Saudi Public Assessment Report

Idacio®

Active Pharmaceutical Ingredient(s): Adalimumab

ATC code/CAS no.: L04AB04

Pharmaceutical/Dosage Form:

Solution for injection in pre-filled syringe (PFS)

Solution for injection in pre-filled pen (PFP)

Dosage Strength: 40 mg/0.8ml

Marketing Authorization Holder: Fresenius Kabi Deutschland GmbH

Shelf life: 24 months

Storage conditions: Store in a refrigerator (2°C – 8°C). Store in the original container, protect from light. A single pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The pre-filled syringe or the pre-filled pen must be protected from light, and discarded if not used within the 14-day period.

Registration No.: 1507210881 - 1507210882

Decision and Decision Date: Approved on 15/07/2021

Table of Contents

1. Terms, Definitions, Abbreviations

Terms	Definitions
ADA	Anti-drug antibody
AE	Adverse Event
ANCOVA	Analysis of covariance
AS	Ankylosing Spondylitis
AUC	Area Under The Curve
AZA	Azathioprine
BMI	Body mass index
BOCF	Baseline-observation-carried-forward
CHO	Chinese hamster ovary
CRP	C-reactive Protein
DMARDS	Disease-Modifying Anti-Rheumatic Drugs
DP	Drug product
DS	Drug substance
EU	European Union
EMA	European Medicines Agency
GCP	Good Clinical Practice
HRQoL	Health related quality of life
HS	Hidradenitis Suppurativa
IBD	Inflammatory Bowel Disease
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IGG	Human Immunoglobulin
INN	International Nonproprietary Names
IRS	An Interim Reference Standard
ITT	Intention-to-treat analysis
JIA	Juvenile idiopathic arthritis
kDa	kilo Daltons
MAB	Monoclonal antibodies
MAR	Missing-at-random
MRI	Magnetic resonance imaging
MSB11022	Idacio company code
6-MP	6-mercaptopurine
N	Total number of subjects randomized
NA	Not Available
NAb	Neutralizing antibody
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PFP	Prefilled pen
PFS	Prefilled syringe
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PP	Per Protocol
PSO	Plaque psoriasis
PSUR	Periodic safety update reports

RMM	Risk Minimization Measures
RMP	Risk Management Plan
RP	Reference Product
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	Serious Adverse Events
SC	Single subcutaneous
SDI	Saudi Drug Information System
SFDA	Saudi Food and Drug Authority
SPC	Summary of Product Characteristics
TB	Tuberculosis Malignancies
TEAE	Treatment Emergent Adverse Event
TNF	Tumor Necrosis Factor
TNFR	TNF receptors
UC	Ulcerative colitis
US	United State
USAN	United States Adopted Names
WCB	working cell bank
WW	Worldwide
6-MP	6-mercaptopurine

2. Background

2.1 Submission Details

Type of submission: New Biosimilar Drug.

Pharmacological class: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors.

Submitted Indication:

- Rheumatoid arthritis : Idacio 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.

  Idacio can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

- Juvenile idiopathic arthritis

  Polyarticular juvenile idiopathic arthritis

  Idacio 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). Idacio can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years.

  Enthesitis-related arthritis

  Idacio 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.

- Axial spondyloarthritis

  Ankylosing spondylitis (AS)

Idacio 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

Idacio 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 who are intolerant to nonsteroidal anti-inflammatory drugs.

- Psoriatic arthritis: Idacio is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.
- Psoriasis: Idacio is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.
- Paediatric plaque psoriasis: Idacio 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 who are inappropriate candidates for topical therapy and phototherapies.
- Hidradenitis suppurativa (HS): Idacio is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy.
- Crohn’s disease: Idacio 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: Idacio 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 Idacio: 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: Idacio is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids,

in patients in need of corticosteroid- sparing, or in whom corticosteroid treatment is inappropriate.

- Paediatric Uveitis: Idacio 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.

Submitted Dosage: 40 mg

2.2 Regulatory Background

This product is considered a Biosimilar Drug for Saudi regulatory purposes.

This product is qualified for a regular submission pathway.

Regulatory status in other countries:

Idacio® is currently authorized as a biosimilar (subcutaneous injection in pre-filled syringe and pre-filled pen) to the reference product Humira® by the EMA since 2/4/2019. The EMAs' initial approval was granted for all the indications for which the reference Humira was approved: Rheumatoid Arthritis, Juvenile Arthritis, Psoriasis Arthritis, Psoriatic, Ankylosing Spondylitis, Uveitis, Hidradenitis Suppurativa, Ulcerative Colitis, and Crohn Disease. The MAH F.Kabi has an agreement with AbbVie, the owner of intellectual property owner of Humira to acquire the right to market the product in US in 30 September 2023.

Country	Trade Name	Strength	Dosage Form	Approving Authority	Date of Approval
Europe	Idacio®	40mg/ml	Injection	EMA	02/04/2019

Registered biosimilar in Saudi food and drug authority (SFDA):

Trade Name	Active Ingredient	Dosage Form/ Strength	MAH	Registration no.
Hyrimoz®	Adalimumab	Injection/ 40mg	Sandoz GmbH	0110200175, 0110200176
Amgevita®	Adalimumab	Injection/ 40mg	AMGEN	1603200041, 1603200042
Abrilada®	Adalimumab	Injection/ 40mg , 20mg	Pfizer	2305210745, 2305210746
Hadlima ®	Adalimumab	Injection/ 40mg	Catalent Belgium SA	3101221655, 3101221656

Information of the reference product:

Trade Name	Strength	Dosage Form	MAH	Registration number
Humira®	100mg/ml	Injection	Abbvie Deutschland Gmbh	1-921-15

2.3 Product Information

The approved Summary of Product Characteristics (SPC) with the submission can be found in Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

3. Scientific discussion about the product:

Idacio® (has been developed as a biosimilar product to Humira® (adalimumab). Adalimumab (MSB11022) is a recombinant human 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. Both biosimilar and reference product (refers to Humira and abbreviated as RP) are produced by recombinant DNA technology in Chinese hamster ovary (CHO). Glycosylation: One N-linked glycosylation site is located at Asn301 on each heavy chain and there are no O- linked glycosylation sites.

Disulfide bridges: there are 16 disulfide bridges, 12 are intrachain bridges, 2 are interchain bridges between the two heavy chains and 2 are between the heavy and light chains, as shown in the following figure.

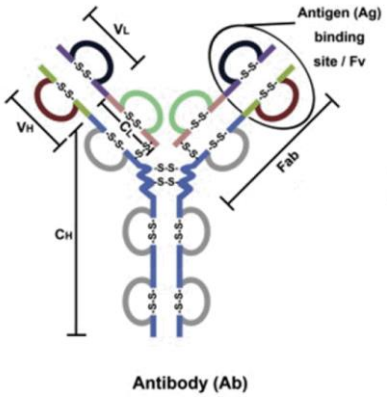


Figure 1 The structure of Adalimumab (source: Drug Bank BTD00049)

Biological Activity: TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Dysregulation of TNF production promotes inflammatory responses that cause many of the clinical symptoms associated with autoimmune disorders. Adalimumab binds specifically to TNF and neutralizes its biological function by blocking the interaction of TNF with the cell surface TNF receptors; (TNFR), TNFR1 (p55) and TNFR2 (p75). Consequently, TNF-driven cellular functions, including cell activation, cell proliferation, cytokine and chemokine production, are down regulated.

3.1 Quality Aspects

3.1.1 Introduction

Idacio has a highly similar structure, purity and biological activity to Humira, based on the assessment of quality data submitted to the SFDA the quality assessors recommended the authorization of Idacio as a biosimilar for SFDA authorized reference product (Humira®).

Idacio is proposed to be marketed as a 40 mg/0.8mL solution for injection in PFS, 40 mg/0.8 mL solution for injection in PFP.

3.1.1 Drug Substance

- **General Information:**
  MSB11022-DS is a clear solution, practically free from visible particles formulated at 60 mg/mL with sodium dihydrogen phosphate dihydrate; disodium phosphate dihydrate; mannitol; sodium chloride; citric acid monohydrate; sodium citrate; polysorbate 80 at pH 5.2.

- **Manufacture, characterization and process controls:**
  Cells from the working cell bank (WCB) are thawed and used for inoculum preparation. These cell cultures are serially expanded in shake–tubes and wave–bags. The inoculum is then further expanded in seed bioreactors and then transferred to a production bioreactor where the cells are cultivated. At the end of the fed–batch production, the crude harvest is clarified by centrifugation followed by depth and membrane filtration. The clarified harvest is then transferred to the downstream process. The process flow diagram for the manufacturing process and in–process controls to entire process has been adequately described accordingly through the validation of each manufacturing step.
  Quality assessor conclusion on the manufacture:
  Manufacturing process of MSB11022-DS is considered typical monoclonal antibody fed-batch manufacturing process, which is well controlled at multiple levels to ensure that it consistently delivers a product of appropriate and consistent quality. All raw materials that are used in this process are comply with the relevant guidelines.

- **Characterization of the drug substance:**
  Characterization tests conducted on MSB11022 DS, the primary amino-acid sequence of the MSB11022 heavy and light chains is verified by peptide mapping coupled with electrospray-mass spectroscopy. Secondary and tertiary structure of MSB11022 are determined with different analytical techniques. Other quality attributes as charge variant profile, post translational modifications, protein content and biological activity are also assessed using appropriate technical methods. Biosimilar development foresees the comparison of purity and impurity profiles of the drug substance (DS) and drug product (DP) both qualitatively and quantitatively by a combination of analytical procedures. The applicant provides an in-depth characterization of all the quality attributes of MSB11022 in comparison with the EU reference product RMP and US RP profile. Based on the quality assessment for the structure elucidation and impurity profile, SFDA assessors concluded that MSB11022 shares similar levels of process-related impurities as the RP.

- **Control of the drug substance:**
  The specification including physicochemical tests, identity, assay product related substances, purity profile and microbial safety profile. The analytical procedures with related validation used for the Quality Control testing and characterization methods are described under relevant sections with satisfactory details and justifications for the selected acceptance criteria.

- **Reference materials:**
  An Interim Reference Standard (IRS) for MSB11022 .The IRS was produced using the same process used for the clinical batches, and is considered to be representative of production that was used during the development of the product. IRS has been employed in the analysis of the drug substance and drug product for release and stability testing during development. Its quality was monitored during an ongoing stability study to support its continued use.

- **Stability:**
  By the assessment of the submitted stability data, SFDA approved the proposed shelf life for the DS when stored in the commercial container.

3.1.2 Drug Product

The finished product is a sterile solution for injection intended for subcutaneous administration. It is presented at a concentration of 50 mg/ml in a 1 ml type I glass syringe combined with a 29 Gauge, 12 mm thin wall steel needle that is protected by a rigid needle shield, closed with a bromobutyl plunger stopper. The other presentation is 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. Each prefilled syringe contains 0.806 ml formulated product, this includes a 0.006 ml fill overage to compensate for dead volume and to assure a nominal amount of 40 mg adalimumab in 0.8 ml is delivered. 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, there are no novel excipients used in the finished product formulation.

- **Description of the product manufacturing process and Pharmaceutical Development:**

  Sufficient containers of the frozen DS to be used for compounding a batch of DP are thawed, the thawed and pooled MSB11022 drug substance is transferred to a single use bag and diluted with the formulated buffer. Compounding is performed based on actual protein content determination. The compounded solution is stirred to homogeneity .The pH is measured and adjusted if necessary, compounded drug product solution undergoes a two-step filtration followed by filling into 1 ml long syringes with staked needles are supplied with a 29 Gauge, 12 mm long needle, with a rigid needle shield (RNS). The syringes are sterile and ready to fill. The material of the primary packaging of each presentation complies with the relevant guidelines and pharmacopeial requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. 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-characterization and characterization studies. The manufacturing process, process control and manufacturing development had been satisfactorily described.

- **Product control:**

  The specification of MSB11022-DP in PFS/PFP for release and shelf-life covering physicochemical tests (including: appearance, clarity and degree of opalescence, degree of coloration, pH, osmolality, particulate contamination and extractable volume), identity, assay, product related substances, purity/impurities and microbiological tests the testing parameters complying with the ICH Q6B guidelines: *Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*.

- **Batch analysis:**

  Batch analysis data from DP in PFS for many batches represent the different manufacturing stages (engineering, clinical, process qualification and commercial batches) had been provided under this section, batches have been released based on the specification acceptance criteria in place at the time of testing no out of specifications test results reported.

- **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.

- **Stability of the product:**

  The results of stability studies held on MSB11022-DP indicate that the product is stable at the long-term storage conditions of 5°C ± 3°C storage for 24 months when stored in the commercial container. DP may be exposed to a room temperature (up to 25°C ± 2°C/60% ± 5% RH) for 2 weeks when stored in the commercial container. In addition, studies to examine the impact of the ambient temperature exposure on MSB11022-DP quality including (Appearance, degree of coloration, clarity and degree of opalescence, protein content, HMW%, charge variants, deamidated and oxidized forms, purity, LMW%, sub-visible particles and biological activity) showed no change over time and that all results remained within the proposed specification limits. All stability studies

have been designed in compliance with ICH Q5C guideline: *Stability Testing of Biotechnological/Biological Products.*

- **Comparability studies:**

  The scope of the comparability studies is adequate under the relevant guidelines. These studies were conducted using United States (US) and EU-sourced Humira® as the reference product. Based on the quality assessors conclusion regarding the identity of Humira products across jurisdictions, no meaningful differences between Idacio and EU/US-Humira were observed and both products are considered highly comparable to each other.

- **Adventitious agents:**
  The approach for adventitious agents testing is described. The only material of animal origin used in the manufacture of Idacio 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.

3.2 Clinical Aspects

3.2.1 Clinical Pharmacology

Adalimumab (MSB11022) is a recombinant fully human immunoglobulin G1 (IgG1) kappa monoclonal antibody (mAb) specific for TNFα. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in both the pathologic inflammation and the joint destruction in multiple inflammatory diseases. Inhibition of the TNF receptor-ligand interaction by TNF antagonist therapy results in down regulation of mediators of the inflammatory cascade and is associated with clinical improvement of inflammatory diseases such RA, psoriasis, and inflammatory bowel disease among others.

In addition to the reference product Humira®, multiple biosimilars have been registered in SFDA; Hyrimoz®, Amgevita®, Abrilada®, and Hadlima®. Idacio's approval will introduce the sixth option of Adalimumab to the market.

3.2.1.1 Pharmacokinetic studies:

List of pharmacokinetic studies

Study	Clinical Trials Identifier	Objective	Findings
EMR200588-001	NCT03014947	**Primary objective:** To investigate and compare the PK profiles of IMP-MSB11022, US-licensed Humira, and EU-approved Humira in healthy subjects **Secondary objective:** To investigate the safety, tolerability, and immunogenicity of IMP-MSB11022, US-licensed Humira, and EU-approved Humira in healthy subjects.	90% CI of MSB11022 vs. EU licensed Humira: · C_{max}: 95.38 (87.58, 103.87) · AUC_{last}: 91.53 (81.33, 103.02) · AUC_{inf}: 89.12 (80.14, 99.10) 90% CI of MSB11022 vs. US licensed Humira: · C_{max}: 97.22 (89.27, 105.88) · AUC_{last}: 96.03 (85.32, 108.08) · AUC_{inf}: 90.46 (81.29, 100.67) 90% CI of US-licensed Humira vs. EU-approved Humira: · C_{max}: 98.10 (90.11, 106.81) · AUC_{last}: 95.32 (84.72, 107.25) · AUC_{inf}: 98.52 (88.56, 109.59)

Title: A Phase I, randomized, double-blind, parallel-group, single-dose trial to compare the pharmacokinetics, safety, tolerability, and immunogenicity of MSB11022, US-reference product, and EU-reference medicinal product (Humira®) in healthy subjects.	
Study identifier	EMR200588-001
Design	Phase I, randomized, double-blind, parallel-group, single dose trial

Hypothesis	Demonstrate the PK similarity
Total study duration including: **Duration of Run-in phase** **And Duration of Main phase** **And Duration of Extension phase**	Duration of Run-in phase: NA Duration of Main phase: 71 days Duration of Extension phase: NA
Treatment arms	MSB11022→ N = 78 Healthy volunteers Humira-EU→ N = 79 Healthy volunteers Humira-US→ N = 80 Healthy volunteers
Randomization	**Randomization ratio** (1:1:1) **Randomization method** The investigator or delegate assigned a unique screening subject identifier number to eligible subjects in chronological order at the time of informed consent signature.
Blinding	The trial was double-blinded with the subject, the investigator, as well as the sponsor being blinded to the study drug administered.
Primary Endpoint	C_{max} , $AUC0_{-inf}$, AUC_{0-last}
Secondary endpoints	T_{max} , $V_{z/F}$, CL/F, λz , T1/2 Safety , immunogenicity
Blood samples	Blood samples were taken in the following time-points: At pre-dose 0 (-1 hr), 4 (± 5 min) , 8 (± 10 min), 12 (± 15 min), 24 (± 15 min), 48 (± 1 hr), 72 (± 1 hr), 96 (± 1 hr), 120 (± 3 hr), 144 (± 3 hr), 168 (± 3 hr), 192 (± 3 hr), 240 (± 3 hr), 336 (± 3 hr), 504 (± 3 hr), 672 (± 1 day), 840 (± 7 day), 1008 (± 7 day), 1344 (± 7 day), 1680 (± 7 day)
Statistical analysis	PK similarity will be determined based on the primary PK parameters (C_{max} and AUC_{0-last}, AUC_{0-inf}) using standard bioequivalence testing methods. The AUC_{0-inf}, AUC_{0-last}, and C_{max} were analyzed using a one-way analysis of variance model. The parameters were log transformed, and the 90% confidence interval (CI) for the difference in mean parameters among the 3 arms was calculated; the 90% CI was re-expressed on the original ratio scale. If the 90% CI for the ratio lay entirely within the 80% to 125% equivalence margin for each comparison (IMP-MSB11022 versus US-licensed Humira; IMP-MSB11022 versus EU-approved Humira; and US-licensed Humira versus EU-approved Humira)
Study Results	<u>90% CI of MSB11022 vs. EU licensed Humira:</u> · C_{max}: 95.38 (87.58, 103.87) · AUC_{last}: 91.53 (81.33, 103.02) · AUC_{inf}: 89.12 (80.14, 99.10)

	90% CI of MSB11022 vs. US licensed Humira: · C_{max}: 97.22 (89.27, 105.88) · AUC_{last}: 96.03 (85.32, 108.08) · AUC_{inf}: 90.46 (81.29, 100.67) 90% CI of US-licensed Humira vs. EU-approved Humira: · C_{max}: 98.10 (90.11, 106.81) · AUC_{last}: 95.32 (84.72, 107.25) · AUC_{inf}: 98.52 (88.56, 109.59)

3.2.1.2 Pharmacodynamics studies:

No well-established pharmacodynamics markers available for TNF inhibitors, and therefore, no pharmacodynamics data is required.

Assessors' comment on clinical pharmacology

Overall, the design is acceptable and appropriate. The three-way comparison, randomized, double blind and adequately powered study design is considered preferable for establishing clinical bridging for the data between IMP-MSB11022 /EU-Humira, and US-Humira/EU-Humira. The parallel group design and duration of study were suitable due to the long half-life of adalimumab (11 to 18 days), which has a potential effect on the PK parameters and immunogenicity response. Frequent blood sampling over a period of 71 days is considered adequate to compare the PK profiles, evaluate the safety and immunogenicity of the product. A single dose of 40 mg adalimumab is appropriate since adalimumab has linear PK. Additionally 40 mg is the recommended therapeutic dose in most of the indications.
Including almost only males (1 female in each group) is accepted in adalimumab biosimilar PK studies, as variability in female is higher than males. Including females was seen to show variability that was not present in male subjects in Hyrimoz PK study, another biosimilar of adalimumab that led to conducting a second PK study excluding females.
The primary PK parameters Cmax and AUC0-inf were used to establish the bioequivalence assessment between IMP-MSB11022 (Idacio) and the reference product (Humira). These PK parameters were justified and consistent with the established guideline requirements and other Humira biosimilars previously approved.

The 90% confidence intervals of the ratios derived from the analyses of the PK parameters were all within the predefined acceptance range (80-125%). Therefore, the bioequivalence was demonstrated for both pairs of comparisons, between IMP-MSB11022 /EU- Humira, and US-Humira/EU-Humira.

3.2.2 Clinical Efficacy

3.2.2.1 List of submitted clinical efficacy studies

Study ID*	No. of study centres / locations	Design	Study Objective	Subjs by arm entered/ compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
EMR200588-002	69 centres in 12 countries	Phase III, 2-arm, randomized, multi-center, double-blind, parallel-group phase equivalence study	Demonstrate equivalence in efficacy of MSB11022 with EU-approved Humira. Primary and key secondary efficacy, safety and immunogenicity outcomes were assessed at Week 16. The study will also assess the efficacy of extended treatment (up to week 52), health related quality of life (HRQoL), safety, tolerability, immunogenicity, and population PK of MSB11022 in comparison to EU-approved Humira.	**Randomized:** MSB11022: 222 EU-Humira: 221 **Treated in Core Treatment Period:** MSB11022: 221 EU-Humira: 220 **Treated in Extended Treatment Period:** MSB11022 to MSB11022: 213 EU-Humira to EU-Humira: 101 EU-Humira to MSB11022: 101 **Completed 24 weeks:** MSB11022 to MSB11022: 210 EU-Humira to EU-Humira: 96 EU-Humira to MSB11022: 99	52 weeks	Patients with moderate to severe chronic plaque psoriasis	**Primary:** Psoriasis area and severity index PASI75 at week 16 **Main secondary:** Percentage change in PASI at week 16 PK, safety, and immunogenicity data

* includes clinical trials registry identifier or sponsor protocol number

3.2.2.2 Data integrity and GCP

The Clinical trials were performed in accordance with Good Clinical Practice (GCP) as claimed by the applicant.

3.2.2.3 Inter-changeability studies

Study EMR300588-002 was designed to evaluate clinical response, safety and immunogenicity after study drug transition (randomized blind single transition) from adalimumab-EU to MSB11022 after 16 weeks of adalimumab-EU treatment.

Assessors' comment on the submitted clinical studies

The applicant submitted two clinical studies that assessed the biosimilarity between MSB11022 and the reference product: Phase I PK study in healthy adult subjects (EMR200588-001) and a comparative Phase III efficacy and safety study in subjects with moderate to severe plaque psoriasis (EMR200588-002). All submitted studies were registered in "clinicaltrial.gov".

The clinical development program of MSB11022 and choice of endpoints for all submitted studies were in accordance to the relevant guidelines on similar biological medicinal products containing monoclonal antibodies.

Main clinical studies:

Study 1

<table>
<tr><td colspan="3"><u>Title:</u> 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.</td></tr>
<tr><td>Study</td><td colspan="2">EMR200588-002</td></tr>
<tr><td rowspan="2">Design</td><td colspan="2">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.</td></tr>
<tr><td>Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>0 - 16 weeks
NA
16 - 54 weeks (treatment extension) 54 – 66 weeks (safety follow-up)</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Equivalence</td></tr>
<tr><td rowspan="2">Treatments arms</td><td colspan="2">Test product:
MSB11022 was administered as an initial subcutaneous dose of 80 mg at week1, followed by 40 mg subcutaneously at week 2 and every other week thereafter, for 14 weeks.</td></tr>
<tr><td colspan="2">Reference product:
The EU-approved Humira was administered as an initial subcutaneous dose of 80 mg at week 1, and 40 mg subcutaneously at week 2 and every other week thereafter, for 14 weeks.</td></tr>
<tr><td>Randomization</td><td colspan="2">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.</td></tr>
<tr><td>Blinding</td><td colspan="2">Double-blinded</td></tr>
</table>

Endpoints and definitions	**Primary endpoints**	PASI	Psoriasis Area and Severity Index score reduction of ≥ 75% response criteria at week 16
	Secondary endpoints (Efficacy)	% PASI-change	Percent change from Baseline in PASI at Week 16
		PASI	Assessment of PASI 50/90/100 at Week 16 Assessments of PASI 50/75/90/100 (ie, percentage reduction from Core Baseline) at Weeks 24 and 52, and Physician Global Assessment (PGA)."
	Secondary endpoints (Health-related quality of life)	DLQI	DLQI at Weeks 16, 24, and 52
		EQ-5D-5L	EQ-5D-5L at Weeks 16, 24, and 52
		HAQ-DI	HAQ-DI (only in subjects with psoriatic arthritis) at Weeks 16, 24, and 52
		PJA-VAS	PJA-VAS (only in subjects with psoriatic arthritis) at Weeks 16, 24, and 52
	Secondary endpoints (Immunogenicity)	ADA	ADA status and ADA titer
		NAb	Neutralizing antibody (NAb) status
	Secondary endpoints (Pharmacokinetics)	C_{trough} & C_{max}	C_{trough} and C_{max} (7 days post dose) concentrations

Statistical methods	The Per Protocol (PP) data set was used to analyze the primary and main secondary outcomes. **Analysis of the primary efficacy endpoint** The two treatment groups were compared using the 2-sided 95% Newcomb (CI) (using Cochran-Mantel-Haenzel weights) for the treatment difference (MSB11022 – EU-approved Humira) in PASI 75 response rate. 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 Imputation missing-at-random (MAR) 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. A tipping point analysis. In the tipping point analysis, data were re-analyzed for all possible combinations of the number of responders/non-responders imputed for drop-outs in each treatment arm. **Analysis of the secondary Efficacy Endpoint** 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 after drop-out, a subject's outcome reverts to a distribution similar to baseline values (i.e. of the PASI score) of the population. MSB11022 was considered equivalent to EU-approved Humira if the 95% CI for the treatment difference was included in the equivalence interval [-15%, 15%].
Database lock	After completion of week 66.

Results and Analysis

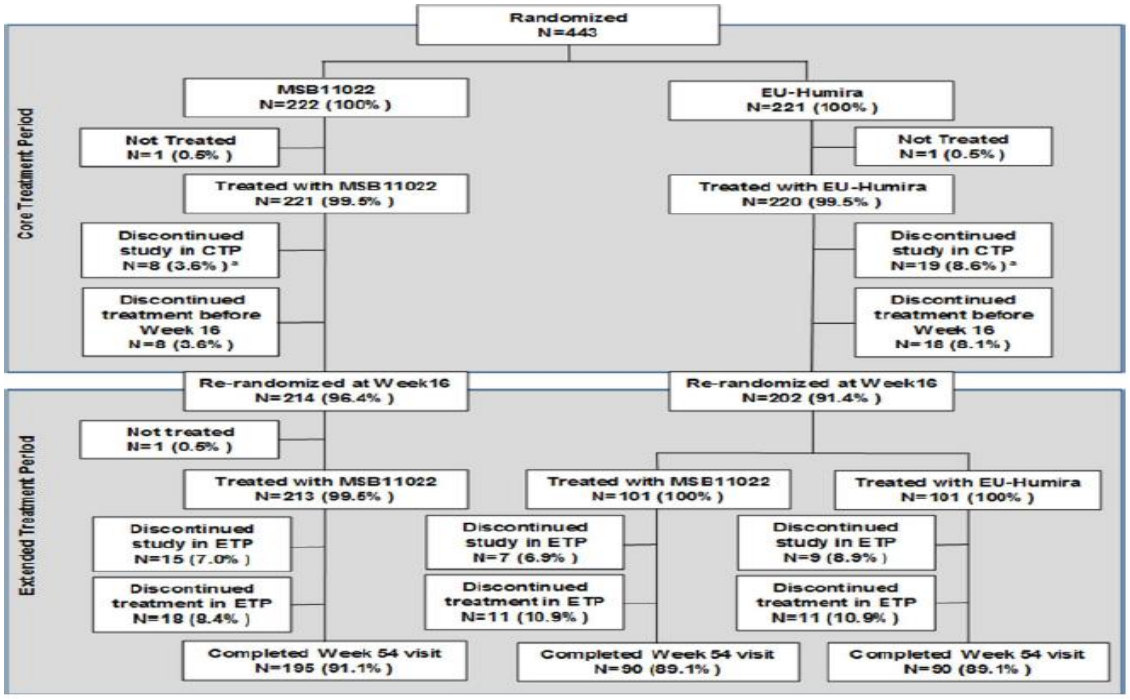
Disposition of subjects

A total of 443 subjects were randomized into the study, with 222 subjects assigned to MSB11022 and 221 subjects assigned to EU-approved Humira. Two randomized subjects (1 in each treatment group) received no treatment.

In the Core Treatment Period, the most common reasons for discontinuation 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).

In the Extended Treatment Period, in total 41 patients discontinued after re-randomization, 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 1. Disposition of subjects



Demographics and Baseline Characteristics

Sex, race, ethnicity, and age were all well balanced between the treatment groups for the ITT analysis set. At baseline of the Core Treatment period, the median age was 44.2 and 41.3 years in the MSB11022 and EU-approved Humira groups, respectively. The majority of subjects were male (66.2%) and White (92.3%).

Efficacy results

Primary Outcome: PASI 75 at Week 16

The PASI75 response at week 16 in the PP set was of similar size in both treatment groups: 89.7% in the MSB1102 group and 91.6% in the EU-Humira group. The 2-sided 95% stratified Newcombe CI for the difference in the proportion of subjects achieving a PASI 75 response at Week 16 was well within the pre-specified equivalence margin (95%CI:-7.82, 4.16)) as shown in table 1.

The sensitivity analysis results using the ITT analysis set were consistent with the results of the primary analysis in the PP analysis set (86% in the MSB11022 group and 83.3% in the EU-Humira group) with (95%CI:-4.0, 9.57).

Table 1: PASI 75 response Rate at week 16 (PP and ITT analysis sets)

	MSB11022	EU-Humira
PP Analysis Set (Primary Endpoint)	**N=203**	**N=191**
Subjects with PASI 75 at Week 16, n (%)	182 (89.7)	175 (91.6)
95% stratified Newcombe CI (%)	-7.82, 4.07	
ITT Analysis Set (Sensitivity Analysis, Nonresponder Imputation)	**N=222**	**N=221**
Subjects with PASI 75 at Week 16, n (%)	191 (86.0)	184 (83.3)
95% stratified Newcombe CI (%)	-4.00, 9.57	

Source: Table 15.2.1.1, Table 15.2.1.2.

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

The 2 treatment groups were compared using the 2-sided 95% stratified Newcombe CI for the difference in PASI 75 response rate. MSB11022 was considered equivalent to EU-Humira if the 95% stratified Newcombe CI for the difference in percentage was included in the equivalence interval [-18%, 18%]. All subjects in the ITT Analysis Set without a Week 16 PASI assessment had been assumed to be nonresponders.

Main secondary outcome: Percent Change From Baseline in PASI at Week 16

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 with mean difference of 0.88.

The 2-sided 95% confidence interval of the treatment difference was (-1.21, 2.98) which was within the predefined equivalence margins of +/- 15%.

Table 2: Mean Percent Change from Baseline in PASI at week 16 (PP analysis set)

		MSB11022		EU-Humira	
		Value	% Change from Baseline	Value	% Change from Baseline
Across Strata					
Baseline	Number of subjects, n	203		191	
	PASI, mean (SD)	20.63 (8.791)		21.18 (8.079)	
Week 16	Number of subjects, n	203	203	191	191
	PASI, mean (SD)	1.84 (2.289)	-90.667 (11.3583)	1.67 (2.170)	-91.752 (9.9570)
	LS Mean (SE)		-92.14 (0.86)		-93.02 (0.87)
	Difference LS Mean (MSB11022 – EU-Humira)	0.88			
	95% CI of the difference	-1.21, 2.98			
Previous Biological Systemic Therapy					
Baseline	Number of subjects, n	25		25	
	PASI, mean (SD)	24.94 (10.843)		26.49 (10.163)	
Week 16	Number of subjects, n	25	25	25	25
	PASI, mean (SD)	1.13 (1.587)	-95.158 (6.9845)	1.20 (1.930)	-94.438 (10.2373)
Previous Nonbiological Systemic Therapy					
Baseline	Number of subjects, n	74		67	
	PASI, mean (SD)	20.61 (8.592)		21.63 (7.919)	
Week 16	Number of subjects, n	74	74	67	67
	PASI, mean (SD)	2.09 (2.425)	-90.015 (10.7648)	2.16 (2.582)	-89.871 (10.9669)
Treatment-Naïve					
Baseline	Number of subjects, n	104		99	
	PASI, mean (SD)	19.61 (8.142)		19.54 (6.998)	
Week 16	Number of subjects, n	104	104	99	99
	PASI, mean (SD)	1.83 (2.314)	-90.052 (12.4069)	1.46 (1.861)	-92.347 (8.9962)

3.2.3 Overall conclusion of clinical efficacy

Overall, the design aspect and trial conduction are considered adequate to compare MSB11022 with EU-Humira. The chosen patient population for the trial is appropriate and sensitive to detect differences between MSB11022 and EU-Humira. The scientific considerations for choosing psoriasis as a sensitive indication to confirm biosimilarity of MSB11022 to Humira are:

- Plaque psoriasis was selected as the lead indication due to the relatively high treatment effect and immunogenicity rates observed in the Humira clinical studies in this indication.
- Plaque psoriasis is a disease where sensitive, clinically meaningful, and measurable clinical efficacy endpoints exist.
- Adalimumab is given as monotherapy in plaque psoriasis, which reduces the confounding effect of concomitant immunomodulatory medications on the evaluation of PK, efficacy, safety, and immunogenicity. This allows for a more objective demonstration of biosimilarity than those preformed in subjects with rheumatoid arthritis, where other immunosuppressive agents would be given concomitantly resulting in lower immunogenicity rates (Humira SPC, 2018; Humira, USPI, 2017).

- The assumptions of the sample size calculation are considered reasonable and the calculated sample size is acceptable. The +/- 18% equivalence margin was justified and established in other biosimilars. The choice of primary endpoint was appropriate and consistence with other biosimilars using the same sensitive population.
- According to study results, the PASI75 response at week 16 in the PP set was similar between treatment groups: 91% in the MSB1102 group and 92% in the EU-Humira group. The 2-sided 95% confidence interval (-7.82, 4.16) of the treatment difference was within the predefined equivalence margins of +/- 18%. Furthermore, the mean percent change in PASI from baseline to week 16 in the PP set was similar in treatment groups: -91% in the MSB11022 group and -92% in the EU-Humira group. The 2-sided 95% confidence interval (-1.21, 2.98) of the treatment difference was within the predefined equivalence margins of +/- 15%. Subgroup analysis showing consistently similar results support the positive comparability established with the reference product.
- Difference in response rate at week 16 was 1.9 (95%CI -7.82, 4.16) for the PP set and 2.8 (95% CI -4.0, 9.57) for ITT set. These results are comparable to the other previously approved adalimumab biosimilar, Hyrimoz, which used similar trial design and primary endpoint 1.8 (95%CI -7.46, 11.15) and 2.2 (95% CI -6.79, 11.1) for PP and full analysis sets respectively.

3.2.4 Clinical Safety

The safety profile of MSB11022 has been investigated in two clinical studies:

- One single subcutaneous (SC) dose PK study in healthy volunteers (EMR200588-001).
- One multi-dose safety and efficacy study in subjects with moderate to severe chronic plaque psoriasis (EMR200588-002).

3.2.3.1 Patient exposure

Table 3: Patient exposure

		Patients enrolled	Patients exposed to adverse event	% of patient exposed to adverse event	total number of patients
Study 1 (EMR200588-001)	US-Humira	80	45	56.3%	80
	EU-Humira	79	49	62.0%	79
	MSB11022	78	49	62.8%	78
Study 2 (EMR200588-002)	MSB11022	221	114	51.6%	221
	EU-Humira	220	117	53.2%	220

3.2.3.2 Immunogenicity studies

Study EMR200588-001

There was no obvious difference in anti-drug antibodies (ADA) positivity across the three treatment arms, with 64 of 78 (82.1%), 65 of 80 (81.3%), and 66 of 79 (83.5%) subjects tested positive overall for IMP-MSB11022, US-licensed Humira, and EU-approved Humira respectively.

Study EMR200588-002

During core treatment period, the proportions of patients positive for ADA increased similarly in both groups and overall amounted to 88% in both treatment groups. The proportion of patients positive for neutralizing antibodies (nAb) as proportion of patients positive for ADA increased in both groups to around 46%.

During extended treatment period, the proportions of patients positive for ADA increased similarly in both groups and amounted overall to 93% EU-Humira and EU-Humira/MSB11022.

Overall, the numbers and proportions of patients with positive ADA responses were similar between the MSB11022 and Humira treatment groups.

3.2.3.3 Adverse events

Serious adverse events and deaths

Study EMR200588-001

Serious AEs were reported in two subjects in the IMP-MSB11022 arm, both considered to be not related to the study drug.

Study EMR200588-002

During core treatment period, serious AEs occurred in eight patients in the MSB11022 group and six patients in the EU-Humira group.

Table 4: Serious TEAEs by Treatment Group in the Core Treatment Period (SAF Analysis Sets)

Preferred Term	Number (%) of subjects	
	MSB11022 (N=221)	EU-Humira (N=220)
Subjects with at least 1 SAE	8 (3.6)	6 (2.7)
Ankle fracture	1 (0.5)	0
Atrial fibrillation	1 (0.5)	0
Cholecystitis chronic	1 (0.5)	0
Erythema multiforme	1 (0.5)	0
Hernia	1 (0.5)	0
Hypertension	1 (0.5)	0
Osteonecrosis	1 (0.5)	0
Respiratory tract infection viral	1 (0.5)	0
Anaphylactic shock	0	1 (0.5)
Arthritis bacterial	0	1 (0.5)
Hepatic enzyme increased	0	1 (0.5)
Intraductal proliferative breast lesion	0	1 (0.5)
Liver function test increased	0	1 (0.5)
Neutropenia	0	1 (0.5)

During overall treatment period, serious AEs occurred in twenty patients in the continuous MSB11022 group and eight patients in the continuous EU-Humira group.

Table 5: Serious TEAEs by Treatment Group in the Overall Period (SAF analysis Sets)

	MSB11022 N=221		EU-Humira N=118		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

During Extended Treatment Period, serious AEs occurred in four subjects in the EU-Humira to MSB11022 group and three subjects in the EU-Humira to EU-Humira group.

Table 6: Serious TEAEs by Treatment Group in the Extended Treatment Period (SAF analysis set)

	MSB11022 N=213		EU-Humira N=101		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	12 (5.6)	16	3 (3.0)	7	4 (4.0)	4
Acute myocardial infarction	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Atrial fibrillation	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Cardiac failure	0 (0.0)	0	2 (2.0)	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 (1.0)	1	0 (0.0)	0
Mitral valve incompetence	0 (0.0)	0	1 (1.0)	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
Appendicitis	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Peritonsillar abscess	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0
Pneumonia	0 (0.0)	0	1 (1.0)	1	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
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
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
Brain oedema	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Cerebral haematoma	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Acute kidney injury	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
Vascular compression	1 (0.5)	1	0 (0.0)	0	0 (0.0)	0

Deaths:

In the extended treatment period of EMR200588-002 study, one death was reported in the continued EU-Humira group. This patient had died after a traumatic event with cerebral hematoma, brain edema, and subsequent cardiac failure. Which were considered not related to the study medication.

Laboratory findings

No major findings reported.

Safety in special populations

MSB11022 was developed as a biosimilar to the reference product Humira; therefore, product information from the reference product Humira also applies to MSB11022. The product information is in line and adequate to the reference product.

Safety related to drug-drug interactions and other interactions

Drug- drug Interactions were not evaluated.

Discontinuation due to AES

Study EMR200588-002

During core treatment period, one patient in the MSB11022 arm and 12 patients in EU-Humira arm discontinued treatment due to a TEAE.

During extended treatment period, nine patients on continuous MSB11022, 6 patients on EU-Humira and 3 patients who had switched to MSB11022 discontinued the treatment due to one or more TEAEs.

Post-marketing experience

Not available.

3.2.3.3 Overall conclusion on clinical safety

The submitted safety and immunogenicity data were generally comparable between the test and reference products and are adequate to support the demonstration of no clinically meaningful differences in safety and immunogenicity between MSB11022 and EU-Humira.

3.2.4 Discussion on Clinical efficacy and safety aspects

Based on the efficacy and safety department review of the submitted dossier, the analysis results from the main studies were within the predefined margins of equivalence. In addition, the confirmed similarity of mechanism of action, efficacy, PK, and safety profile between MSB11022 (Idacio) and Humira supports the extrapolation of all the submitted indications. Therefore, the clinical studies section recommends approval of the product for the submitted indications.

4. Risk Management Plan (RMP)

Every new drug approved in Saudi Arabia has an RMP in place to ensure that the drug or vaccine is used as safe as possible. The RMP is a comprehensive document describing current knowledge about the safety and efficacy of a drug. The SFDA has reviewed the Idacio RMP version 4.0 and concluded the following safety concerns:

Table of Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Serious infections • Tuberculosis (TB) • Malignancies • Demyelinating disorders (including MS, GBS and optic neuritis) • BCG disease following live BCG vaccination in infants with in utero exposure to MSB11022
Important potential risks	• Progressive Multifocal Leukoencephalopathy (PML) • Reversible Posterior Leukoencephalopathy Syndrome (RPLS) • Adenocarcinoma of colon in Ulcerative colitis (UC) patients
Missing information	• Patients with immune-compromised conditions • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease • Episodic treatment in Psoriasis , UC, and Juvenile idiopathic arthritis (JIA) • Long-term safety data in the treatment of adults and children with uveitis

4.1 Pharmacovigilance Activities

4.1.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse drug reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for PML, Malignant events, HBV reactivation, Off-label use in pediatric patients.
- Other forms of routine pharmacovigilance activities for all included risks and missing information:

Follow up of case reports: The minimum desired case information for rituximab includes the brand name and batch number of the suspect product.

4.1.2 Additional Pharmacovigilance Activities

The following categories 2 studies are additional pharmacovigilance activities.

Table of additional pharmacovigilance activities:

Activity title/type	Objectives	Safety concerns addressed
Participation in a Medical Society Registry established in one of the major EU markets for patients with Rheumatoid Arthritis (RA) following a prospective cohort design and collecting data on MSB11022.	The purpose of the study is to contribute to the overall evidence base in support of adalimumab, in particular the estimation of incidence rates of adverse events of special interest for adalimumab as identified in the summary of safety concerns in the risk management plan.	Captured specific data on the identified and potential risks.
Participation in a Medical Society Registry established in one of the major EU markets for patients with Inflammatory Bowel Disease (IBD) following a prospective cohort design and collecting data on MSB11022.	The purpose of the study is to contribute to the overall evidence base in support of adalimumab, in particular the estimation of incidence rates of adverse events of special interest for adalimumab as identified in the summary of safety concerns in the risk management plan.	Captured specific data on the identified and potential risks.

4.2 Risk Minimization Measures

4.2.1 Routine Risk Minimization Measures:

Measures to minimize the risks identified for medicines can be:

- Specific information, such as warnings, precautions.
- Important information on the medicine packaging.
- The authorized package size.
- The medicines legal status.

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

4.2.2 Additional Risk Minimization Measure:

1. Patient reminder card.

   Objectives:

   The objective of the measure is to remind patients (or caregivers) on the key risks for adalimumab for the following risks:

   - Infections
   - TB.
   - Malignancies.
   - Demyelinating disorders.
   - BCG disease following live BCG vaccination in infants with in utero exposure to MSB11022.

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

Proposed trade Name	Dosage Form
Idacio	Solution for injection

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

Idacio name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP

Confused Drug Name List, INN International Nonproprietary Names and USAN United States Adopted Names STEM) and the pharmaceutical characteristic of the product:

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

Trade Name Recommendation:

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

Outer and Inner Package:

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

5. Overall Conclusion

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

- Rheumatoid arthritis : Idacio 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.

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

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

- Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Idacio 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 (DMARDs). Idacio can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Idacio 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.

- Axial spondyloarthritis

Ankylosing spondylitis (AS)

Idacio 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

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

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

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

- Hidradenitis suppurativa (HS): Idacio is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS.

- Crohn’s disease: Idacio 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: Idacio 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: Idacio 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-MP) or (AZA), or who are intolerant to or have medical contraindications for such therapies.

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

- Paediatric Uveitis: Idacio 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.

6. Appendix


Idacio® 40 mg
ايداسيو ٤٠ ملجم
solution for injection in pre-filled syringe
محلول للتسريب الوريدي في حقنة مسبقة التعبئة
adalimumab
أداليموماب
Subcutaneous use
للحقن تحت الجلد
2 pre-filled syringes
2 alcohol pads
٢ حقنة مسبقة التعبأة
٢ قطعة مشربة بالكحول
FRESENIUS KABI


Idacio® 40 mg
ايداسيو ٤٠ ملجم
solution for injection in pre-filled pen
محلول للتسريب الوريدي في قلم مسبق التعبئة
adalimumab
أداليموماب
Subcutaneous use
للحقن تحت الجلد
2 pre-filled pens
2 alcohol pads
٢ قلم مسبق التعبئة
٢ قطعة مشربة بالكحول
FRESENIUS KABI


Idacio® 40 mg
ايداسيو ٤٠ ملجم
solution for injection in pre-filled syringe
محلول للتسريب الوريدي في حقنة مسبقة التعبئة
adalimumab
أداليموماب
One 0.8 mL pre-filled syringe contains 40 mg adalimumab
Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, mannitol, sodium chloride, citric acid monohydrate, sodium citrate, polysorbate 80, sodium hydroxide and water for injections.
For single use only.
Read the package leaflet before use.
Store in a refrigerator. Do not freeze.
Refer to package leaflet for alternative storage details.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep out of the sight and reach of children.
Manufacturing by:
Merck Serono S.p.A. (MS-Bari)
Italy
Packaging and releasing by:
Fresenius Kabi Austria GmbH
Hafnerstraße 36
A-8055 Graz
Austria
For MAH:
Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1
61352 Bad Homburg vd. Höhe
Germany
EU/1/19/1356/004


Idacio® 40 mg
ايداسيو ٤٠ ملجم
solution for injection in pre-filled pen
محلول للتسريب الوريدي في قلم مسبق التعبئة
adalimumab
أداليموماب
One 0.8 mL pre-filled pen contains 40 mg adalimumab
Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, mannitol, sodium chloride, citric acid monohydrate, sodium citrate, polysorbate 80, sodium hydroxide and water for injections.
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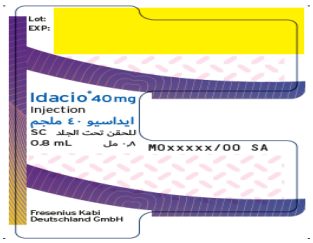
61352 Bad Homburg v.d.Höhe
Germany
EU/1/19/1356/004


Idacio® 40 mg
Injection
ايداسيو ٤٠ ملجم
SC للحقن تحت الجلد
0.8 mL ٠٫٨ مل
Fresenius Kabi Deutschland GmbH
MOxxxxx/00 SA
Lot:
EXP:


Lot:
EXP:
Idacio® 40 mg
Injection
ايداسيو ٤٠ ملجم
SC للحقن تحت الجلد
0.8 mL ٠٫٨ مل
MOxxxxx/00 SA
Fresenius Kabi Deutschland GmbH

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

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