.9)	95 (94.1)	96 (95.0)	394 (94.7)
Number of subjects in ETP-SAF Analysis Set [c]	213 (99.5)	101 (100.0)	101 (100.0)	415 (99.8)
Number of subjects in ETP-PK Analysis Set [d]	198 (92.5)	87 (86.1)	92 (91.1)	377 (90.6)

Source: Table 15.1.1.4

ETP = Extended Treatment Period; EU-Humira = EU-approved Humira; ITT = Intent-to-Treat; PK = pharmacokinetic; PP = Per-protocol; SAF = Safety.

a All subjects re-randomized to extended treatment.

b All subjects who were in the PP Analysis Set were re-randomized and received treatment in the Extended Treatment Period.

c All re-randomized subjects who received at least 1 dose of MSB11022 or EU-approved Humira in the Extended Treatment Period. One subject from the ETP-ITT Analysis Set was excluded (reason given was "as requested by patient").

d All subjects in the ETP-SAF set who had at least 1 measurable postdose concentration in the Extended Treatment Period.

Baseline data

Baseline characteristics were overall similar for the MSB11022 and EU-Humira treated groups. At baseline of the **Core Treatment Period**, the majority of patients was male (~67%) and white (~92%), with a mean (range) age of ~44 (20-74) years. The proportion of patients heavier than 90 kg was 10%. Baseline disease characteristics reflect a population with moderate to severe psoriasis (Table 9). The average PASI score was about 20, the minimum PASI score was 12. The majority of patients had previously used therapies for psoriasis.

Table 3 Baseline Disease Characteristics at Core Baseline – ITT Analysis Set

	MSB11022 N=222 (100.0%)	EU-Humira N=221 (100.0%)
Time since first diagnosis plaque-type psoriasis [months]		
Median (min, max)	185.130 (7.98; 651.79)	176.330 (7.26; 772.34)
Mean (SD)	207.198 (141.7469)	200.310 (141.1636)
Psoriatic arthritis, n (%)	26 (11.7)	25 (11.3)
Time since first diagnosis psoriatic arthritis [months]		
Median (min, max)	75.860 (0.66; 447.84)	41.230 (5.82; 510.06)
Mean (SD)	87.925 (86.5731)	80.030 (106.1607)
Previous biologic or other therapy for psoriasis, n (%)		
Yes	192 (86.5)	192 (86.9)
No	30 (13.5)	29 (13.1)
Previous biologics and other therapies, n (%)		
Etanercept	24 (10.8)	26 (11.8)
Infliximab	2 (0.9)	1 (0.5)
Other	189 (85.1)	190 (86.0)
PASI score, mean (SD)	20.5 (8.65)	21.0 (8.20)
Percent of body surface affected, mean (SD)	28.3 (14.08)	29.7 (13.72)
PGA, n (%)		
Clear	0	0
Almost clear	0	0
Mild	0	0
Moderate	159 (71.6)	151 (68.3)
Severe	63 (28.4)	70 (31.7)

Source: CSR EMR200588-002 Week 54, Table 15.1.6.1, Table 15.1.6.3, Table 15.1.6.11

ITT=Intent-to-treat; PASI= Psoriasis Area and Severity Index; PGA= Physician's Global Assessment; SD=standard deviation

After re-randomisation for the **Extended Treatment Period**, the baseline (i.e. at week 16) characteristics of the between the MSB11022, EU-Humira and EU-Humira/MSB11022 group were similar between the three treatment groups (Table 4) and comparable to the results described above.

Table 4 **Baseline Disease Characteristics at Extended Baseline – ETP-ITT Analysis Set**

	MSB11022 N=214 (100.0%)	EU-Humira N=101 (100.0%)	EU-Humira/MSB11022 N=101 (100.0%)
Weight [kg], mean (SD)	82.04 (14.193)	81.61 (14.377)	80.47 (13.417)
Body mass index [kg/m^2], mean (SD)	26.72 (3.274)	26.72 (3.343)	26.42 (3.208)
Time since first diagnosis plaque-type psoriasis [months]			
Median (min, max)	188.105 (11.43; 655.24)	186.970 (10.78; 775.79)	164.040 (15.80; 595.22)
Mean (SD)	210.636 (142.3337)	204.830 (143.1472)	206.389 (143.5526)
Psoriatic arthritis, n (%)	23 (10.7)	9 (8.9)	13 (12.9)
Time since first diagnosis psoriatic arthritis, mean (SD) [months]			
Median (min, max)	83.190 (4.01; 451.22)	30.490 (19.98; 179.65)	67.680 (13.80; 200.61)
Mean (SD)	95.990 (89.8353)	62.560 (55.1527)	75.298 (62.7751)
Previous Etanercept use	19 (8.9)	10 (9.9)	9 (8.9)
Duration [months], mean (SD)	11.286 (2.0980)	13.495 (4.7557)	11.666 (1.2119)
Previous Infliximab use	2 (0.9)	0 (0.0)	0 (0.0)
Duration [months], mean (SD)	11.070 (15. 2876)	0 (0.0)	0 (0.0)
PASI score, mean (SD)	1.90 (2.437)	2.22 (3.124)	1.39 (1.908)
Percent of body surface affected, mean (SD)	5.09 ± 7.549	6.31 ± 9.417	3.80 ± 6.492
PGA, n (%)			
Almost	108 (50.5)	38 (37.6)	50 (49.5)
Clear	72 (33.6)	37 (36.6)	38 (37.6)
Mild	30 (14.0)	24 (23.8)	12 (11.9)
Moderate	4 (1.9)	2 (2.0)	1 (1.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table Q104-002.1, Table Q104-002.3, Table Q104-002.7, Table Q104-002.11

Compliance

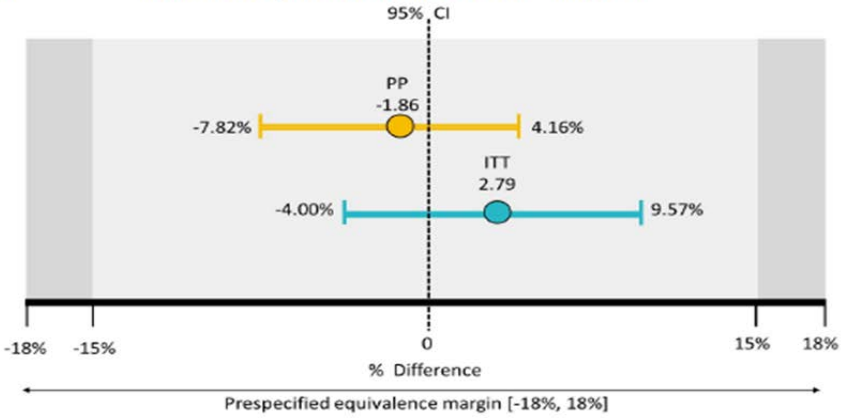
Treatment compliance was defined as the total injections received / the number of planned injections. In the Core Treatment Period, mean compliance in the MSB11022 group and the EU-Humira group was about 99%. In the Extended Treatment Period, compliance was 98%-99% in all three treatment groups.

Outcomes and estimation

Primary outcome

The PASI75 response at week 16 in the PP set was of similar size in both treatment groups: 90% in the MSB1102 group and 92% in the EU-Humira group. The 2-sided 95% confidence interval of the treatment difference was within the predefined equivalence margins of +/- 18% (Figure 3), in PP and in ITT sets. In both the PP and the ITT set the 95% confidence interval included 0 (no difference).

Figure 3 **PASI 75 Response Rates at Week 16 – PP, ITT**



Source: CSR EMR200588 002 Week 24, Figure 15.2.1.42, Figure 15.2.1.53
PP Analysis Set (orange); ITT Analysis Set (light blue); treatment difference= MSB11022 minus EU-Humira.
Stratified difference in PASI75 response rate along with stratified Newcombe 95% CI is displayed. [-18%,18%] corresponds to the prespecified equivalence margin for the primary endpoint; [-15%,15%] corresponds to the narrower equivalence margin that was prespecified for the key secondary endpoint. All subjects in the ITT Analysis Set without a Week 16 PASI assessment had been assumed to be nonresponders.
ITT=Intent-To-Treat; PASI= Psoriasis Area and Severity Index; PP=Per Protocol

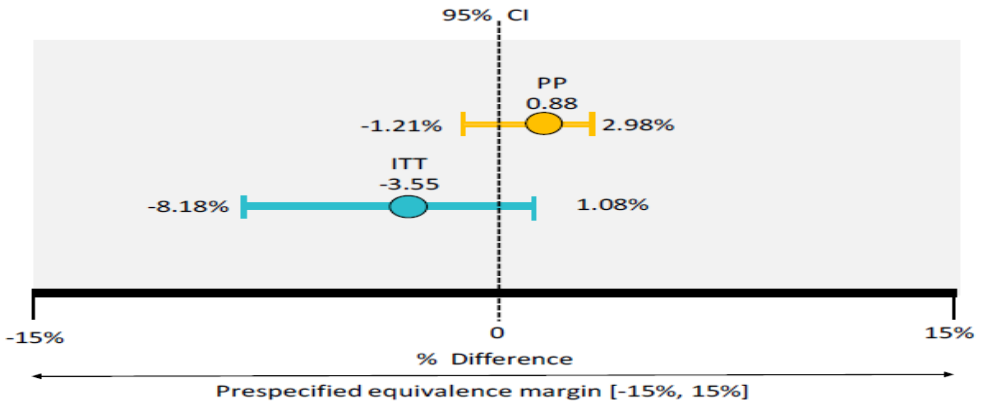
Two sensitivity analyses with different imputation methods were used in the ITT set. Both sensitivity analyses provided 95% confidence intervals for the difference in treatment effects that were within the +/- 18% equivalence limits, while including 0. The additional 'tipping point' analysis showed that for all ~1000 scenario's the results were within the equivalence margins.

Main secondary outcome

The mean percent change in PASI from baseline to week 16 in the PP set was similar in size for both treatment groups: -91% in the MSB11022 group and -92% in the EU-Humira group. This was based on a change in baseline PASI score from approximately 21 to less than 2 in both treatment groups. The 2-sided 95% confidence interval of the treatment difference was within the predefined equivalence margins of +/- 15% (Figure 4), in PP and in ITT sets. In both the PP and the ITT set the 95% confidence interval included 0 (no difference).

Two sensitivity analyses with different imputation methods (including one with a BOCF-like multiple imputation approach) were used in the ITT set. Both sensitivity analyses provided 95% confidence intervals for the difference in treatment effects that were within the +/- 15% equivalence limits, while including 0.

Figure 4 **Mean Percent Change from Baseline in PASI Score at Week 16 – PP, ITT Analysis Sets**

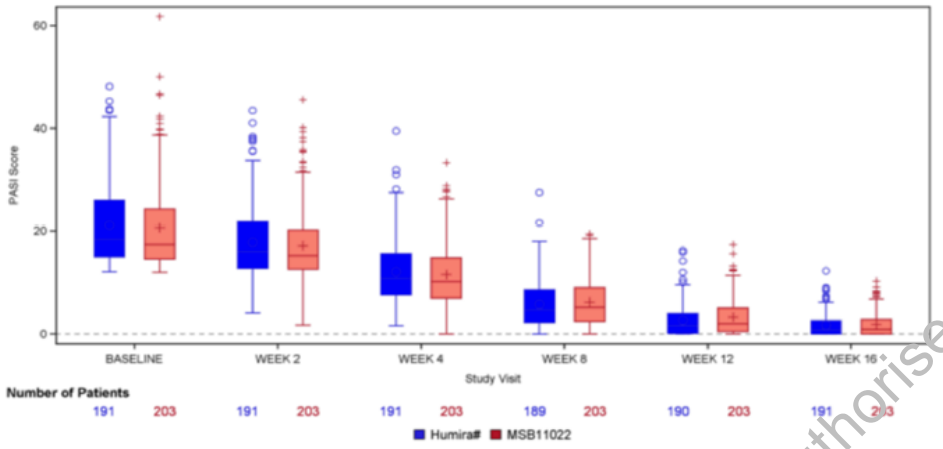


Source: CSR EMR200588-002 Week 54, Table 15.2.1.4, Table 15.2.1.5
ITT=intent-to-treat; PASI= Psoriasis Area and Severity Index; PP=Per Protocol
PP Analysis Set (orange); ITT Analysis Set (light blue). ITT: pattern-mixture imputation strategy combining a baseline-observation-carried-forward-like multiple imputation approach (for subjects who discontinued from study treatment due to adverse events) with a missingness at random. [-15%,15%] corresponds to the prespecified equivalence margin for the key secondary endpoint.

Further secondary outcomes

The **mean PASI scores** of the MSB1102 and EU-Humira groups showed a similar decline from around 21 at baseline to just below 2 at week 16 in the PP set (Figure 5) and in the ITT set. The medians showed a similar pattern.

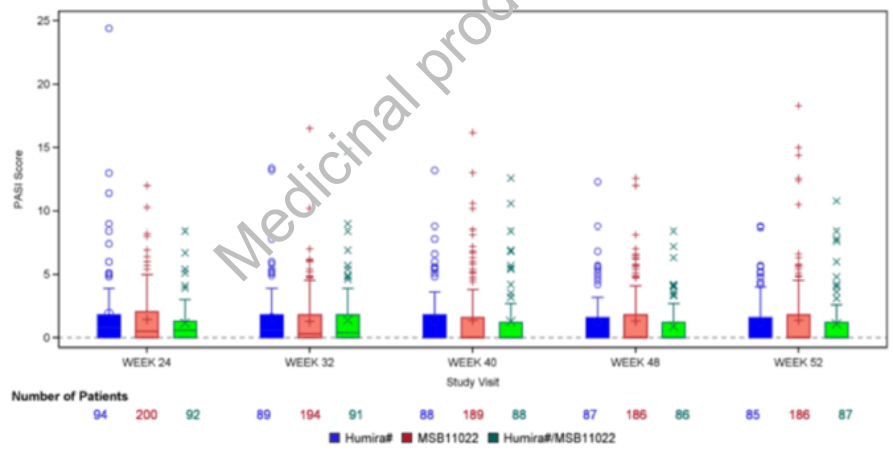
Figure 5 **PASI Score Through Week 16 (Core Treatment Period) - PP Analysis Set**



Source: Figure Q096-002.1
Humira#= EU-approved Humira

In the Extended Treatment Period the baseline PASI was low, and remained similarly low in all three treatment groups (Figure 7).

Figure 7 **PASI Score Through Week 52 (Extended Treatment Period) - ETP-PP Analysis Set**



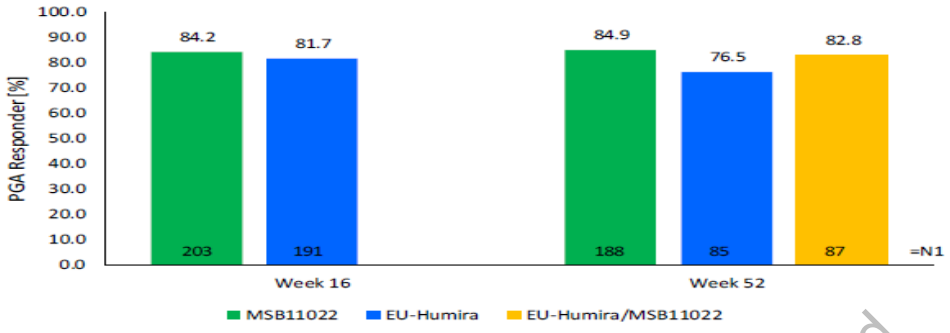
Source: Figure Q096-002.2
Humira#= EU-approved Humira

Consequently, the **mean percentage PASI change** in the Core Treatment Period and in the Extended Treatment Period was similar for all treatment groups over all time points, in the PP and ITT sets.

The proportions of **PASI50**, **PASI90** and **PASI100** responders at week 16 were similar in the MSB11022 and EU-Humira group, in PP and ITT sets. At week 52, the proportions of PASI50, **PASI75**, PASI90 and PASI100 responders were similar in the two groups continuing treatment and the group who switched from EU-Humira to MSB11022. The between-group differences were 9% at the largest (for PASI90).

The proportions of **PGA responders** at week 16 were similar in the BMS11022 and EU-Humira group, in PP (Figure 13) and ITT sets. At week 52, the proportions of PGA responders were similar in the two groups continuing treatment and the group who switched from EU-Humira to MSB11022 (Figure 13).

Figure 13 **PGA Responder at Week 16 and Week 52 – PP, ETP-PP Analysis Sets**



Source: CSR EMR200588-002 Week 54, Table 15.2.2.1, Table 15.2.2.4
ETP=Extended Treatment Period; PGA= Physician's Global Assessment; PP=Per Protocol.
N1 is the number of subjects who were considered to have had the visit. Number of subjects in PP: MSB11022=202, EU-Humira=189; number of subjects in ETP-PP: MSB11022=202, EU-Humira=93, EU-Humira/MSB11022=96.
Subjects were considered a PGA responder if they achieved a score of 0 (clear) or 1 (almost clear) and improved by at least 2 points on the PGA scale compared to baseline. Baseline was defined as the last nonmissing assessment on or prior to Day 1

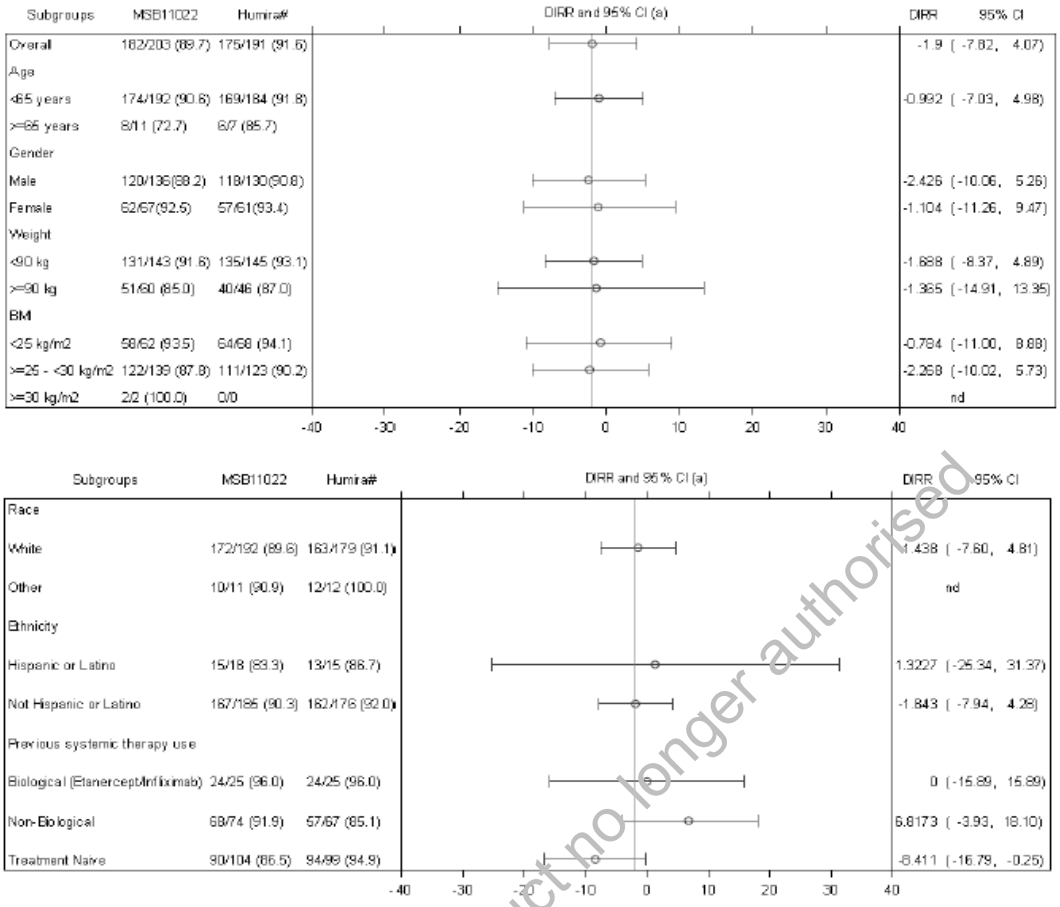
Subgroup analyses

Subgroup analyses were performed for demographic variables and for previous use of systemic therapy (the randomisation stratification factor), for PASI75 (Figure 15) and for PGA response as outcomes. In the subgroup analyses of PASI75, the 95% confidence intervals of all subgroups included 0 and nearly all estimates of the treatment difference were close to 0. The largest deviation was seen in the subgroup of previous users of 'non-biological' systemic therapy in favour of MSB11022 (Figure 15). The upper limit of the 95% confidence interval of the difference aligned with the upper limit of the +18% equivalence margin. The same kind of results were seen in the subgroup analyses with PGA response as outcome.

Anti-drug antibodies (ADA) were detected in the majority of (~90%) of patients in both groups over the course of 16 weeks. The PASI 75 response responder rates (primary outcome) were slightly lower (about 5-7%) in ADA positive patients than in ADA negative patients, to a similar extent in patients treated with MSB11022 and patients treated with EU-Humira (Figure 17). Similar results were obtained for the mean percentage change in PASI (main secondary outcome) from week 2 up to and including week 16.

Over 54 weeks, all ADA negative patients in all three treatment groups were PASI75 responders. Of the vast majority who were ADA positive, ~91% of patients were PASI75 responders in the three treatment groups. Also in mean percentage change in PASI, differences in response between ADA positive patients of the three treatment groups were small.

Figure 15 **Forest Plot PASI 75 Response at Week 16 Overall and by Subgroups– PP Analysis Set**



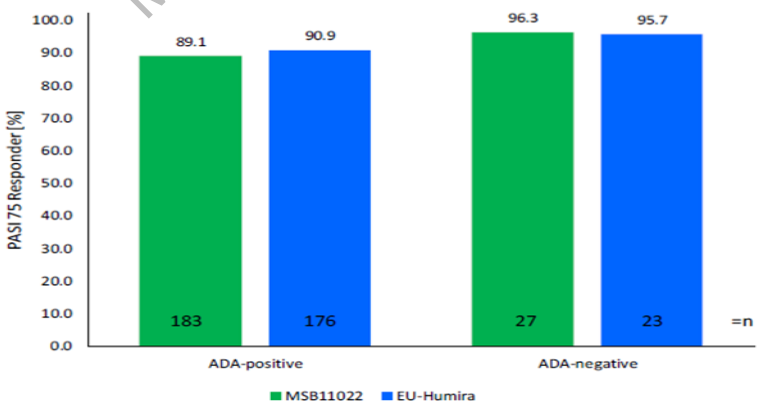
Source: CSR EMR200588-002 Week 54, Figure 15.2.1.4.2

PASI 75 was the reduction since baseline in PASI score of ≥ 75%.

BMI=body mass index; DIRR=difference (%) in response rates (MSB11022 minus EU-Humira); nd=not done; PASI=Psoriasis Area and Severity Index; PP=Per Protocol

The 2-sided 95% stratified Newcombe CI is shown for the difference in PASI 75 response rates (MSB11022 minus EU-Humira). For the previous systemic therapy use subgroups, the 2-sided 95% unstratified Newcombe CI was used. For weight and BMI, the pooled groupings of the respective measurements at Baseline are displayed.

Figure 17 **PASI 75 up to Week 16 Compared to Core Baseline, by ADA Status – SAF Analysis Set**



Source: CSR EMR200588-002 Week 54, Table 15.3.7.7

ADA=anti-drug antibody; PASI=Psoriasis Area and Severity Index; SAF=Safety Analysis Set

Percentages are calculated based on subjects with available data, ie treatment-induced ADA-positive or ADA-negative up to Week16. Number of subjects in SAF: MSB11022=221, EU-Humira=220. Core Baseline is defined as the last nonmissing assessment on or prior to Day 1. Treatment-induced ADA positivity is defined as negative at Baseline but positive at post-Baseline visit. For subjects positive at Baseline, treatment-induced ADA positivity is defined as a ≥4-fold increase of the ADA titer at the specified post-Baseline visit compared to the ADA titer at Baseline.

Summary of main efficacy results

The following table summarises the efficacy results from the single main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the **benefit risk** assessment (see later sections).

Table 10 Summary of efficacy for trial EMR200588-002

Title: A Randomized, Double-blind, Confirmatory Trial to Evaluate the Efficacy, Safety, and Immunogenicity of MSB11022 Compared with European Union-approved Humira® in Subjects with Moderate to Severe Chronic Plaque Psoriasis.			
Study identifier	**EMR200588-002**		
Design	Study EMR200588-002 was designed to test the clinical equivalence of MSB1102 in comparison to EU-sourced Humira, in terms of efficacy, safety, and immunogenicity, in patients with moderate to severe plaque psoriasis. It was a 52-week randomized, double-blind, Phase III study, consisting of a 15-week Core Treatment Period followed by a 37-week Extended Treatment Period. It was planned to include approximately 382 patients.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		0 - 16 weeks NA 16 - 54 weeks (treatment extension) 54 – 66 weeks (safety follow-up)
Hypothesis	Equivalence		
Treatment groups	Core Treatment Period		
	MSB11022		N=222 randomized to MSB11022 sc injection of 80 mg at week 1 and 40 mg at week 2 and every other week thereafter, for 14 weeks.
	EU-Humira		N=221 randomized to EU-Humira sc injection of 80 mg at week 1 and 40 mg at week 2 and every other week thereafter, for 14 weeks.
	Extension Treatment Period		
	MSB11022 to MSB11022		N=214 re-randomized to continue MSB11022 40 mg sc every other week.
	EU-Humira to MSB11022		N=101 re-randomized to switch to MSB11022 40 mg sc every other week.
	EU-Humira to EU-Humira		N=101 re-randomized to continue EU-Humira 40 mg sc every other week.
Endpoints and	Primary endpoint	PASI75 response	At least 75% change in PASI (yes/no) at week 16 compared to baseline.

definitions	Secondary endpoint	%PASI-change	Percent change in PASI at weeks 16 and 24 compared to baseline.
	Secondary endpoint	PASI75 response	At least 75% change in PASI (yes/no) at week 24 compared to baseline.
	Secondary endpoint	PASI score	Absolute values of PASI score at baseline and follow-up.
	Secondary endpoint	PGA response	PGA response at week 16 and week 24 compared to baseline
Database lock	After completion of week 66.		

Results and Analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Baseline to week 16 in the PP-set.		
Descriptive statistics and estimate variability	Treatment group	MSB11022	EU-Humira
	Number of subjects	202	189
	PASI75 response	90%	92%
	Variability	Not provided	Not provided
Effect estimate per comparison	PASI75 response	Comparison groups	MSB11022 - EU-Humira
		Difference in proportions	-1.86%
		95%CI	-7.82% – 4.16%
		Equivalence margins	+/-18%
Analysis description	**Secondary analyses**		
Analysis population and time point description	Baseline to week 16 in the PP-set.		
Descriptive statistics and estimate variability	**Treatment group**	**MSB11022**	**EU-Humira**
	Number of subjects	203	191
	%PASI-change	-91%	-92%
	SD	11%	10%
	PGA response	84%	82%

	Variability	Not provided		Not provided
	PASI, mean (SD) Baseline	20.6 (8.8)		21.2 (8.1)
	Week 2	17.2 (7.6)		17.9 (7.5)
	Week 4	11.5 (6.4)		12.1 (6.6)
	Week 8	6.2 (4.8)		5.8 (4.8)
	Week 10	3.3 (3.5)		2.7 (3.1)
	Week 16	1.8 (2.3)		1.7 (2.2)
Effect estimate per comparison	%PASI-change	Comparison groups		MSB11022 - EU-Humira
		Difference in means		0.88
		95%CI		-1.21 – 2.98
		Equivalence margins		+/-15%
Analysis population and time point description	Baseline (week 0) to week 52 in the PP-set.			
Descriptive statistics and estimate variability	Treatment group	MSB11022	EU-Humira	EU-Humira to MSB1102
	Number of subjects	203	95	96
	PASI75 response	91%	93%	93%
	Variability	Not provided	Not provided	Not provided
	%PASI-change	-93%	-94%	-95%
	SD	14%	10%	10%
	Median PASI	0.0	0.0	0.0
	(P25-P75)	(0.0-1.8)	(0.0-1.6)	(0.0-1.2)
	PGA response	85%	77%	83%
	Variability	Not provided	Not provided	Not provided

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The design and conduct of the clinical equivalence study is generally considered as adequate. EU-sourced Humira is a relevant comparator. The overall design has been agreed by the CHMP in the Scientific Advice. The study appears to be reasonably well conducted, as the number of drop-outs and missing values was

low and adherence to the medication was good. The MSB11022 study product used in the clinical studies is representative for the to-be-marketed product. The dose of EU-Humira and MSB11022 used in the equivalence trial is in accordance with the posology in the Humira SmPC. Remarkably, the randomisation was not stratified on centre, in contrast to what is customary in multi centre trials. However, absence of probably relevant centre effects was sufficiently documented, using numbers of enrolment and drop-outs per centre and country/region, and by analysing treatment effects by country/region.

As concluded in the SAWP/CHMP advice, the patient population chosen for the trial is considered as appropriate and sensitive to detect differences between MSB11022 and EU-Humira. The main reasons are: within 12 weeks relatively large treatment effects with adalimumab can be attained in psoriasis; concomitant immunosuppressive therapies that may interfere with treatment effects and immunogenicity are generally not used in psoriasis; established and sensitive outcome measures (notably PASI) are available for psoriasis trials.

However, as expressed in the CHMP advice, the PASI75 responder rate at week 16 as primary outcome is considered less suitable than a continuous endpoint, such as mean change in PASI score, for purpose of testing equivalence of MSB11022 and EU-Humira. Week 16 is already at the plateau of efficacy, and a dichotomy like PASI75 is less sensitive than the continuous 'parent' PASI outcome. Therefore, in addition to the primary and main secondary outcomes, evaluation of PASI scores of the treatment groups over all time points of the first 16 weeks of the study is considered important. Descriptive results of the course of continuous PASI were provided.

The assumptions of the sample size calculation based on the primary outcome and for the main secondary outcome (percent change from Baseline in PASI score at week 16) are considered reasonable and the calculated sample size is acceptable.

The 18% equivalence margin for PASI75 was justified by the applicant statistically (preservation of 70% of the treatment effect) and based on clinical arguments (25% is the difference between PASI75 that nowadays substitutes PASI50). Margins of either 15% (percent PASI change) or of 18% (PASI75 response) have been accepted previously by the CHMP.

While the margins are perceived as rather wide, in absence of a minimal clinically important difference for PASI and for PASI75, it is difficult to find clear scientific justification for smaller margins (e.g. 10%). However, the 15% and 18% equivalence margins are quite wide relative to the treatment effects and the upper margin actually exceeds 100%. Additionally, the applicant did not explain how far the responses close to the 'ceiling' are artificially favouring the conclusion of equivalence. However, as the continuous PASI score shows equivalence, the issue is not pursued further.

In general the statistical methods used are considered acceptable. However, an analysis stratifying on centre (or country) was initially missing for both the primary and main secondary endpoint and no subgroup analyses were performed based on centre or country. The analysis of the main secondary endpoint, mean PASI change, was not performed with the most simple model including only stratification factors, but it also included gender and BMI that were regarded important prognostic factors. However, analysis without gender and BMI lead to similar results. The analysis including (pooled) country and country by treatment interaction as fixed effect supported the primary analysis.

In the study there overall was not much discontinuation. Most discontinuations were due to TEAEs, and occurred in the first period after baseline which can be expected. However, there were considerable more discontinuations in EU-Humira group as compared to the MSB11022 group. There was no clear pattern in causes of discontinuations, and since most of these were not treatment related, it is considered that these are likely chance findings.

Efficacy data and additional analyses

Results of the equivalence study show that MSB11022 and EU-Humira are similarly effective regarding the main secondary outcome (mean percent change in PASI) as well as the primary outcome (PASI75). The mean percent change in PASI from baseline to week 16 in the PP set was similar in size for both treatment groups: -91% in the MSB11022 group and -92% in the EU-Humira group. The 2-sided 95% confidence interval of the treatment difference was within the predefined equivalence margins of +/- 15% and included 0 (no difference).
The PASI75 response at week 16 in the PP set was of similar size in both treatment groups: 90% in the MSB1102 group and 92% in the EU-Humira group. The 2-sided 95% confidence interval of the treatment difference was within the predefined equivalence margins of +/- 18% (Figure 3) and included 0 (no difference).

For both outcomes, the results of the ITT analyses were similar to the PP-analyses, and also the sensitivity analyses supported the results of the main analyses.

The results of the secondary outcomes, including the mean PASI scores over time, supported the results of the main analyses. Importantly, the mean PASI scores of the MSB1102 and EU-Humira groups showed a similar decline from baseline, week 2, 4, 8, 12 and 16. Baseline scores were around 21 and decreased to just below 2 at week 16 in the PP and ITT sets.

From week 16 (re-randomization) to week 24 and week 52, the PASI score remained similarly low in the groups continuing EU-Humira, continuing MSB11022 or switching to MSB11022. Consequently, the mean percentage change in PASI, PASI 50, 75 and 90 were similar for all three treatment groups, which also occurred for the proportions of PGA responders.

The results of the subgroup analyses are regarded to be supportive for equivalence of MSB11022 and EU-Humira. Subgroup analyses were performed for demographic variables and for previous use of systemic therapy (the randomisation stratification factor) for PASI75 and for PGA response, the results provided no indication that MSB11022 and EU-Humira performed dissimilar. Further subgroup analysis was performed for ADA positivity. In both treatment groups most (~90%) patients had developed Antidrug Antibodies (ADA) in the course of the first 16 weeks. Patients who were ADA positive showed on average a slightly decreased PASI75 response, similarly for MSB11022 and EU-Humira.

Notably, the effects of MSB11022 and of EU-Humira on PASI and on PASI75 at week 16 were large in comparison to the previous expectations. It is most likely that several factors played a role in causing the high responses, notably PP analysis as opposed to ITT analysis and the study design with 2 active treatments, which may influence expectations about the treatment effect and thus influences scoring by investigators. An average PASI75 response of 60% was expected from a meta-analysis of historic data, while the PASI75 response in the equivalence study amounted to 90%, in both treatment groups. While this approaches the 'ceiling' of what can be measured with PASI75, it makes these outcomes less sensitive for detecting differences between MSB11022 and EU-Humira. Illustratively, the upper equivalence margin of 18% exceeds 100% now the PASI75 response was 90%. The 'parent' continue PASI scores are regarded to be more sensitive to detect between-group differences. Therefore, it can be considered supportive for equivalence in efficacy that also in the early course of the study, the decrease in PASI scores was similar for MSB11022 and EU-Humira. While most other secondary outcomes are mere transformations of the PASI score (PASI50/75/90/100), it is also supportive for equivalence that the results on PGA and BSA were similar for MSB11022 and EU-Humira.

It is remarkable that within the first 16 weeks of the equivalence study, the vast majority patients developed ADA positivity (about 90%). The proportion of ADA positive (yes/no) patients was similar in both groups. However, as this also approaches the upper limit of the measurement scale, it may not be

sensitive to detect small differenced in immunogenicity, if present. Therefore, for assessing equivalence it is useful to also evaluate ADA titres and nAB over the course of the study. While the proportion of ADA positivity is much higher than in previous studies, this may be due to the specific assay used (refer to PK section). Although the group of ADA negative patients is much smaller than the group of ADA positive patients and therefore difficult to analyse, it appeared that there was only a small reduction in efficacy, in PASI75 as well as in the more sensitive percent PASI change, in ADA positive patients.

Extrapolation in other indications

MSB11022 is proposed for the same indications as for Humira, including Rheumatoid Arthritis, Juvenile idiopathic arthritis, Axial spondyloarthritis, Psoriatic arthritis, Psoriasis, Paediatric plaque psoriasis, , Crohn's disease, Paediatric Crohn's disease, Ulcerative colitis, Uveitis. The main equivalence study was performed in patients with psoriasis. It is considered that extrapolation of clinical equivalence from psoriasis to those disorders where the effect of adalimumab is primarily attained through inhibition of soluble TNF (e.g. rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis) can be agreed. This is in line with the CHMP Scientific Advice.

However, in inflammatory bowel disease (IBD, including Ulcerative Colitis and Crohn's disease) an important part of the effect of adalimumab is thought to be mediated via the membrane-bound TNF receptor. In line with the CHMP advice, extrapolation to inflammatory bowel disease would require convincing evidence from the preclinical studies related to these other potential mechanisms, e.g. the binding and effector functions in the setting of membrane bound TNF. There were uncertainties for the non-clinical and Quality data whether MSB11002 is equally potent to Humira in effector functions which are relevant subsequent to binding of adalimumab to the membrane-bound TNF (i.e. differences in high mannose content related to differences in ADCC activity and absence of data on regulatory macrophages). These uncertainties have now been solved (see quality and non-clinical sections). Further, the Applicant argued that extrapolation to IBD indications from the psoriasis study is justified, considering that the doses of adalimumab are similar, irrespective of the indication and their assumed main targets (membrane-bound TNF for IBD or soluble TNF for psoriasis and arthritis indications). Another argument from the Applicant was that the PK is equivalent between MSB11002 and Humira, whereas the PK profile is also determined by binding to the target. The psoriasis study and the PK study are in general supportive of equivalence however these studies do not univocally support an extrapolation to IBD.

Consequently, it is considered that therapeutic equivalence can be extrapolated from psoriasis to inflammatory bowel disease because therapeutic equivalence is considered supported by the pre-clinical evidence related to membrane-bound TNF-associated modes of action.

2.5.3. Conclusions on clinical efficacy

It is considered that all efficacy results of the equivalence study in patients with moderate to severe plaque psoriasis are supporting comparable efficacy of MSB11022 and EU-Humira. Psoriasis is regarded as a sensitive model and the study was sufficiently powered. The period from baseline up to plateau of the effect is regarded to be most sensitive to detect differences between MSB11022 and EU-Humira, if they exist. According to the results of the study, MSB11022 and EU-Humira were similarly effective at week 16 in change in PASI score and in PASI75 response.

The 95%CI of the differences between MSB11022 and EU-Humira was small, clearly within the equivalence margins, and included zero. Importantly, these findings are supported by the mean PASI scores over all visits of the 16 week Core Treatment Period,that were similar for MSB11022 and EU-Humira, without a tendency for MSB11022 to be worse. Together with the consistent results of the subgroup analyses, other secondary outcomes, 52 week data and switching data, this supports that MSB11022 and EU-Humira have equivalent efficacy in moderate to severe plaque psoriasis.

The PASI75 responder rates are much higher than anticipated based on historical data. Therefore, the chosen NI margin and the effect of the high response rate on the interpretation of the primary endpoint is unclear; it is conceivable that PASI75 is less sensitive. As the continuous PASI scores support equivalence, the issue was not pursued further.

Extrapolation from the psoriasis model to inflammatory bowel disease is supported by the pre-clinical evidence related to membrane-bound TNF-associated modes of action.

2.6. Clinical safety

The Clinical Study Report was submitted including the 54-week data and an addendum to the Clinical Study Report including the 66-week safety data (final database lock).

Patient exposure

Given the two-phase design of study **EMR200588-002**, the safety data were organised to describe the Core Treatment Period, the Extended Treatment Period, and the Overall Treatment Period (Table 5). In both study phases, nearly all randomised patients remained in the Safety Analysis Set.

Table 5 **Exposure in Study EMR200588-002 - SAF, ETP-SAF**

Variable	Core Treatment Period		Extended Treatment Period			Overall Treatment Period	
	MSB11022	EU-Humira	MSB11022 to MSB11022	EU-Humira to EU-Humira	EU-Humira to MSB11022	Continuous MSB11022	Continuous EU-Humira
Treated, n%	221 (100.0)	220 (100.0)	213 (100.0)	101 (100.0)	101 (100.0)	221 (100.0)	119 (100.0)
Treatment ongoing at Week 16 [a]	213 (95.9)	202 (91.4)	-	-	-	213 (95.9)	101 (84.9)
Duration of treatment (weeks), mean (SD)	14.6 (1.92)	14.3 (2.63)	34.44 (5.77)	33.42 (7.83)	34.00 (6.75)	47.92 (9.89)	42.17 (16.75)
Administered injections, mean (SD)	8.7 (1.02)	8.6 (1.36)	17.1 (2.90)	16.5 (3.95)	16.8 (3.42)	25.2 (5.03)	22.3 (8.39)
Total exposure (subject years)	70.5	68.9	140.6	68.6	69.6	211.2	100.7
Compliance (%), mean (SD)	98.8 (4.2)	98.7 (4.3)	99.2 (2.52)	98.9 (5.03)	98.0 (6.7)	99.0 (3.16)	98.5 (4.78)
Compliance, n%							
< 80%	4 (1.8)	3 (1.4)	0	2 (2.0)	4 (4.0)	2 (0.9)	2 (1.7)
80%-100%	217 (98.2)	217 (98.6)	213 (100.0)	101 (100.0)	99 (98.0)	219 (99.1)	117 (98.3)
> 100%-120%	0	0	0	0	0	0	0
> 120%	0	0	0	0	0	0	0

Source: CSR EMR200588-002 Week 54, Tables 15.1.1.1, 15.1.1.2, 15.3.0.1, 15.3.0.4, 15.3.0.7, 15.3.1.1, 15.3.1.2, and 15.3.1.3.
ETP = Extended Treatment Period, SAF = safety analysis set, SD = standard deviation.
[a] Percentages hand-calculated.

Adverse events

In the **Core Treatment Period** of study EMR200588-002 (baseline – week 16), about half of the patients had at least 1 TEAE, similar in each of the two treatment groups (Table 11). The majority of TEAEs were of mild or moderate severity. Serious AEs occurred in eight patients in the MSB11022 group and in six patients in the EU-Humira group. By the investigators, two and four of the Serious AEs were considered to be related to the study drug, deaths did not occur (see section 'Serious adverse events and Deaths'). The occurrence of adverse events of special interest (AESI's) was low. In the EU-Humira group, more patients than in the MSB11022 group discontinued the treatment and the study due to TEAEs (Table 11).

Table 11 Summary of AEs of Study EMR200588-002, Core Treatment Period - SAF

TEAE category	Number (%) of subjects	
	MSB11022 (N=221)	EU-Humira (N=220)
Any TEAE	114 (51.6)	117 (53.2)
Drug-related TEAE	49 (22.2)	51 (23.2)
SAE	8 (3.6)	6 (2.7)
Drug-related SAE	2 (0.9)	4 (1.8)
Death	0	0
AESI	2 (0.9)	1 (0.5)
Drug-related AESI	1 (0.5)	1 (0.5)
TEAE leading to treatment discontinuation	1 (0.5)	12 (5.5)
TEAE leading to study termination	1 (0.5)	10 (4.5)

Source: CSR EMR200588-002 Week 54, Table 15.3.1.1 and Table 15.3.1.4.
AESI = adverse events of special interest, SAE = serious adverse event, TEAE = treatment emergent adverse event, SAF = safety analysis set.

In the Core Treatment Period, the most common AEs (≥2%) by organ class for MSB11022 and EU-Humira were: infections and infestations (19% and 21%), general disorders and administration site conditions (15% and 16%), metabolism and nutrition disorders (8% and 6%). Neoplasms (benign, malignant and unspecified) occurred in 1 (0.5%) and 7 (3%) of patients in the MSB11022 and the EU-Humira group. Blood and lymphatic system disorders occurred in 6 (2.7%) and 1 (0.5%) of patients in the MSB11022 and the EU-Humira group. The commonest AEs (≥2%) by preferred term were: nasopharyngitis, injection site erythema and injection site pain, headache (Table 14).

Table 14 AEs Reported in ≥ 2% of Subjects in Either Treatment Group, by Preferred Term in Study EMR200588-002, Core Treatment Period - SAF

Preferred term	Number (%) of subjects	
	MSB11022 (N=221)	EU-Humira (N=220)
Any TEAE	113 (51.1)	117 (53.2)
Nasopharyngitis	13 (5.9)	15 (6.8)
Injection site erythema	11 (5.0)	13 (5.9)
Injection site pain	11 (5.0)	11 (5.0)
Headache	8 (3.6)	7 (3.2)
Hypertension	8 (3.6)	1 (0.5)
Hypertriglyceridaemia	8 (3.6)	2 (0.9)
Pharyngitis	7 (3.2)	2 (0.9)
Arthralgia	5 (2.3)	2 (0.9)
Hyperuricaemia	5 (2.3)	0
Alanine aminotransferase increased	4 (1.8)	6 (2.7)
Injection site bruising	4 (1.8)	5 (2.3)
Injection site pruritus	3 (1.4)	6 (2.7)

Source: CSR EMR200588-002 Week 54, Table 15.3.1.7.
AE = adverse event, SAF = safety analysis set.

In the Core Treatment Period, 2 patients in the MSB11022 group (n=222) and 1 patient in the EU-Humira group (n=221) were reported to have adverse events of special interest (AESIs). Of the serious infections, these were chronic cholecystitis and respiratory tract viral infection in the MSB11022 group and bacterial arthritis in the EU-Humira group. Latent or active TB did not occur in this period.

Hypersensitivity reactions occurred in 5 patients in the MSB11022 group (n=222) compared with 6 patients in the EU-Humira group (n=221). Injection site reactions occurred in a similar frequency and pattern in the MSB11022 (11%) and EU-Humira (14%) groups.

In the **Overall Treatment Period** of study EMR200588-002 (baseline – week 54), the frequency of occurrence of AEs (Table 12) was raised compared to the Core Treatment Period of the first 16 weeks (Table 11). The occurrence of SAEs was highest in the continuous MSB11022 group, but a minority of the occurrences were considered to be drug-related. Occurrence of AESIs was also highest in the continuous MSB11022 group (Table 12).

Table 12 **Summary of AEs of Study EMR200588-002, Overall Treatment Period - SAF**

TEAE category	Number (%) of subjects	
	Continuous MSB11022 (N=221)	Continuous EU-Humira (N=119)
Any TEAE	173 (78.3)	91 (76.5)
Drug-related TEAE	69 (31.2)	41 (34.5)
SAE	20 (9.0)	8 (6.7)
Drug-related SAE	3 (1.4)	5 (4.2)
Death	0	1 (0.8)
AESI	12 (5.4)	4 (3.4)
Drug-related AESI	8 (3.6)	1 (0.8)
TEAE leading to treatment discontinuation	10 (4.5)	16 (13.4)
TEAE leading to study termination	9 (4.1)	13 (10.9)

Source: CSR EMR200588-002 Week 54, Table 15.3.1.3 and Table 15.3.1.6.
AESI = adverse events of special interest, SAE = serious adverse event, SAF = safety analysis set, TEAE = treatment emergent adverse event.

The most frequent AEs according to SOC term in the continuous MSB11022 and the continuous EU-Humira groups (Table 15) were: infections and infestations (51% and 38%), general disorders and administration site conditions (20% and 21%), musculoskeletal and connective tissue disorders (15% and 10%), investigations (14% and 18%), metabolism and nutrition disorders (13% and 4%), skin and subcutaneous tissue disorders (13% and 17%). The largest differences between continuous MSB11022 and continuous EU-Humira occurred in the SOCs infections and infestations, musculoskeletal and connective tissue disorders, metabolism and nutrition disorders, blood and lymphatic disorders (5% and 1.7%).

Table 15 **AEs Reported in ≥ 2% of Subjects in Either Treatment Group by System Organ Class in Study EMR200588-002, Overall Treatment Period - SAF**

System Organ Class	Number (%) of subjects	
	Continuous MSB11022 (N=221)	Continuous EU-Humira (N=119)
Infections and infestations	112 (50.7)	45 (37.8)
General disorders and administration site conditions	44 (19.9)	25 (21.0)
Musculoskeletal and connective tissue disorders	34 (15.4)	12 (10.1)
Investigations	31 (14.0)	21 (17.6)
Metabolism and nutrition disorders	29 (13.1)	5 (4.2)
Skin and subcutaneous tissue disorders	28 (12.7)	20 (16.8)
Injury, poisoning and procedural complications	20 (9.0)	8 (6.7)
Nervous system disorders	17 (7.7)	4 (3.4)
Gastrointestinal disorders	15 (6.8)	8 (6.7)
Vascular disorders	12 (5.4)	6 (5.0)
Respiratory, thoracic and mediastinal disorders	10 (4.5)	9 (7.6)
Blood and lymphatic system disorders	11 (5.0)	2 (1.7)
Renal and urinary disorders	9 (4.1)	3 (2.5)
Reproductive system and breast disorders	7 (3.2)	4 (3.4)
Cardiac disorders	6 (2.7)	4 (3.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (0.9)	5 (4.2)
Pregnancy, puerperium and perinatal conditions	1 (0.5)	3 (2.5)

Source: CSR EMR200588-002 Week 54, Table 15.3.1.9.
SAF = safety analysis set.

The occurrence of AEs according to Preferred Term (Table 16) appeared to be dissimilar (in %) between the two groups continuing on MSB11022 or EU-Humira for: hypertriglyceridaemia/'blood triglycerides increased', hypertension, bronchitis but not upper respiratory tract infection, pharyngitis but not nasopharyngitis, tonsillitis, headache. For some of these AEs, smaller dissimilarities can be noted already at the end of the Core Treatment Period (Table 14).

Regarding infections and infestations, it can be seen in Table 16 that for every tabulated infection, except herpes simplex, occurrence in continuous MSB11022 was slightly higher than in continuous EU-Humira: nasopharyngitis, upper respiratory tract infection, pharyngitis, bronchitis, tonsillitis, viral infection, latent tuberculosis. There also were relatively more patients on continuous MSB11022 having an infection that occurred in few or single patients (not shown).

Table 16 **AEs Reported in ≥ 2% of Subjects in Either Treatment Group by Preferred Term in Study EMR200588-002, Overall Treatment Period - SAF**

Preferred term	Number (%) of subjects	
	Continuous MSB11022 (N=221)	Continuous EU-Humira (N=119)
Any TEAE	173 (78.3)	91 (76.5)
Nasopharyngitis	41 (18.6)	19 (16.0)
Injection site erythema	17 (7.7)	8 (6.7)
Injection site pain	17 (7.7)	6 (5.0)
Hypertriglyceridaemia	13 (5.9)	1 (0.8)
Upper respiratory tract infection	12 (5.4)	6 (5.0)
Arthralgia	12 (5.4)	5 (4.2)
Pharyngitis	12 (5.4)	2 (1.7)
Injection site bruising	11 (5.0)	7 (5.9)
Hypertension	11 (5.0)	3 (2.5)
Bronchitis	10 (4.5)	2 (1.7)
Headache	10 (4.5)	1 (0.8)
Alanine aminotransferase increased	7 (3.2)	4 (3.4)
Injection site induration	7 (3.2)	4 (3.4)
Blood triglycerides increased	6 (2.7)	5 (4.2)
Tonsillitis	6 (2.7)	1 (0.8)
Injection site pruritus	5 (2.3)	4 (3.4)
Back pain	5 (2.3)	2 (1.7)
Nausea	5 (2.3)	1 (0.8)
Pruritus	5 (2.3)	6 (5.0)
Viral infection	5 (2.3)	0
Hyperuricaemia	5 (2.3)	1 (0.8)
Latent tuberculosis	5 (2.3)	0
Psoriasis	4 (1.8)	5 (4.2)
Blood creatinine phosphokinase increased	4 (1.8)	3 (2.5)
Hypophosphataemia	3 (1.4)	3 (2.5)
Asthenia	1 (0.5)	4 (3.4)
Herpes simplex	1 (0.5)	3 (2.5)
Pregnancy	1 (0.5)	3 (2.5)
Rhinorrhoea	0	3 (2.5)

Source: CSR EMR200588-002 Week 54, Table 15.3.1.9.
SAF = safety analysis set.

In the **Extended Treatment Period** (week 16 – week 54), the occurrence of TEAEs was generally similar in the groups of patients who switched to MSB11022 or who continued EU-Humira and (Table 23). Most occurring TEAEs (SOC) in the respective two treatment groups were: infections and infestations (39% and 29%), general disorders and administration site conditions (14% and 13%), musculoskeletal and connective tissue disorders (7% and 8%), investigations (9% and 9%), skin and subcutaneous tissue disorders (6% and 16%). There were no PT terms for infections clearly dominating the difference between 'switchers' and the patients continuing EU-Humira. A part of the higher occurrence of AEs in the SOC 'skin and subcutaneous tissue disorders' for continuous EU-Humira is explained by a higher frequency of AEs concerning psoriasis and pruritis in that patient group.

Table 23 **Summary of AEs in Study EMR200588-002, Extended Treatment Period - ETP-SAF**

TEAE category	Number (%) of subjects	
	EU-Humira to MSB11022 (N=101)	EU-Humira to EU-Humira (N=101)
Any TEAE	61 (60.4)	64 (63.4)
Drug-related TEAE	16 (15.8)	22 (21.8)
SAE	4 (4.0)	3 (3.0)
Drug-related SAE	0	1 (1.0)
Death	0	1 (1.0)
AESI	4 (4.0)	1 (1.0)
TEAE leading to treatment discontinuation	3 (3.0)	6 (5.9)
TEAE leading to study termination	2 (2.0)	5 (5.0)

Source: CSR EMR200588-002 Week 54, Table 15.3.1.2 and Table 15.3.1.5.
AESI = adverse events of special interest, ETP = Extended Treatment Period, SAE = serious adverse event, TEAE = treatment emergent adverse event, SAF = safety analysis set.

Adverse events of special interest

Adverse events of special interest were pre-defined as: serious infections and latent or active tuberculosis infections. In addition, hypersensitivity and anaphylactic reactions, and injection site reactions were analysed.

In the **Overall Treatment Period**, 12 AESIs were reported in the continuous MSB11022 group (n=221) and 6 AESIs in the continuous EU-Humira group (n=119). In the continuous MSB11022 group these were: chronic cholecystitis, respiratory tract infection (both had occurred in the Core Treatment Period), chronic cholecystitis, herpes zoster, tuberculosis, 5 cases of latent tuberculosis, positive tuberculosis test, viral respiratory tract infection. In the continuous EU-Humira group these were: bacterial arthritis, 2 cases of positive tuberculosis test, (all had occurred in the Core Treatment Period), a case of false-positive tuberculosis test. In the continuous MSB11022 group there were 10 (4.5%) patients and in the continuous EU-Humira 4 (3.4%) patients with a hypersensitivity reaction. There was one case with anaphylactic shock, that was attributed to bee sting, which occurred in the EU-Humira group. The occurrence of injection site reactions was similar in the groups continuing MSB11022 and continuing EU-Humira (Table 20, below).

In the **Extended Treatment Period**, 5 patients in the group who had switched to MSB11022 had an AESI: 2 cases of latent tuberculosis, lip infection, pneumonia, allergic dermatitis. One patient in the 'switch' group to MSB11022 and 2 patients in the continuous EU-Humira group had a hypersensitivity reaction; anaphylactic shock did not occur. The occurrence and pattern of injection site reactions was similar in the groups switching to MSB11022 (13%) and continuing EU-Humira (11%).

Table 20 **Injection Site Reactions in Study EMR200588-002, Overall Treatment Period - SAF**

Injection site reaction	Number (%) of subjects	
	Continuous MSB11022 (N=221)	Continuous EU-Humira (N=119)
Any injection site reaction [a]	37 (16.7)	21 (17.6)
Injection site erythema	17 (7.7)	8 (6.7)
Injection site pain	17 (7.7)	6 (5.0)
Injection site bruising	11 (5.0)	7 (5.9)
Injection site induration	7 (3.2)	4 (3.4)
Injection site pruritus	5 (2.3)	4 (3.4)
Injection site swelling	3 (1.4)	1 (0.8)
Injection site haematoma	1 (0.5)	0
Injection site haemorrhage	1 (0.5)	0
Injection site oedema	1 (0.5)	0
Injection site rash	1 (0.5)	0

Source: CSR EMR200588-002 Week 54, Table 15.3.1.33.
SAF = safety analysis set.
[a] Corresponding to the system organ class of general disorders and administration site conditions.

Serious adverse events and deaths

In the 54-week period of study EMR200588-002 one death was reported. After the week 24 visit, one patient in the continued EU-Humira group had died after a traumatic event with cerebral hematoma, brain edema, and subsequent cardiac failure. These events were considered not to be related to the study medication.

In the **Core Treatment Period**, 8 SAEs occurred in the MSB11022 group and 6 SAEs occurred in the EU-Humira group (Table 18), all SAEs occurred in single patients. In the MSB11022 group, 2 SAEs were rated as related to study medication: respiratory tract infection viral and erythema multiforme. In the EU-Humira group, 4 SAEs were rated as treatment-related: intraductal proliferative breast lesion, bacterial arthritis, increased hepatic enzyme, and increased liver function test.

In the **Overall Treatment Period**, 9% in the continuous MSB11022 group and 7% of patients in the continuous EU-Humira group had SAEs. Most SAEs occurred in single patients (Table 53). In the MSB1102 group, 1 subject had 3 cardiac SAEs.

Table 53 **Serious TEAEs by Treatment Group in the Overall Treatment Period (SAF Analysis Sets)**

	MSB11022 N=221		EU-Humira N=119		EU-Humira/ MSB11022 N=101	
Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Subjects with at least 1 event and total events	20 (9.0)	24	8 (6.7)	12	5 (5.0)	5
Neutropenia	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Acute myocardial infarction	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Atrial fibrillation	2 (0.9)	2	0 (0.0)	0	0 (0.0)	0
Cardiac failure	0 (0.0)	0	2 (1.7)	2	0 (0.0)	0
Cardiomyopathy	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Coronary artery stenosis	1 (0.5)	2	0 (0.0)	0	0 (0.0)	0
Hypertensive cardiomyopathy	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Mitral valve incompetence	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Myocardial infarction	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Conjunctival cyst	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Inguinal hernia	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Hernia	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0

Cholecystitis chronic	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Anaphylactic shock [a]	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Appendicitis	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Arthritis bacterial	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Peritonsillar abscess	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Pneumonia	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Respiratory tract infection viral	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Sinusitis	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Staphylococcal abscess	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Accidental overdose	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Ankle fracture	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Facial bones fracture	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Ligament sprain	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Hepatic enzyme increased	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Liver function test increased	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Intervertebral disc protrusion	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Osteoarthritis	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Osteonecrosis	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Intraductal proliferative breast lesion	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Brain oedema	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Cerebral haematoma	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0
Acute kidney injury	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Erythema multiforme	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Hypersensitivity vasculitis	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Hypertension	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Vascular compression	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0

Source: Table 15.3.1.15.

MedDRA Version 20.1.

If a subject has more than 1 event for a particular SOC/PT, the subject is counted only once but the full number of events is displayed.

Only events that started up to and including the Week 54 analysis cutoff date are included.

EU-Humira = EU-approved Humira; SAF = Safety.

a This subject suffered a bee sting leading to anaphylactic shock, which was assessed as not related to IMP, but due to an underlying history of bee sting allergy. See the subject narrative in Section 15.3.4 for additional information.

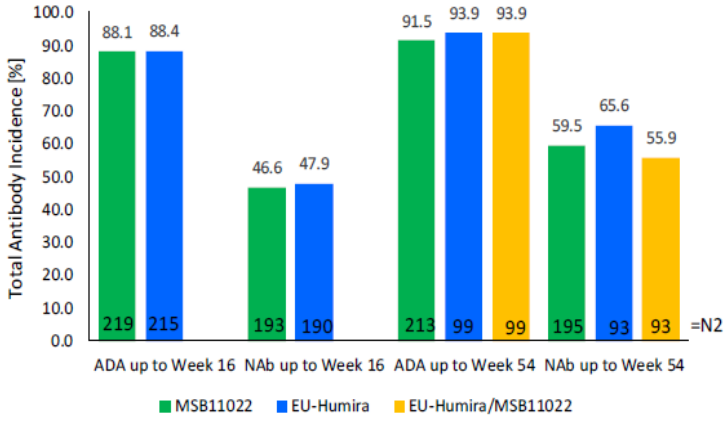
In the **Extended Treatment Period** (week 16 – week 54), 4 (4%) patients in the group who 'switched' to MSB11022 had 4 SAEs (myocardial infarction, conjunctival cyst, appendicitis, staphylococcal abcess). (The case with anaphylactic shock, attributed to bee sting, in Table 53 had occurred in the core treatment period while on EU-Humira.) Over the same period, 12 (5.6%) patients from the group who continued MSB11022 had SAEs.

Immunogenicity

In the **Core Treatment Period**, the proportions of patients positive for anti-drug antibody (ADA) increased similarly in both groups and overall amounted to 88% in both treatment groups (Figure 18). The proportion of patients positive for neutralising antibody (nAb) as proportion of patients positive for ADA) increased in both groups to around 46%. The ADA titers over the course of the Core Treatment Period were similar for the MSB11022 and EU-Humira groups (Figure 11).

In the **Extended Treatment Period** the proportions of ADA and nAb positive patients up to week 54 were similarly high for the continued MSB11022 and the continued EU-Humira group, as well as the group that had switched from EU-Humira to MSB11022 (Figure 18). There were no apparent differences in ADA titres between the groups who continued MSB11022, continued EU-Hunira, or 'switched' from Eu-Humira to MSB11022 (not shown).

Figure 18 **Anti-drug Antibodies and Neutralizing Antibodies Summary Results up to Week 16 and up to Week 54 – SAF**

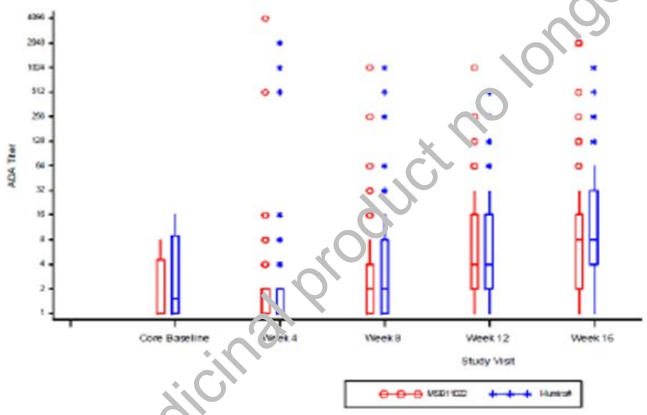


Source: CSR EMR200588-002 Week 54, Table 15.3.7.1, Table 15.3.7.2

ADA=anti-drug antibody; NAb=neutralizing antibody; SAF=safety Analysis Set; N2=the number of subjects who had an assessment at the visit

Week 16 data displayed reflect the overall ADA and NAb incidence up to Week 16, ie, at least 1 positive result postdose at any time during the Core Treatment Period. Only assessments before the extended treatment administration were included. Week 54 data displayed reflect the overall ADA and NAb incidence up to Week 54, ie, at least 1 positive result postdose at any time during the Extended Treatment Period.

Figure 11 **Box Plot of ADA Titer Versus Time During Core Treatment Period by treatment - SAF**



Source: CSR EMR200588-002 Week 54, Figure 15.3.7.10

Core Baseline is defined as the last nonmissing assessment on or prior to Day 1

ADA=anti-drug antibody; SAF=Safety Analysis Set

The influence of ADA positivity on the clinical response (PASI75) was similar for MSB11022 and EU-Humira.

In the Core Treatment Period and the **Overall Treatment Period**, injection site reactions in patients who were ADA positive occurred similarly in continuous MSB11022 (16%) and the continuous EU-Humira groups (19%). The proportions of ADA- were too low for meaningful comparisons.

Laboratory findings

There were overall no clinical meaningful differences between treatment groups in mean or median hematology values (except a small difference in eosinophilea), biochemistry values (including liver function tests), or urine analysis, across treatment groups in the Core Treatment Period, Overall Treatment Period or Extended Treatment Period.

Discontinuation due to AEs

In the 16 weeks of the **Core Treatment Period**, one patient in the MSB11022 group discontinued the treatment due to a TEAE, while 12 patients in the EU-Humira discontinued treatment (Table 11). These TEAEs were erythema multiforme in the MSB11022 group, and in the EU-Humira group these were: neutropenia, atrial fibrillation, extrasystoles, hepatic steiatosis, bacterial arthritis, arthropod bite, hepatic ezyme increased, liver function test increased, positive tuberculosis test, intraductal proliferatuive breast lesion, uterine leiomyoma, pregnancy (2 patients), allergic dermatitis.

In the **Extended Treatment Period**, 9 patients on continuous MSB11022 (hepatic steatosis, latent tuberculosis (3 subjects), tuberculosis, pregnancy, acute kidney injury, hypersensitivity vasculitis, psoriasis), 6 patients on EU-Humira (cardiac failure, hypertensive cardiomyopathy, mitral valve incompetence, liver function test increased, brain edema, cerebral hematoma, pregnancy, psoriasis, pustular psoriasis) and 3 patients who had switched to MSB11022 (latent tuberculosis, anti-double stranded DNA positive, pregnancy) had discontinued the treatment due to one or more TEAEs.

Four-month safety follow-up data

The 4-month safety follow-up data that were provided as amendment did not change the picture and pattern as was derived by the evaluation of the week 54 data.

2.6.1. Discussion on clinical safety

The clinical development program consisted of two studies: a single dose PK study of 70 days in healthy volunteers (EMR200588-001) comparing MSB110022 with EU-Humira and US-Humira and a 52-week equivalence trial with safety follow-up to week 66, in adult patients with moderate-severe plaque psoriasis (EMR200588-002) comparing MSB11022 with EU-Humira. The main clinical study in plaque psoriasis is meanwhile completed and safety and immunogenicity data up to week 54 and an addendum concerning the week 66 safety follow-up data were submitted. In case of chronic administration, one-year follow up data is normally required pre-authorisation for evaluation of immunogenicity as mentioned in the relevant guideline [EMEA/CHMP/BMWP/42832/2005 Rev1].

In the 16-week Core Treatment Period, n=222 patients were treated with MSB11022 and n=221 were treated with EU-Humira, nearly all patients remained in the Safety Analysis Set of the Core Treatment Period and of the Extended Treatment Period from week 16 up to and including week 54.

Overall, the occurrence of TEAEs appears to be similar for MSB11022 and EU-Humira.
In the Core Treatment Period of study EMR200588-002 (baseline – week 16), about half of the patients had at least 1 TEAE, similar for MSB11022 and EU-Humira. The majority of TEAEs were of mild or moderate severity. The most common AEs (≥2%) by organ class for MSB11022 and EU-Humira were: infections and infestations (19% and 21%), general disorders and administration site conditions (15% and 16%), metabolism and nutrition disorders (8% and 6%). The most common AEs (≥2%) by preferred term were: nasopharyngitis, injection site erythema and injection site pain, headache. This was similar for both treatment groups and the pattern is in line with the Humira SmPC. Some of the less common AEs (hypertension, hypertriglyceridaemia) occurred in more cases with MSB11022 than with EU-Humira. 'Lipids increased' and 'hypertension' are listed as a very common AE in the Humira SmPC, and therefore this does not lead to further concern by the CHMP.
In the Core Treatment Period there also were notable differences in the occurrence of neoplasms (more in EU-Humira) and blood/lymphatic system disorders (more in MSB11022). While the frequency of occurrence is low and the number of organ classes/preferred terms is relatively high, these may well be chance findings. Moreover, as the time from baseline to occurrence is relatively short for development of malignancies, a causal relation of malignancies with study treatment is not very likely. Serious AEs

occurred in eight patients in the MSB11022 group and in six patients in the EU-Humira group. More patients on EU-Humira group than on MSB11022 discontinued the treatment and/or the study due to TEAEs, most had done so at or before week 16. There was no clear pattern and it is likely that the numerical difference is a chance finding, therefore no concern was raised by the CHMP.

The results of the Overall Treatment Period (baseline – week 54) of patients continuing MSB11022 or EU-Humira were largely similar to the Core Treatment Period. As may be expected, the incidence of AEs increased with longer exposition. Due to the re-randomization at week 16, the treatment group continuing MSB1102 was about twice as large (n=221) as the continuous EU-Humira group (n=119). The overall occurrence of TEAEs was similar for continuous MSB11022 (78%) and continuous EU-Humira (77%). Serious AEs occurred in 20 (9%) patients in the continuous MSB11022 group and in 8 (7%) patients in the continuous EU-Humira group. There was no clear pattern, usually SAEs occurred in single patients, and few of them can be considered drug related.

The largest differences between continuous MSB11022 and continuous EU-Humira occurred in the SOCs: infections and infestations (51% and 38%), musculoskeletal and connective tissue disorders (15% and 10%), metabolism and nutrition disorders (13% and 4%), blood and lymphatic disorders (5% and 1.7%). Regarding infections, it seems that the difference is explained by a 'generally' raised occurrence in the MSB11022 group, rather than raised occurrence of some specific kinds of infection. The dissimilarity in occurrence of infections is valued as most likely attributable by chance, there are no apparent dissimilarities in non-clinical functional tests, PK or PD that would explain this difference in occurrence of infections. Commonness of infections in the source population and the large number of AEs evaluated may increase the likelihood of chance findings.

Neoplasms occurred dissimilar in the Core Treatment period: neoplasms (benign, malignant and unspecified) occurred in 1 (0.5%) and 7 (3%) of patients in the MSB11022 and the EU-Humira group. Due to low numbers and short exposure to EU-Humira or MSB11022, this likely was a chance finding. In the Overall Treatment Period, two additional events occurred: one in the switch group and one in the MSB11022 group. This does not lead to further concerns about dissimilarity on safety.

There also are dissimilarities between the two groups continuing on MSB11022 or EU-Humira for: hypertriglyceridaemia/'blood triglycerides increased' and hypertension. However, the dissimilarities regarding hypertriglyceridaemia/blood triglycerides increased/hypertension are valued as chance findings, given commonness in the source population and the large number of AEs evaluated. The planned measurements of serum triglycerides and of blood pressure did not give rise for concerns.

The results on immunogenicity do not show differences between MSB11022 and EU-Humira. The proportions of patients with ADA increased similarly in both groups and amounted to ~90% in the MSB11022 group and the EU-Humira group already within 16 weeks. Towards 54 weeks, the occurrence of ADA positivity increased slightly to ~95% in all three treatment groups, while 56%-66% were nAB positive. ADA positivity lead to a slightly reduced efficacy (PASI75 response) and did not appear to influence safety events, similarly in patients treated with MSB11022 or with EU-Humira.

Already after 16 weeks, nearly all patients had developed ADA and this is much more than in previous studies. Reassuringly, the ADA titers over the course of the Core Treatment Period and Overall Treatment Period/extended Treatment Period were comparable for the MSB11022 and EU-Humira groups, and the group of patients switching to MSB11022.

In the patients who switched from EU-Humira to MSB11022, the occurrence of AEs by Organ Class and by Preferred Term was generally similar as compared to the other two treatment groups (EU-Humira and MSB11022). Similar as in patients on continuous MSB11022, in patients who switched to MSB11022, the occurrence of infections and infestations was raised by 10% as compared to patients continuing EU-Humira. Again, there were no PT terms for infections clearly dominating the difference between

'switchers' and the patients continuing EU-Humira. Consequently, switching from EU-Humira to MSB11022 does not lead to a safety signal in the commonest TEAEs. Switching from EU-Humira to MSB11022 did not lead to a further increase in ADA positivity.

2.6.2. Conclusions on clinical safety

The safety profile and immunogenicity of MSB11022 and EU-Humira appear to be similar.

Overall, the occurrence of AEs was similar for MSB11022 and EU-Humira, and both MSB11022 and EU-Humira appeared to be safe over 54 weeks of the study. Numerical differences in the occurrence of infections and in metabolism disorders, that were higher in MSB11022, are valued as chance findings. There were no other major differences in occurrence and pattern of TEAEs, AESIs, SAEs, immunogenicity and other laboratory findings. It did not appear that switching from EU-Humira to MSB11022 lead to a safety signal.

The percentage of subjects with ADA-positive samples was very high (near 90%) after a relatively short treatment period, thus providing little 'assay sensitivity' in this study population to detect difference in immunogenicity, if present. However, given the similarity of ADA titers over time similarity of immunogenicity is not doubted.

The responses to questions related to safety do currently not impact the safety specification in the Risk Management Plan.

2.7. Risk Management Plan

Identified risks

Safety concern	Risk minimization measures	Pharmacovigilance activities
Safety Concern 1		
Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB	Text in SmPC (refer to SmPC section 4.3, 4.4, 4.8): Section 4.3: Contraindications for active TB or other severe infections such as sepsis, and opportunistic infections. Section 4.4: Warnings regarding active TB and serious infections such as sepsis due to bacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis. Warning regarding a higher risk of infections in the elderly population 65 years. Section 4.8: Diverticulitis is listed as an adverse reaction. In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risks of serious infections associated with the use of: • Patient Reminder Card • HCP Educational Material	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient. Additional pharmacovigilance activity: This safety concern will be monitored in the proposed category 3 studies, as feasible.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Safety Concern 2		
Reactivation of hepatitis B	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding hepatitis B reactivation is included in the Special warnings and precautions for use section. Section 4.8: The reactivation of hepatitis B is also listed as an adverse reaction identified in post marketing surveillance in the Undesirable effects section (Section 4.8) of the SmPC. The SmPC recommends testing for HBV before initiating treatment with Kromeya®. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 3		
Pancreatitis	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.8: Pancreatitis is listed as an uncommon adverse reaction seen in clinical trials. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 4		
Lymphoma	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding lymphoma and malignancies in the adult and pediatric population. Section 4.8: Information on incidence rates from clinical trials. In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Reminder Card • HCP Educational Material	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 5		
HSTCL	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding hepatosplenic T-cell lymphoma and malignancies in the adult and pediatric population. Section 4.8: Information on incidence rates from post marketing is included.	Routine pharmacovigilance surveillance is being performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	The SmPC also highlights that some of the cases of HSTCL occurred with concomitant use of azathioprine or 6-mercaptopurine, and that the potential risk combination of azathioprine or 6-mercaptopurine and MSB11022 should be carefully considered. In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Reminder Card • HCP Educational Material	
Safety Concern 6		
Leukemia	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Warning regarding the risk of leukemia and malignancies in the adult and pediatric population In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Reminder Card • HCP Educational Material	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 7		
NMSC	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding the risk of NMSC and malignancies in the adult and pediatric population. Section 4.8: Incidence rates for NMSC from clinical trials are included. In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Reminder Card • HCP Educational Material	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 8		
Melanoma	Section 4.4: Warning regarding malignancies in the adult and pediatric population. Section 4.8: Melanoma is listed as an adverse reaction identified in clinical trials. In order to inform patients of these	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is

Safety concern	Risk minimization measures	Pharmacovigilance activities
	risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Reminder Card • HCP Educational Material	provided by the patient.
Safety Concern 9		
Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin)	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warning regarding Merkel cell carcinoma (neuroendocrine carcinoma of the skin). Section 4.8: MCC is also listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet To educate prescribers and patients about the risk of malignancies associated with the use of: • Patient Reminder Card • HCP Educational Material	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient Additional pharmacovigilance activity: This safety concern will be monitored in the proposed category 3 studies, as feasible.
Safety Concern 10		
Demyelinating disorders (including MS, GBS, and optic neuritis)	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warnings on demyelinating disorders are included. Further details for the uveitis patient population are also included. Section 4.8: Demyelinating disorders are also listed as adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding Text is also present in the package leaflet. To educate prescribers and patients about 1) the risk of demyelinating disorders associated with the use of, and 2) the underlying risk of demyelinating disorders associated with uveitis, particularly intermediate uveitis: • Patient Reminder Card • HCP Educational Material	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 11		
Immune reactions (including lupus-like reactions and allergic reactions) with long term use of MSB11022	Text in SmPC (refer to SmPC section 4.4, 4.8): Section 4.4: Warnings regarding lupus-like reactions and serious	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	allergic reactions are included. Section 4.8: Lupus-like syndrome and anaphylaxis are also listed as adverse reactions identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 12		
Sarcoidosis	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Sarcoidosis is listed as an uncommon adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed. Including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 13		
Congestive Heart Failure	Text in SmPC (refer to SmPC section 4.3, 4.4 and 4.8): Section 4.3: Moderate to severe CHF as contraindication to Kromeya® use is contained in the Contraindication section. Section 4.4: Warning regarding including worsening and new onset CHF is included. It advises that MSB11022 should be used with caution patients with mild heart failure with instructions to stop adalimumab in patients who develop new or worsening of symptoms of CHF. Section 4.8: CHF is also listed as an adverse reaction identified in clinical studies. In order to inform patients of these risks, corresponding text is also present in the package leaflet. To educate prescribers and patients about the risk of CHF associated with the use of: • Patient Reminder Card • HCP Educational Material	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 14		
Myocardial Infarction	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Myocardial infarction is listed as an adverse reaction identified in patients taking adalimumab in originator's post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Safety Concern 15		
Cerebrovascular accident	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Cerebrovascular accident is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 16		
Interstitial Lung Disease	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Interstitial lung disease is listed as an adverse reaction identified in clinical studies. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 17		
Pulmonary embolism	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Pulmonary embolism is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 18		
Cutaneous vasculitis	Text in SmPC Text in SmPC (refer to SmPC section 4.8): Section 4.8: Cutaneous vasculitis is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 19		
Stevens-Johnson Syndrome	Text in SmPC (refer to SmPC section 4.8): Section 4.8: SJS is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 20		
Erythema multiforme	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Erythema multiforme is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is

Safety concern	Risk minimization measures	Pharmacovigilance activities
	risks, corresponding text is also present in the package leaflet.	provided by the patient.
Safety Concern 21		
Worsening and New Onset of Psoriasis	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Worsening and New Onset of Psoriasis is listed as an adverse reaction identified in post marketing surveillance Text in PIL: Worsening and new onset of Ps is addressed in section 4.8: Table 2: Worsening and New Onset of Psoriasis (including palmoplantar pustular psoriasis) is listed as an adverse drug reaction with a frequency of 'common' (includes spontaneous data). No text in relation to these risks is present in the package leaflet	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 22		
Hematologic disorders	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Warning regarding hematologic reactions including medically significant cytopenias is included. It advises that discontinuation of MSB11022 therapy should be considered in patients with confirmed significant hematologic abnormalities. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 23		
Intestinal perforation	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Intestinal perforation is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 24		
Intestinal strictures in CD	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Warning regarding small bowel obstruction and intestinal stricture is included. No text in relation to this risk is present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 25		
Liver failure and Other Liver Events	Text in SmPC (refer to SmPC section 4.8): Section 4.8: Liver failure is listed as an adverse reaction identified in post marketing surveillance Hepatitis is listed as an adverse	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability,

Safety concern	Risk minimization measures	Pharmacovigilance activities
	reaction with a frequency of 'rare.' In order to inform patients of these risks, corresponding text is also present in the package leaflet.	whenever the information is provided by the patient.
Safety Concern 26		
Elevated ALT levels	Text in SmPC (refer to SmPC section 4.8): Section 4.8: The risk of elevated ALT levels and elevated liver enzymes is listed as an adverse reaction identified in clinical studies. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient. Additional pharmacovigilance activity: This safety concern will be monitored in the proposed category 3 studies, as feasible.
Safety Concern 27		
Autoimmune hepatitis	Text in SmPC (refer to SmPC section 4.8) Section 4.8: AIH is listed as an adverse reaction identified in post marketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed. Including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient. Additional pharmacovigilance activity: This safety concern will be monitored in the proposed category 3 studies, as feasible.
Safety Concern 28		
Medication errors and maladministration	Text in the SmPC: None. Instructions for preparing and giving an injection of adalimumab are outlined in the Package Leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.

Potential risks

Safety concern	Risk minimization measures	Pharmacovigilance activities
Safety Concern 1		
Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma)	Text in SmPC (refer to SmPC section 4.8): Section 4.4: Warning regarding malignancies and malignancies in the pediatric population in the warning section and information on rates from clinical trials are included. Section 4.8: Warning regarding malignancies and malignancies in the pediatric population in the warning section and information on	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	rates from clinical trials are included. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	
Safety Concern 2		
Vasculitis (Non-cutaneous)	Text in SmPC (refer to SmPC section 4.8): Section 4.8 contains vasculitis as uncommon.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient
Safety Concern 3		
PML	Text in SmPC: None Other routine risk minimization measures: Prescription only medicine.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 4		
Reversible posterior leukoencephalopathy syndrome	Text in SmPC: None Other routine risk minimization measures: Prescription only medicine.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient
Safety Concern 5		
ALS	Text in SmPC: None Other routine risk minimization measures: Prescription only medicine.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 6		
Adenocarcinoma of colon in UC patients	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Recommendation that all patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient. Additional pharmacovigilance activity: This safety concern will be monitored in the proposed category 3 studies, as feasible.
Safety Concern 7		
Infections in infants exposed to adalimumab in utero	Text in SmPC (refer to SmPC section 4.6): Section 4.6: Information regarding	Routine pharmacovigilance surveillance will be performed including cumulative analysis of

Safety concern	Risk minimization measures	Pharmacovigilance activities
	the risk of infections in infants exposed to adalimumab in utero is listed. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient
Safety Concern 8		
Medication errors with pediatric vial	Text in the SmPC: None. Detailed usage description of the single use pediatric vial outlined in the Patient Leaflet and the vial is clearly labelled for single use only.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 9		
Off-label use	Text in SmPC: None Other routine risk minimization measures: Prescription only medicine.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.

Missing information

Safety concern	Risk minimization measures	Pharmacovigilance activities
Safety Concern 1		
Patients 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.	Text in SmPC (refer to SmPC section 4.4): Section 4.4: Warnings regarding patients with immune-compromised conditions are included. There is currently no information on patients with a history of clinically significant drug or alcohol abuse listed in the SmPC. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient
Safety Concern 2		
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with pedCD and pedERA.	Text in SmPC (refer to SmPC section 4.2): Section 4.2: Statements that the safety and efficacy of in these populations is yet to be established In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient
Safety Concern 3		
Pregnant and lactating women	Text in SmPC (refer to SmPC section 4.6): Section 4.6: Limited clinical data on exposed pregnancies are available and, therefore, administration of adalimumab is not recommended during pregnancy. Contraception is	The safety profile of adalimumab is not established for pregnant or lactating women. Retrieval of relevant data related to MSB11022 from an existing registry for reports of pregnancy associated with use of adalimumab. Spontaneous reports

Safety concern	Risk minimization measures	Pharmacovigilance activities
	recommended to women while on MSB11022 therapy and for a least 5 months after last treatment. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	of pregnancies will be aggregated and included in addition in the PSUR. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 4		
Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and JIA	The SmPC currently contains no text regarding remission-withdrawal-retreatment in nr-axSpA or episodic treatment in Ps, CD, UC, and JIA. Other routine risk minimization measures: Prescription only medicine.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient
Safety Concern 5		
Long-Term Safety Information in the Treatment of Adults with HS	Text in SmPC (refer to SmPC section 4.2): Section 4.2: Statements that the long-term safety and efficacy of MSB11022 in this population will be periodically re-evaluated. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.
Safety Concern 6		
Long term safety data in the treatment of adults with uveitis	Text in SmPC (refer to SmPC section 4.2): Section 4.2: Statements that the long-term safety and efficacy of MSB11022 in this population will be periodically re-evaluated. In order to inform patients of these risks, corresponding text is also present in the package leaflet.	Routine pharmacovigilance surveillance will be performed including cumulative analysis of adverse event reports in PSURs. Brand name and batch number will be recorded for traceability, whenever the information is provided by the patient.

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable provided that the applicant submits an RMP aligned to the originator's 3 months after Commission Decision.

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.*

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

MSB11022 was developed as a biosimilar product of adalimumab, with Humira for subcutaneous use as the reference product. Dosage, route of administration and indications are proposed to be identical to Humira.

The proposed indications are: Rheumatoid Arthritis, Juvenile idiopathic arthritis, Axial spondyloarthritis, Psoriatic arthritis, Psoriasis, Paediatric plaque psoriasis, Crohn's disease, Paediatric Crohn's disease, Ulcerative colitis, Uveitis, Paediatric uveitis.

Three pharmaceutical forms are proposed, which are similar to three of the pharmaceutical forms of Humira containing 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).

For the paediatric formulation (40 mg/0.8 ml solution for injection), only the paediatric indications are proposed.

Summary of analytical comparability (quality data)

The applicant has performed an extensive comparability analysis to demonstrate biosimilarity to the reference product (Humira). The approach chosen is in line with current guidance and a scientific advice received by EMA-CHMP on 24 September 2015 (EMA/CHMP/SAWP/593876/2015).

Batches from the EU; US and rest of the world (RoW) markets; with various expiry dates were used in the analysis. Individual (raw) batch data from each batch are provided and traceability is ensured. Several batches of the biosimilar, manufactured using different active substance batches were included in the analysis, representing independent data points. The presented analysis falls into two broad categories; a comparison of all the finished product batches to the QTPP of the originator (with separate QTPP analyses for EU batches and aggregated EU/US/RoW batches); and three specific side-by-side analytical exercises, performed at separate points in time during different stages of development. Where a quantitative analysis was possible, Min-Max ranges for the finished product were established and compared to Mean$\pm$3SD intervals calculated for the originator; age at the time of testing is appropriately taken into account; the data are presented both in tabular and graphical format.

Descriptions of analytical methods and summary qualification data have been provided and considered acceptable.

Summary of non-clinical data

Comparative *in vitro* data were presented on:

- Binding of MSB11022 and Humira (EU/US/RoW) to the target, TNFα (soluble and transmembrane).

- Binding to relevant Fc receptors (FcRn, FcγRI, FcγRIIa (R131 & H131), FcγRIIb, FcγRIIIa (V158 & F158) and FcγRIIIb.
- Binding to Complement component 1q (C1q).
- Effects on Fab-related functionality due to the binding of sTNFα. This was evaluated in a wide range of assays.
- Effects on Fab-related functionality due to the binding to tmTNFα. Apoptosis of Jurkat:tmTNF cells.

The *in vitro* data were presented by the applicant in Module 3, however, functional data were assessed in the non-clinical AR in line with EMA presubmission advice.

Comparative *in vivo* data were presented on:

- Activity of MSB11022 and Humira (US) in Tg197 mice, a model for RA.
- Activity of MSB11022 and Humira (US) in a Tg197/TNBS mouse model, proposed as a model for IBD.
- Toxicokinetics, safety and immunogenicity in cynomolgus monkeys.

Summary of clinical equivalence data

- PK study (EMR200588-001): a single-dose (40 mg sc) randomised double-blind three-arm parallel PK trial in healthy volunteers comparing MSB11022, EU-sourced Humira and US-approved Humira (79 subjects per arm); supportive PK data in patients with psoriasis in the clinical efficacy and safety study.
- Efficacy and safety study (EMR200588-002): a 54-week randomised double-blind equivalence study comparing MSB11022 and EU-Humira (80 mg loading dose followed by 40 mg sc every 2 weeks) in patients with moderate to severe psoriasis who are candidates for systemic therapy (~220 patients per arm). The primary outcome was PASI75 at Week 16 (core period), with a non-inferiority margin of +/- 18%. Main secondary outcome was percentage change in PASI score from baseline to week 16 (non-inferiority margin of 15%). Patients on EU-Humira in the core period were re-randomised at week 16 to continuation or switching to MSB11022.

3.2. Results supporting biosimilarity

Quality and in vitro pharmacology data

High similarity between MSB11022 and originator can be considered demonstrated with regard to the following attributes:

- Primary structure
- Higher order structure
- Dimers, aggregates and fragments
- Oxidation and related microheterogeneity
- Glycosylation, with the exception of total afucosylation/mannosylation/galactosylation; it is noted that sialylation is different but the levels are so low that this is not considered relevant
- TNF-alfa binding (both soluble and membrane bound)
- Binding to Fc-receptors, except FcγRIIIa-158F (low affinity) binding

- C1q-binding and CDC
- ADCC activity (whole blood assay using healthy and patient blood, ADCC FcγRIIIa reporter) except NK-enriched PBMC ADCC assay using healthy and patient blood.

Non-clinical data

Comparable efficacy in binding of sTNFα by both products was also shown in functional assays including a reporter gene assay coupled to the TNF receptor (used as potency assay), measurement of apoptosis (caspase 3/7 activity) and release of cytokines (IL-6 and IL-8) and of ICAM.

Following tmTNFα-binding on Jurkat:tmTNF cells comparable levels of apoptosis was observed.

In a mixed lymphocyte reaction, proliferation of T-cells was inhibited and induction of regulatory macrophages stimulated at a comparable level.

Both compounds have a dose-related effect on body weight, arthritic score and histopathological score in the Tg197 mouse model.

No differences in toxicokinetics, safety and immunogenicity (ADA) were apparent in the cynomolgus monkey study.

Clinical data

Pharmacokinetics

Similar pharmacokinetics has been shown between MSB11022 and the EU reference products in the pivotal PK study using healthy volunteers.

Adalimumab Ctrough values in psoriasis patients the core period (0-16 weeks) were similar between MSB11022 and EU-Humira.

Efficacy

Both the primary and main secondary outcomes support equivalence of MSB11022 with EU-Humira in patients with moderate to severe plaque psoriasis. The mean percent change in PASI from baseline to week 16 in the PP set was similar in size for both treatment groups: -91% in the MSB11022 group and -92% in the EU-Humira group. The 2-sided 95% confidence interval of the treatment difference was within the predefined equivalence margins of +/- 15% and included 0 (no difference), in PP and in ITT sets. The primary outcome PASI75 response at week 16 in the PP set was of similar size in both treatment groups: 90% in the MSB1102 group and 92% in the EU-Humira group. The 2-sided 95% confidence interval of the treatment difference was within the predefined equivalence margins of +/- 18% and included 0, in PP and in ITT sets.

Importantly, these findings are supported by the (more sensitive) mean PASI scores over all intermediate visits of the 16 week Core Treatment Period, that were similar for MSB11022 and EU-Humira, without a tendency for MSB11022 to be worse. Together with the consistent results of the subgroup analyses, other secondary outcomes, 52 week data and switching data, this supports that MSB11022 and EU-Humira have equivalent efficacy in moderate to severe plaque psoriasis.

Safety

Overall, the occurrence of AEs appears to be similar for MSB11022 and EU-Humira. Both MSB11022 and EU-Humira appeared to be reasonably well tolerated, without major differences in occurrence and pattern of TEAEs, AESIs, SAEs, and laboratory findings. The exception is that infections, triglyceridaemia and hypertension appeared to occur more frequently in patients on ongoing MSB11022 and switching to

MSB11022, as compared to patients continuing EU-Humira, which however is likely attributable to chance. Switching from EU-Humira to MSB11022 did not lead to a safety signal.

Immunogenicity

The results on immunogenicity did not show differences between MSB11022 and EU-Humira. The proportions of patients with anti-drug antibody (ADA) increased similarly in both groups to ~90% in the MSB11022 group and the EU-Humira group. Overall, ~50% of ADA positive patients were positive for nAb, in both groups. The ADA titers over the course of the Core Treatment Period were similar for the MSB11022 and EU-Humira groups. Switching from EU-Humira to MSB11022 did not appear to lead to a further increase in ADA positivity. As may be expected, ADA positivity leads to a slightly reduced efficacy (PASI75 response). Most patients with injection site reactions were ADA positive, similarly in patients treated with MSB11022 or with EU-Humira and the overall study population.

3.3. Uncertainties and limitations about biosimilarity

Quality and *in vitro* pharmacology data

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

- Galactosylation (ranges for biosimilar and originator overlap, but not all values of the biosimilar are within range of the originator): no impact on the related parameters C1q-binding and CDC was observed

  A lower total afucosylation was noted for MSB11022 . This was mainly due to lower levels of high mannose variants (MSB11022: 1.9-2.5%; Humira-EU: 5.3-12.0%).

- The K_D-ranges (as determined by SPR) for FcγRIIIa F158 binding overlap but are not 'within range': For MSB11022 a range of 6.2-10.1 nM was found; Humira-EU: min-max 3.8-8.0 nM.

- The applicant presented data from several ADCC-type assays. For the most sensitive format, ADCC of MSB11022 is lower than for Humira: NK-PBMC ADCC assay using $\%EC_{50}$ as read-out.

  - Similar to results as found with the healthy donors, data with blood cells from UC, CD, PsO or RA patients show similar responses, meaning similarity with Humira in the whole blood ADCC assay and lower (RA, PsO, healthy) or lower but overlapping (CD, UC) in the NK-PBMC ADCC assay.

- High CVs (low sensitivity) are seen with the SPR method investigating Fc-receptor binding.

- Taken together, the differences seen in the FcγRIIIa F158 by SPR and NK-PBMC ADCC assay, although internally consistent, are likely either due to analytical variability (low sensitivity of SPR), or clinically irrelevant (see results of other ADCC assays), or both.

- The MLR assay, potentially reflecting an important mechanism for adalimumabs efficacy in IBD, is only a semi-quantitative method, limiting its applicability for establishing biosimilarity.

Non-clinical data

The mouse Tg197/TNBS colitis model showed a lack of sensitivity. Body weight change and TNFα release in colon thick organ cultures were affected by both compounds, but without a dose-response relationship. This study does not contribute to the establishment of biosimilarity

Due to the low number of animals and inter-animal variability in response, the cynomolgus monkey study lacks sensitivity to detect relevant differences. The available quality and *in vitro* data did not indicate a

need to perform a study in this species. Consequently, this study does not provide decisive information and should not have been performed.

Clinical data

Pharmacokinetics

The upper limit of 90%CI for AUCinf excludes 1 (90% CI 80.14 – 99.10) in the pivotal PK study in healthy subjects.

Efficacy

None

Safety

None

Immunogenicity

Already after 16 weeks, nearly more than 80% of the patients had developed ADA and this is higher than in previous studies. This may be caused by the sensitive bio-analytical assay but also disease related. Incidence of ADA is lower in patients with RA compared to patients with psoriasis. Given the high rates of subjects with ADA-positive serum samples, the incidence of ADA positivity may not be sensitive enough to detect possible differences in immunogenicity, but given the similarity of ADA titers over time similarity of immunogenicity is not doubted.

3.4. Discussion on biosimilarity

The data on quality attributes demonstrate a high level of similarity.

For the following quality parameters, the applicant sufficiently argued that uncertainties and limitations could be considered as minor and/or not clinically relevant.

With regard to galactosylation: ranges for biosimilar and originator overlap, but not all values of the biosimilar are within range of the originator; however, no impact on the related parameters C1q-binding and CDC was observed.

A more complex issue is the lower level of high mannosylated afucosylated glycans. This seems to be correlated to the potentially slightly higher K_D for FcγRIIIa receptor (F158 low affinity variant) and lower activity in ADCC assays when more sensitive assay formats, like the NK-PBMC assay (%EC50), are used. The Applicant argues that these assays with higher sensitivity are artificial constructs not representing the physiological conditions in a patient. The applicant showed that addition of serum or IgG to these assays diminishes the observed differences in the ADCC assays or even abolishes ADCC activity all together. The Applicant also claims that one assay, utilising NK effector cells and LPS activated primary monocytes, expressing physiological levels of tmTNF, could not detect any ADCC activity in the presence of adalimumab (both products). According to the applicant this assay is a more physiological representative assay. In the literature, it is argued that a functional Fc part of an anti-TNF pharmaceutical is essential for efficacy in IBD. One mode of action proposed for anti-TNF mAbs (adalimumab and infliximab) in IBD is ADCC, involving binding to both tmTNFα and FcγRIIIa receptor. Binding to tmTNF was shown to be similar, as was binding to FcγRIIIa V158 (high affinity) receptor and, in addition, similar ADCC activity was shown in the whole blood ADCC assay using blood from healthy and patient (RA, PsO, CD, UC) donors and in the FcγRIIIa reporter ADCC assay. Finally, the clinical relevance of the differences seen in the NK-PBMC ADCC assay per se is questioned as the addition of serum or IgG up to clinical levels, dose-dependently diminishes or even completely abolishes the ADCC response by MSB11022 as well as by RMP/RP.

Another mode of action proposed for adalimumab efficacy in IBD is inhibition of proliferation of activated T-cells, involving regulatory macrophages (Vos et al, 2011). In this mode of action, also both tmTNFα (on the activated T-cell) and Fc receptors (on the regulatory macrophage) are involved. To evaluate the activity of both products with respect to this mode of action, the applicant performed a Mixed Lymphocyte Assay (MLR) and generated semi-quantifiable, but comparable results on inhibition of T-cell proliferation and also on induction of regulatory macrophages, which lends support to comparable activity of MSB11022 and Humira in IBD indications.

Binding to tmTNFα (using flow cytometry) and a functional effect of this binding (apoptosis in Jurkat:tmTNF cells) was shown to be comparable. This leaves differences in binding to FcγRIIIa F158 receptor as the most plausible explanation for differences observed in the more sensitive ADCC assays. Differences in binding to FcγRIIIa receptor may be explained by the differences observed in afucosylated glycans.

The clinical significance of observed differences in ADCC were further addressed with additional data and scientific discussion. In addition, no meaningful differences in another tm-TNF dependent mechanism, i.e. induction of regulatory macrophages in addition to the inhibition of T-cell proliferation were found suggesting a similar activity. This is especially important for the extrapolation to inflammatory bowel disease (see section 5.5 on extrapolation).

Similarity in the pharmacokinetic study using healthy volunteers has been demonstrated between MSB11022 and the two Humira reference products as the primary parameters $AUC_{0-\infty}$ AUC_{0-t} and $C_{max,}$ the 90% CI for the ratio of the test and reference products fell within the acceptance range of 80.00-125.00% when comparing MSB11022 to the reference product from EU as well as from US, and also when comparing the US versus the EU reference products. Further support for similarity between MSB11022 and EU-Humira was obtained in the study in psoriasis patients (study EMR200588-002). The Ctrough concentrations of MSB11022 and EU-Humira appear comparable, with exposure of EU-Humira slightly higher than MSB11022.

Although the 90% CI for the ratio of MSB11022 and EU-Humira fell within the acceptance range of 80.00-125.00%, the upper limit of 90% CI for AUC_{inf} excludes 1; 80.14 – 99.10. This statistical difference in AUCinf might indicate a difference in clearance. Sensitivity analyses were conducted for protein content and ADA status. When corrected for protein content, similarity was demonstrated for AUCinf, AUCt, and Cmax with 90% CI within 80-125% similarity margin including unity for all parameters. The pharmacokinetics in ADA-negative subjects are of particular interest as this allows direct evaluation of elimination of the substances without interference of ADAs. The results for ADA negative subjects were similar between MSB11022 and Humira supporting the conclusion for biosimilarity between MSB11022 and Humira based on the overall study population. The elimination of adalimumab seemed somewhat faster for MSB11022 than for Humira in the ADA positive subjects but sensitivity analysis of elimination half-life by consideration of the time at which subjects became ADA positive indicated that there was no consistent pattern that elimination half-life of adalimumab was shorter for MSB11022 than for Humira. In addition, in psoriasis patients, the adalimumab concentrations of MSB11022 were comparable or slightly higher at all time points compared to EU-Humira. Overall, the PK results for ADA negative subjects and the Ctrough values in patients with psoriasis support the conclusion for biosimilarity between MSB11022 and Humira.

The results of the main clinical study show that MSB11022 and EU-Humira have equivalent efficacy, in a sensitive (psoriasis) model in an adequately powered study. After 16 and after 54 weeks, MSB11022 and EU-Humira are considered equivalent in immunogenicity and safety. The higher occurrence of infections, triglyceridaemia and hypertension in the groups of patients continuing or switching to MSB11022 as compared to EU-Humira are likely due to chance. There is an uncertainty considering the height of PASI75 response in relation to the size of the equivalence margins, which however is mitigated by

similarity of the 'parent' continuous PASI scores. The continuous PASI scores were highly similar between MSB11022 and EU-Humira over all time points, making relevant dissimilarity unlikely. Further, similarity was also supported by other outcomes, notably PGA and BSA.

3.5. Extrapolation of safety and efficacy

MSB11022 is proposed for the same indications as for Humira, including Rheumatoid Arthritis, Juvenile idiopathic arthritis, Axial spondyloarthritis, Psoriatic arthritis, Psoriasis, Paediatric plaque psoriasis, Crohn's disease, Paediatric Crohn's disease, Ulcerative colitis, Uveitis and Paediatric uveitis.

PK similarity of MSB11022 with EU-Humira was established. It is agreed with the applicant that it is justified to extrapolate PK profiles of adalimumab across all target populations and conditions of use, including dose escalation and use with or without background immunomodulatory therapy.

The clinical efficacy of MSB11022 was shown to be similar to EU-Humira in the Psoriasis model, which is a sensitive model to study equivalence. Similarity of MSB11022 and EU-Humira is demonstrated in both main outcomes, all sensitivity analyses, all secondary outcomes, and between-group differences are consistently small over study time. Also, the occurrence and pattern of adverse events and of immunogenicity was generally similar between MSB11022 and EU-Humira and no new safety signals appeared.

It is considered that extrapolation of clinical equivalence from psoriasis to those disorders where the effect of adalimumab is primarily attained through binding of soluble TNF (e.g. rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis) can be agreed, because therapeutic equivalence is supported by the pre-clinical evidence related to membrane-bound TNF-associated modes of action.

It is also considered that therapeutic equivalence can be extrapolated from psoriasis to inflammatory bowel disease, because therapeutic equivalence is considered supported by the pre-clinical evidence related to membrane-bound TNF-associated modes of action.

3.6. Additional considerations

None.

3.7. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Outcome

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

Rheumatoid arthritis; Juvenile idiopathic arthritis; Enthesitis-related arthritis; Axial spondyloarthritis; Psoriatic arthritis; Psoriasis; Paediatric plaque psoriasis; Crohn's disease; Paediatric Crohn's disease; Ulcerative colitis; Uveitis; Paediatric Uveitis

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 Kromeya 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 Kromeya is marketed, all healthcare professionals who are expected to prescribe Kromeya are provided with the following educational package:

• Physician educational material

• Patient information pack

The physician educational material should contain:

• The Summary of Product Characteristics

• Guide for healthcare professionals

• Patient reminder 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 reminder 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 Kromeya.

• That Kromeya 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.