BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	761255
Received Date	December 13, 2021
BsUFA Goal Date	December 13, 2022
Division/Office	Division of Rheumatology and Transplant Medicine Division of Dermatology and Dentistry Division of Gastroenterology
Review Completion Date	See DARRTS stamped date
Product Code Name	MSB11022
Proposed Nonproprietary Name[1]	Adalimumab-aacf
Proposed Proprietary Name[1]	Idacio
Pharmacologic Class	Tumor necrosis factor blocker
Applicant	Fresenius Kabi, LLC
Applicant Proposed Indication(s)	• Rheumatoid arthritis (RA) • Juvenile idiopathic arthritis (JIA) (2 years of age and older) • Psoriatic arthritis (PsA) • Ankylosing spondylitis (AS) • Crohn's disease (CD) in adults and pediatric patients 6 years of age and older • Ulcerative Colitis (UC) in adult patients • Plaque Psoriasis (PsO)
Recommendation on Regulatory Action	• Approval of MSB11022 single-dose prefilled pen and single-dose prefilled glass syringe (Original 1) (b) (4)

[1]Section 6.5.3 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DDD = Division of Dermatology and Dentistry
DG = Division of Gastroenterology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRM = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMAMES	Division of Mitigation and Medication Error Surveillance
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
EU-Humira	EU-approved Humira
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OPMA	Office of Pharmaceutical Manufacturing Assessment
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
U.S.-Humira	U.S.-licensed Humira

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1. Executive Summary

1.1. Product Introduction

Fresenius Kabi, LLC (also referred to as "Applicant" in this review) has submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for MSB11022 40 mg/0.8 mL as a proposed biosimilar to US-licensed Humira (US-Humira, adalimumab) 40 mg/0.8 mL

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

FDA has determined that animal studies are unnecessary in this 351(k) application.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

MSB11022 has the same mechanism of action as that of US-Humira.

MSB11022 product is a sterile liquid solution with the following proposed presentations:

- Injection: 40 mg/0.8 mL in a single-dose prefilled pen
- Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe

(b) (4)

The strength of MSB11022 in each of the above presentations is the same as that of US-Humira. MSB11022 also has the same dosage form and route of administration as that of US-Humira.

1.4. Inspection of Manufacturing Facilities

FDA's Office of Pharmaceutical Manufacturing Assessment (OPMA) conducted an assessment of the manufacturing facilities for this BLA.

- (b) (4)) is responsible for drug substance (DS) manufacturing. A pre-license inspection (PLI) was conducted from (b) (4). The inspection concluded with a three-item FDA Form 483 and a facility recommendation of approve.
- (b) (4) is responsible for drug product manufacturing for the single-dose prefilled pen and the single-dose prefilled glass syringe. OPMA determined that this drug product manufacturing facility was adequate.
- (b) (4)

(b) (4)

The OPMA team recommended the following:

- Approval action of the single-dose prefilled pen and the single-dose prefilled glass syringe presentations in BLA 761255 from the standpoint of facilities assessment.
- (b) (4)

The CDTL and Division Signatory agree with the above assessments and recommendations.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

The Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated from the comparative clinical study EMR200588-002, which used EU-Humira as the comparator, for the assessment of biosimilarity:

- The Office of Pharmaceutical Products, OPQ, CDER has determined, that based on the data provided by the Applicant, the analytical component of the scientific bridge between MSB11022, US-Humira, and EU-Humira was established.
- The Office of Clinical Pharmacology (OCP) has determined, that based on the data provided by the Applicant, the PK data established the PK component of the scientific bridge.

1.6. Biosimilarity Assessment

Table 1. Summary and Assessment of Biosimilarity

Comparative Analytical Studies[2]

[2]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Summary of Evidence	• MSB11022 is highly similar to US-Humira notwithstanding minor differences in clinically inactive components. • Each of the presentations (PFS, prefilled pen, (b) (4) of MSB11022 40 mg/0.8 mL has the same strength as that of US-Humira 40 mg/0.8 mL. • The dosage form and route of administration is also the same as that of US-Humira. • The analytical component of the scientific bridge between MSB11022, US-Humira, and EU-Humira was established to support the relevance of the data generated from studies using EU-Humira as the comparator to the assessment of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment.

Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• PK similarity between MSB11022, US-Humira, and EU-Humira was evaluated in two three-way PK similarity studies in healthy subjects to compare MSB11022 (C/Acetate), MSB11022 (A/Citrate) (i.e., Idacio approved in Europe) and U.S.-Humira in Study FKS022-002, and MSB 11022 (A/Citrate), U.S.-Humira and E.U.-Humira in Study EMR200588-001. • PK similarity between MSB11022 and US-Humira was established and supports a demonstration of no clinically meaningful differences between MSB11022 and US-Humira. • PK similarity between MSB11022, EU-Humira, and US-Humira provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Humira to the assessment of biosimilarity. • Comparable incidence of ADA and NAb formation between MSB11022 and US-Humira in healthy subjects supported a demonstration of no clinically meaningful differences between MSB11022 and US-Humira (Studies FKS022-002 and EMR200588-001). • Given that the scientific bridge was established (based on the analytical and PK comparisons) between MSB11022, US-Humira, and EU-Humira to justify the relevance of data generated with EU-Humira as the comparator, the similar incidence of ADA and NAb formation between MSB11022, EU-Humira, and US-Humira in healthy subjects (Studies FKS022-002 and EMR200588-001) and between MSB11022 and EU-Humira in patients with plaque psoriasis (Study EMR200588-002) supports a demonstration of no clinically meaningful differences between MSB11022 and US-Humira. • PK of MSB11022 administered using PFS and AI was comparable (Studies FKS022-002 and EMR200588-001).

Assessment of Residual Uncertainties	• There are no clinical pharmacology residual uncertainties from a clinical pharmacology perspective.
Additional Clinical Studies	
Summary of Evidence	• In Study EMR200588-002, there were no meaningful differences in terms of efficacy between MSB11022 and EU-Humira. The frequency of treatment emergent adverse events, serious events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms. • Given that the scientific bridge was established (based on the analytical and PK comparisons) between MSB11022, US-Humira, and EU-Humira to justify the relevance of the data generated with EU-Humira as the comparator, the collective evidence from submitted clinical studies, including the comparative clinical study EMR200588-002, supports a demonstration of no clinically meaningful differences between MSB11022 and US-Humira in the studied indication (plaque psoriasis, PsO).
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or statistical perspective regarding the demonstration of no clinically meaningful differences between MSB11022 and US-Humira.
Extrapolation	

Summary of Evidence	• DG, DDD, and DRTM teams have determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and safety) to support extrapolation of data, and information submitted, including clinical data from the studied population (PsO), to support licensure of MSB11022 as a biosimilar, under section 351(k) of the PHS Act, for the following indications for which US-licensed Humira has been previously approved: o Treatment of inflammatory bowel disease indications (adult Ulcerative colitis and Crohn's disease 6 years of age and older) o Treatment of juvenile idiopathic arthritis 2 years of age and older o Treatment of adult psoriatic arthritis o Treatment of adult ankylosing spondylitis o Treatment of adult rheumatoid arthritis
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of MSB11022 as biosimilar to US-Humira for the above indications.

1.7. Conclusions on Approvability

The Applicant is seeking licensure of MSB11022 for the following indications: RA, JIA in patients 2 years of age and older, PsA, AS, PsO, CD in patients 6 years of age and older, and UC in adults. The totality of the evidence submitted by the Applicant supports our conclusion that MSB11022 is highly similar to U.S.-licensed Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between MSB11022 and U.S.-licensed Humira in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of MSB11022 for RA, JIA in patients 2 years and older, PsA, AS, CD in patients 6 years and older, and adult UC. The Applicant has sufficiently demonstrated that MSB11022 40 mg/0.8 mL is biosimilar to U.S.-licensed Humira 40 mg/0.8 mL for each of the requested indications for which U.S.-licensed Humira is currently licensed.

(b) (4)

Therefore, the FDA review team recommended the following actions for this application:

- an Approval action for the two proposed MSB11022 (40 mg/0.8 mL)

presentations, single-dose prefilled pen and single-dose prefilled glass syringe.

- (b) (4)

The CDTL and the Division Signatory agree with the above recommendation.

Author:
Anil Rajpal, MD, MPH
Cross-Discipline Team Leader (CDTL)

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

A summary of presubmission regulatory history related to the current submission is summarized in Table 2.

Table 2. Summary of Presubmission Regulatory History

Meeting Type (Date)	Major Agreements/Outcomes
BPD Type 2 Meeting (08Dec2014)	The objective of the meeting was to discuss the proposed quality (Chemistry, Manufacturing and Controls), nonclinical and clinical development plans. -Agency did not agree with the proposed analytical method panel to demonstrate analytical similarity and provided additional comments. -Agency had concerns on ADCC, CDC and high mannose profiles in relation to analytical similarity. -Agency found the clinical development strategy acceptable (comparative PK study in healthy subjects comparing MSB11022 (A/Citrate), US-RP and EU-RMP and a comparative safety and efficacy study in psoriasis patients (MSB11022 (A/Citrate) VS. EU-RMP).
BPD Type 2 Meeting (01Dec2015)	The objective of the meeting was to discuss quality (Chemistry, Manufacturing and Controls), nonclinical and clinical development plans. -In general Agency agreed with the proposed development program that included a PK similarity study in healthy subjects and a comparative clinical study in psoriasis patients. Agency reviewed the PK data for healthy subject study and agreed that it established a PK bridge between MSB11022 (A/Citrate), EU-RMP and US-RP. -Agency did not agree that ADCC is not a MoA of adalimumab in chronic inflammatory disease, Agency voiced concern related to differences in critical Fc functional attributes, in particular ADCC activity and indicated that a proposed demonstration of no clinically meaningful differences will not obviate the need to demonstrate that MSB11022 is highly similar to US-Humira. Agency reminded the Applicant that they should address the analytical differences and show that their

	product is highly similar first before initiating clinical studies to support a demonstration of no clinically meaningful differences. -Agency requested simulated human factor studies for the auto injector presentation and a PK bridging study between the PFS and auto-injector presentations.
Agency Advice Letter (26Oct2016)	In the letter received in response to the analytical similarity data submitted to the IND, the Agency indicated that the Agency did not believe that the analytical data generated at the time would support a demonstration that MSB11022 (A/Acetate) is highly similar to US-RP, in particular ADCC activity. Agency requested that no clinical study be conducted until process is improved.
BPD Type 2 Meeting (23July2018)	The objective of the meeting was to obtain feedback on the suitability of MSB11022 (C/Acetate) to be developed as a biosimilar, acceptability of the proposed analytical similarity approach and bridging strategy based on small scale data. -Agency confirmed that MSB11022 (C/Acetate) small scale data more closely matched the US-RP and requested to review large scale data. -Agency agreed that DP manufacturing process may not need to be revalidated Agency requested clinical PK and immunogenicity data with MSB11022 (C/Acetate) which is the to-be-marketed product in the US. -Agency requested that the comparative PK study for the autoinjector be conducted with MSB11022 (C/Acetate) and that actual use study with autoinjector (AI) is not needed since physioject is commercialized since 20111 and approved/used in several indication including RA.
BPD Type 3 Meeting (29Jul2019)	The objective of the meeting was to obtain feedback on the proposed criticality risk ranking of quality attributes, proposed statistical methods to demonstrate similarity for very high, high and moderate risk attributes, strategy and clinical bridging strategy between MSB11022 (A/Citrate) VS. MSB11022 (C/Acetate) -Agency concurred that large scale data for MSB11022 (C/Acetate) more closely matched the US-Humira profile and Agency expectations. Agency found the proposed criticality ranking acceptable. Agency in general agreed with the proposed statistical methods and provided additional recommendations. -Agency requested that the analytical similarity is fully run for the 3 pair wise comparison: MSB11022 (C/ Acetate; to be commercialized product in US) vs. US Humira Vs EU-Humira -Agency recommended that: *Control strategy for afucosylated and galactosylated species should be based on specifications for these species by 2AB glycan assay and Release test (b) (4) for ADCC, CDC effector functions comprising with either cell based or binding assay (to be scientifically justified). *For clinical bridging from MSB11022 (A/Citrate) to MSB11022 (C/Acetate) Agency recommended a single PK study, powered for the 3 comparisons: MSB11022 (A/Citrate) vs. MSB11022 (C/Acetate) vs. US-Humira.
BPD Type 2 Meeting (16Mar2021)	The objective of the meeting was to get feedback on the implementation of change related to addition of (b) (4) in the DS manufacturing process. -Agency agreed to the overall proposal to include as assessment of release, characterization and stability data to demonstrate comparability of pre-change and post-change batches at the MSB11022 DS stage. In addition, the Agency also provided recommendations on how to assess comparability.
BPD Type 2 Meeting (16Jul2021)	The objective of the meeting was to get agreement on the overall manufacturing changes comparability strategy, reference standard implementation strategy and

	CDC and ADCC testing strategy. Nonclinical and procedural clinical and regulatory topics were included to ensure that the planned BLA met the Agency expectations. -The Agency agreed with the proposed comparability and bridging strategy for the manufacturing changes; The Agency agreed with the reference standard implementation strategy and provided additional comments. The Agency considered implementation of ADCC and CDC testing for DS release reasonable. -The Agency also agreed with the Applicant's proposal to not include animal data generated with MSB11022 (A/Citrate) in the BLA. Agency agreement was also obtained for the procedural clinical and regulatory proposals made in the briefing package. As there were no additional points for clarification, the Applicant requested the meeting to be cancelled.
BPD Type 4 Meeting (04Oct2021)	The objective of the meeting was to discuss content and format of the 351(k) BLA for MSB11022 including CMC, device, nonclinical and clinical aspects. Concept of labelling development including packaging configurations was also presented in the package. -The Agency found acceptable the proposed strategies for CMC, regulatory topics including manufacturing schedule/strategy for pre-approval inspection (PAI), labelling concept and overall content and format of the BLA. The Agency indicated that while studies EMR200588-003 and MS200588-0004 are not necessary to support the demonstration of biosimilarity between MSB11022 (C/Acetate) and US-licensed Humira, submission of data from these studies is left to the Applicant's discretion. -The Agency clarified their expectations for safety summary for the comparative safety and efficacy study in patients with psoriasis (Study EMR200588-002) with regards to AESI and subject narratives and the Agency requested additional categories to be included in the BLA. During the meeting Agency agreed to receiving this additional data in the 4-month safety update. The Agency requested post-marketing safety data with EU-Idacio till date and agreed to receive the safety findings in the 4-month safety update. The Agency also indicated that their recommendation has evolved regarding primary efficacy endpoint and equivalence margin (% change in PASI at Wk 16 evaluated using 90% CI and with +10% margin) for the psoriasis patient study (Study EMR200588-002) and indicated that they prefer to receive the corresponding statistical analyses (with 90% CI) in the initial BLA, and if not possible, within 30 days from the BLA submission.

2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

No nonclinical animal studies with MSB11022 were submitted (see Section 4).

Table 3. Table Listing All Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
Study FKS022-002	unknown	Comparative pharmacokinetics, immunogenicity and safety of MSB11022(C/Acetate), U.S.-Humira, and MSB11022 (A/Citrate)	Double-blind, randomized,single-dose, parallel-group, active-controlled, three-way pairwise	Healthy Subjects	MSB11022 (C/Acetate): 150 U.S.-Humira: 152 MSB11022 (A/Citrate): 150
Study FKS022-001	NCT 04018599	Comparative pharmacokinetics and safety of MSB11022 (C/Acetate) given with pre-filled syringe (PFS) and MSB11022 (C/Acetate) given with auto-injector (AI)	Open-label, randomized,single-dose, two-arm, parallel-group	Healthy Subjects	MSB11022 (C/Acetate) in PFS: 107 MSB11022 (C/Acetate) in AI: 106
Study EMR200588-001	NCT 03014947	Comparative pharmacokinetics, immunogenicity and safety of MSB11022(A/Citrate), U.S.-Humira, and E.U.-Humira	Double-blind, randomized,single-dose, parallel-group, active-controlled, three-way pairwise	Healthy Subjects	MSB11022 (A/Citrate): 78 U.S.-Humira: 80 E.U.-Humira: 79
Comparative Clinical Study(ies)					
Study EMR200588-002	NCT 02660580	Comparative efficacy, safety, and immunogenicity of MSB 11022 (A/Citrate) vs EU-Humira	Double-blind, randomized, parallel-group, active-controlled	Moderate to severe chronic plaque psoriasis	Core Treatment Period (Weeks 1-16): MSB 11022: 221 EU-Humira: 220 Extended Treatment Period (Weeks 16-54):

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
					Remained on MSB 11022: 213 Transitioned from EU-Humira to MSB11022: 101 Remained on EU-Humira: 101 Overall Treatment Period (Weeks 1-54): Continuous MSB 11022: 221 Continuous EU-Humira: 119

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3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Products, OPQ, CDER, has completed review of BLA 761255 for MSB11022 (40 mg/0.8 mL) manufactured by Fresenius Kabi, LLC.

- (b) (4)

(b) (4)

- OPQ recommends approval of the other two proposed MSB11022 (40 mg/0.8 mL) presentations in this application, single-dose prefilled pen and single-dose prefilled glass syringe. Refer to the integrated quality assessment and related primary reviews for detailed information. The OPQ team determined that the data submitted for these proposed presentations in this application are adequate to support the following conclusions:
  - The manufacture of MSB11022 40 mg/0.8 mL is well-controlled and leads to a product that is pure, potent, and safe.
  - MSB11022 40 mg/0.8 mL is highly similar to US-Humira 40 mg/0.8 mL notwithstanding minor differences in clinically inactive components.
  - The strength of MSB11022 40 mg/0.8 mL in a single-dose prefilled pen and single-dose prefilled glass syringe is the same as that of US-Humira 40 mg/0.8 mL.
  - MSB11022 40 mg/0.8 mL also has the same dosage form and route of administration as that of US-Humira 40 mg/0.8 mL.

The CDTL and Division Signatory agree with the above assessments and recommendations.

3.2. Devices

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH recommends approval based on assessment of device constituent parts of the combination product. Also, refer to the full CDRH OPEQ review.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

The human factors evaluator Damon Birkemeir, PharmD from DMEPA reviewed a human factors (HF) validation study report for MSB11022 40 mg/0.8 mL Autoinjector (AI), four- and six- AI starter packs, (b) (4) The safety evaluator provided the following conclusion and recommendations:

> "The results of the HF validation studies demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient. However, Fresenius Kabi proposed revisions to the product user interface to further mitigate the risk for use errors. We found Fresenius Kabi's proposed

> changes to the user interface to be reasonable and identified additional risk mitigations. Additionally, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table A for Fresenius Kabi. We ask that the Division of Rheumatology and Transplant Medicine (DRTM) convey Table A in its entirety to Fresenius Kabi so that recommendations are implemented. We have determined that in this particular case, we do not need to review additional HF validation study data to support these changes."

It should be noted that the recommendations in the referenced "Table A" were sent to the Applicant on November 21, 2022. The Applicant responded to these recommendations on November 29, 2022. The safety evaluator provided the following conclusion and recommendations:

> "The Applicant implemented most of our recommendations and we find their proposal (b) (4) acceptable. However, Fresenius includes an example date in DD/MM/YY format. We recommend Fresenius update the example date to be in United States standard date format (MM/DD/YY)."

It should be noted that the recommendations regarding standard date format were sent to the Applicant on December 2, 2022.

The Applicant responded on December 6, 2022, and agreed to implement these recommendations.

Refer to the reviews by Damon Birkemeier / Oluwamurewa Oguntimein dated September 21, 2022 and December 1, 2022 for additional information.

The CDTL and Division Director concur that additional data are not needed, and the proposed labeling is appropriate and sufficient to ensure the safe and effective use of the single-dose prefilled pen and single-dose prefilled glass syringe presentations of MSB11022.

3.3. Office of Study Integrity and Surveillance (OSIS)

OSIS inspections were requested for both bioanalytical and clinical sites for Study FKS022-002 and Study EMR200588-001.

- OSIS conducted a Remote Record Review (RRR) of the bioanalytical portion of Study FKS022-002 performed at (b) (4) OSIS noted that data from Study FKS022-002 are reliable. Of note, all PK and ADA samples from both Study FKS022-002 and Study EMR200588-001 were analyzed by (b) (4)

- OSIS determined that inspections for the clinical sites (Quintiles Ltd. and Hammersmith Medicines Research Ltd.) for Study EMR200588-001 were not warranted, as these sites had been previously inspected within 1 to 1.5 years.
- OSIS conducted an inspection of clinical site (MTZ Clinical Research, sp. z o.o., Warsaw, Poland) and observed no objectionable conditions and data from the audited study FKS022-002 are reliable.
- OSIS does not plan to conduct any additional inspections based on adequate history as outlined in the decline memo and the results of the OSIS review.

Refer to the review memos by Dr. James Lumalcuri dated April 11, 2022, by Drs. Kara Scheibner / Xingfang Li dated June 15, 2022 and by Drs. Xikui Chen / Michael Skelly dated October 27, 2022 for additional information.

3.4. Office of Scientific Investigations (OSI)

The following clinical study sites were selected from the comparative clinical study EMR200588-002 for inspection by CDER Office of Scientific Investigations (OSI).

- Site 206 (Dr. Charles Lynde, Ontario, Canada): enrolled n=5
- Site 0702 (Dr. Efren Sanchez Campos, Yucatan, Mexico); enrolled n=10

These sites were selected for inspection based on risk ranking in the Clinical Site Selection Tool, taking into account numbers of enrolled subjects, treatment effect, and prior inspectional history. Upon completion of the study site investigations, OSI concluded that the study data derived from these clinical sites, based on the inspections, are considered reliable and appear to have been conducted adequately. Refer to the review by Dr. Tina Chang on November 1, 2022 for detailed information regarding the clinical site inspections.

Author:
Anil Rajpal, MD, MPH
Clinical Team Leader

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

No nonclinical animal studies with MSB11022 were submitted. Of note, a 4-week toxicology study in cynomolgus monkeys with MSB11022 (Process A/Citrate formulation) was conducted but was not submitted to the BLA. According to the Applicant, the to-be-marketed product, MSB11022 (Process C/Acetate formulation), matches the US-Humira profile more closely and the animal study performed with MSB11022 (Process A/Citrate formulation) is not considered to provide additional

support to the totality of evidence; and FDA found justification to be acceptable.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The MSB11022 drug product is a sterile, preservative-free solution for injection by the subcutaneous (SC) route of administration. The drug product is formulated at a concentration of 50 mg/mL (40 mg/0.8 mL) and is provided as either a single-dose prefilled glass syringe in (b) (4) device, single-dose prefilled syringe in autoinjector pen (Idacio pen), (b) (4)

The prefilled syringe consists of a 1 mL (b) (4) glass syringe combined with a 29 Gauge, 12 mm thin wall steel needle protected by a rigid needle shield that is closed with a (b) (4) plunger stopper. The prefilled syringe and plunger stopper comply with Ph. Eur. and USP pharmacopeial requirements. Table 4 (Applicant's Table) shows the composition of the MSB11022 drug product formulation in a prefilled syringe in the (b) (4) device and in the autoinjector pen.

Table 4. Composition of MSB11022 Drug Product Formulation in Prefilled Syringe (Applicant's Table)

Ingredient	Function	Quality Grade	Nominal quantity per mL	Nominal quantity per syringe
Adalimumab	Active ingredient	In-House	50.0 mg*	40.0 mg
Glacial acetic acid	(b) (4)	Ph. Eur., USP	0.6 mg	0.5 mg
Trehalose (b) (4)		Ph. Eur., USP/NF	(b) (4) mg	(b) (4) mg
Polysorbate 80		Ph. Eur., NF	1.0 mg	0.8 mg
Sodium chloride		Ph. Eur., USP	2.9 mg	2.3 mg
Sodium hydroxide		Ph. Eur., NF	q.s. to pH 5.2: (b) (4)	q.s. to pH 5.2: (b) (4)
Water for injection		Ph. Eur., USP	q.s. to 1.0 mL	q.s. to 0.8 mL

Ph. Eur.: European Pharmacopoeia; USP: United States Pharmacopoeia; NF: National Formulary
q.s.: quantum satis (for as much as required)
* The target quantity of Adalimumab is (b) (4) mg per mL, refer to Section 3.2.P.2.2 Pharmaceutical Development – Drug Product – PFS.

(b) (4)

Comments on Excipients

The excipients in the MSB11022 drug product include: glacial acetic acid, trehalose (b) (4) polysorbate 80, sodium chloride, sodium hydroxide, and water for injection. There are no novel excipients present in the drug product formulation. The levels of each excipient are withing the ranges that are found in FDA-approved SC products.

For comparison, per Section 11 of the Humira USPI, accessed November 9, 2022, the excipients in the 40 mg/0.8 mL prefilled syringe, prefilled pen, or single-dose institutional use vial of US-Humira include: citric acid monohydrate (1.04 mg), dibasic sodium phosphate dihydrate (1.22 mg), mannitol (9.6 mg), monobasic sodium phosphate dihydrate (0.69 mg), polysorbate 80 (0.8 mg), sodium chloride (4.93 mg), sodium citrate (0.24 mg) and water for injection, USP. Sodium hydroxide is added as necessary to adjust pH.

Comments on Impurities of Concern

No impurities of concern are identified.

The Applicant conducted extractables and leachables studies of the container closure systems for the MSB11022 drug substance and MSB11022 drug product (prefilled syringe (b) (4)). There are no nonclinical safety concerns for extractables and leachables based on results from these studies (refer to Nonclinical Primary Review dated September 2, 2022 under BLA 761255 in DARRTS [Reference ID: 5040765]).

Authors:

Eleni Salicru, PhD
Nonclinical Reviewer

Timothy Robison, PhD, DABT
Nonclinical Supervisor/Team Leader

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	PK similarity between the to-be-marketed formulation of MSB11022 and U.S.-Humira was established and supports a demonstration of no clinically meaningful differences between MSB11022 (C/Acetate) and U.S.-Humira.
Pharmacodynamics	Not applicable
Immunogenicity	Comparable incidence of ADA and NAb formation between MSB11022 and U.S.-Humira in healthy subjects and between MSB11022 and E.U.-Humira in patients with psoriasis supports a demonstration of no clinically meaningful differences between MSB11022 (C/Acetate) and U.S.-Humira.

During the development of MSB11022, the Applicant developed two different drug substance processes (process A and C) and two different formulations (citrate and acetate buffer). In this review, different MSB11022 products will be denoted with process/ formulation in the following way:
MSB11022 (A/Citrate): Process A in citrate formulation
MSB11022 (A/Acetate):Process A in acetate formulation
MSB11022 (C/Acetate): Process C in acetate formulation

The formulation of MSB11022 (C/Acetate) is proposed to seek approval in the U.S.. Of note, MSB11022 (A/Citrate) was approved in the E.U. under the trade name Idacio. In addition to the changes mentioned above, a manufacturing process change in development of the drug substance was made in 2021 on the MSB11022 (C/Acetate) formulation after the completion of PK studies (FKS022-002 and FKS022-001). The Applicant provided comparative analytical assessment to support the bridging for MSB11022 (C/Acetate) used in the PK similarity studies and final to-be-marketed MSB11022 (C/Acetate) product. See Section 3 for assessment of the comparative analytical assessment.

The formulation MSB11022 (C/Acetate) was not evaluated in any comparative clinical studies. The Applicant submitted two comparative clinical studies in patients with psoriasis (Study EMR200588-003) and RA (Study MS200588-004) using MSB11022 (A/Citrate) and MSB11022 (A/Acetate), respectively. The comparator product that was used in both clinical studies was E.U.-Humira.

In order to support the bridging among different formulations, the Applicant conducted two three-way PK similarity studies in healthy subjects to compare MSB11022 (C/Acetate), MSB11022 (A/Citrate) (i.e., Idacio approved in Europe) and U.S.-Humira in Study FKS022-002, and MSB 11022 (A/Citrate), U.S.-Humira and E.U.-Humira in Study EMR200588-001.

In addition, the Applicant also submitted a PK study to bridge two dosage presentations [autoinjector (AI) vs. pre-filled syringe (PFS)] of MSB11022 (C/Acetate) (Study FKS022-001). The two PK similarity studies (Study FKS022-002 and EMR200588-001) only used PFS presentation.

As there was no direct PK similarity study performed to compare MSB11022 (A/Acetate) used in the RA study (Study MS200588-004) and to-be-marked formulation MSB11022 (C/Acetate) to support the bridging between these formulations, study MS200588-004 will not be reviewed. In summary, the following studies will be included in this review:

1. Study FKS022-002: a PK similarity study to compare PK, safety, tolerability and immunogenicity of MSB11022 (C/Acetate), U.S.-Humira, and MSB11022 (A/Citrate) (i.e., E.U.-Idacio) in healthy subjects
2. Study EMR200588-001: a PK similarity study to compare PK, safety, tolerability and immunogenicity of MSB11022 (A/Citrate), U.S.-Humira and E.U.-Humira
3. Study EMR200588-002: a comparative clinical study in adult patients with psoriasis to compare efficacy, safety and immunogenicity of MSB11022 (A/Citrate) and E.U-Humira as well as a single transition from E.U.-Humira to MSB11022 (A/Citrate).
4. Study FKS022-001: a PK study to compare the PK of two presentations (autoinjector and pre-filled syringe) for MSB11022 (C/Acetate)

The results of the PK similarity study (Study FKS022-002) demonstrated PK similarity among to-be-marketed formulation MSB11022 (C/Acetate), U.S.-Humira and MSB11022 (A/Citrate). The data established the PK component of a bridge to support the relevance of comparative data collected using MSB11022 (A/Citrate). In this study, the 90% confidence interval (CI) for the least square (LS) geometric means ratios (GMRs) for area under the serum concentration-time curve (AUC) from time 0 to infinity (AUC_{inf}) and AUC from time 0 to last sampling time (AUC_{last}) were contained within the pre-defined criteria of 80 to 125% (Table 6).

Table 6. Summary of statistical analyses for assessment of PK similarity (Study FKS022-002)

Parameter	LS Geometric Mean (n)			LS GMR[a] (90% CI)		
	MSB11022 (C/Acetate)	U.S.-Humira	MSB11022 (A/Citrate)	MSB11022 (C/Acetate) vs U.S.-Humira	MSB11022 (C/Acetate) vs MSB11022 (A/Citrate)	MSB11022 (A/Citrate) vs U.S.- Humira
$AUC_{0\text{-}inf}$ (ng*h/mL)	2193260.1 (138)	2226078.7 (139)	2287121.2 (137)	98.53 (89.96, 107.90)	95.90 (87.53 , 105.06)	102.74 (93.80, 112.54)
AUC_{last} (ng*h/mL)	1786469 (148)	1730045.4 (152)	1844398.8 (150)	103.26 (92.51, 115.27)	96.86 (86.74, 108.16)	106.61 (95.54, 118.96)
C_{max} (ng/mL)	3154.93 (149)	3078.16 (152)	3285.47 (150)	102.49 (94.43, 111.24)	96.03 (88.45, 104.25)	106.73 (98.37,115.81)

Source: Reviewer's analysis based on ADPC.xpt for Study FKS022-002. Only Subject (b) (6) treated with MSB11022 C/Acetate with a predose concentration > 5% of C_{max} was excluded from the analysis
[a] Presented as percent.

The results of the PK similarity study (Study EMR200588-001) demonstrated PK similarity among MSB11022 (A/Citrate), U.S.-Humira and E.U.-Humira. The data established PK component of scientific bridge to support the relevance of comparative data using E.U.-Humira to the assessment of biosimilarity. In this study, the 90% CI for the LS GMRs for AUC_{inf} and AUC_{last} were contained within the pre-defined criteria of 80 to 125% (Table 7) .

Table 7Summary of statistical analyses for assessment of PK similarity (Study EMR200588-001)

Parameter	LS Geometric Mean (n)			LS GMR[a] (90% CI)		
	MSB11022 (A/Citrate)	U.S.-Humira	E.U.-Humira	MSB11022 (A/Citrate) vs U.S.- Humira	MSB11022 (A/Citrate) vs E.U.-Humira	E.U.-Humira vs U.S.-Humira
$AUC_{0\text{-}inf}$ (ng*h/mL)	2299560.9 (76)	2536528 (75)	2581285.5 (77)	90.66 (81.5, 100.81)	89.08 (80.17, 98.99)	101.76 (91.55, 113.12)
AUC_{last} (ng*h/mL)	2006634.1 (78)	2030998.1 (80)	2190799.3 (79)	98.80 (87.40, 111.69)	91.59 (81.00, 103.58)	107.87 (95.46, 121.89)
C_{max} (ng/mL)	3434.70 (78)	3511.16 (80)	3601.14 (79)	97.82 (89.83, 106.53)	95.38 (87.56, 103.89)	102.56 (94.21, 111.66)

Source: Reviewer's analysis based on ADPC.xpt for Study EMR200588-001. Subject (b) (6) treated with U.S.-Humira who were excluded from Applicant's analysis included in the reviewer's analysis. This subject withdrew consent during the study but have PK samples collected until Day 9.
[a] Presented as percent.

The immunogenicity of to-be-marketed formulation MSB11022 (C/Acetate) was comparable to that of U.S-Humira and to that of MSB11022 (A/Citrate) after a single dose in healthy subjects. The immunogenicity of MSB11022 (A/Citrate) was comparable to that of U.S.-Humira after a single dose in healthy subjects. The immunogenicity of MSB11022 (A/Citrate) was also comparable to that of E.U.-Humira after a single dose in healthy subjects and after multiple doses in patients with psoriasis. Also, in patients with

psoriasis, the immunogenicity after a single transition from E.U.-Humira to MSB11022 (A/Citrate) was comparable to patients who did not undergo a single transition.

The immunogenicity of MSB11022 (C/Acetate) was not evaluated following multiple doses. As the immunogenicity of MSB11022 (C/Acetate) and MSB11022 (A/Citrate) was comparable after a single dose in healthy subjects with high incidence rates (>90% for ADA positive and >80% for NAb positive) observed for both formulations (Study FKS022-002). It is reasonable to believe that the immunogenicity of MSB11022 (C/Acetate) following multiple doses is expected to be similar to that of MSB11022 (A/Citrate).

The OSIS inspection was requested for both analytical sites and clinical sites for the two PK similarity studies (FKS022-002 and EMR200588-001). Refer to Section 3.3 above for details.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

PK similarity was demonstrated through a 3-way comparison among MSB11022 (C/Acetate), U.S.-Humira, and MSB11022 (A/Citrate) in Study FKS022-002 as well as through the 3-way comparison among MSB11022 (A/Citrate), U.S-Humira and E.U.-Humira in Study EMR200588-001. There was no clinical pharmacology residual uncertainty regarding the PK or immunogenicity assessment to support a demonstration of biosimilarity.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

The comparative clinical study (Study EMR200588-002) that evaluated the efficacy and safety in patients with psoriasis was conducted using MSB11022 (A/Citrate) and E.U.-Humira, a non-U.S.-Licensed comparator product.

Study FKS022-022 adequately demonstrated the PK similarity among the to-be-marketed formulation MSB11022 (C/Acetate), U.S.-Humira and MSB11022 (A/Citrate), supporting the PK component of the bridge to use MSB11022(A/Citrate) in the comparative clinical study (EMR200588-002).

Study EMR200588-001 adequately demonstrated the PK similarity among MSB11022 (A/Citrate), U.S.-Humira and E.U-Humira, supporting the PK component of the scientific bridge to use E.U.-Humira in the comparative clinical study (EMR200588-002) to assess similarity.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

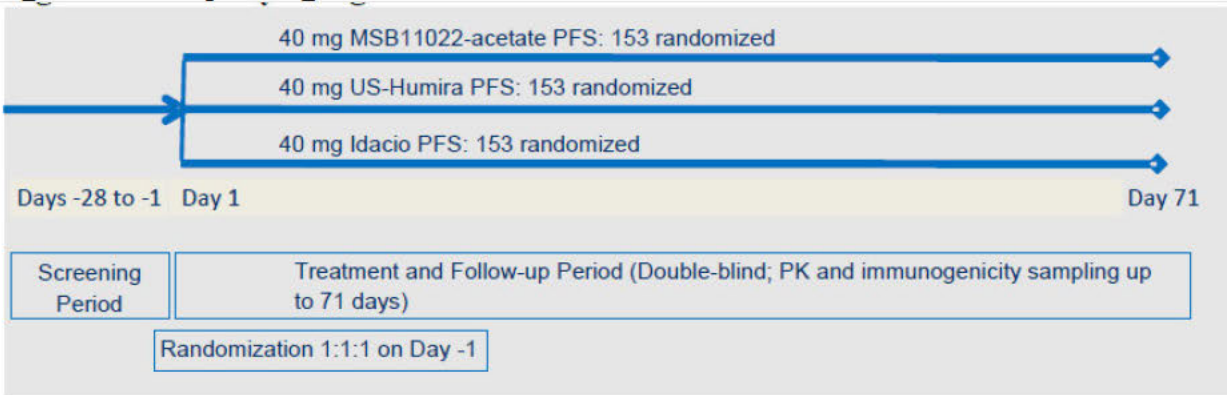
5.3.1. Study FKS022-002: "A randomized, double-blind, parallel group, single dose study to compare the pharmacokinetics, safety, tolerability and immunogenicity of MSB11022 (acetate formulation) versus US-licensed reference product Humira and Idacio in healthy subjects"

Clinical Pharmacology Study Design Features

The PK similarity study comparing MSB11022 (C/Acetate), U.S.-Humira, and MSB11022 (A/Citrate) (i.e., Idacio approved in E.U.) was conducted in healthy subjects (Figure 1). The study was conducted at MTZ Clinical Research Sp. z.o.o (Poland: Warsaw and Plonsk locations) between Nov. 20, 2019 and December, 30, 2020.

A total of 459 healthy subjects were randomized (153 in each treatment group) and 452 subjects received a single dose [150 in MSB11022 (C/Acetate), 152 in U.S.-Humira and 150 in MSB11022 (A/Citrate)]. Healthy subjects received a single dose of either MSB11022 (C/Acetate) 40 mg (PFS), U.S.-Humira 40 mg (PFS) or MSB11022 40 mg (A/Citrate) (PFS) via subcutaneous injection. Serum PK samples were collected on PK: Day 1 at 0 (pre-dose), 4, 8, 12 hours post-dose and Day 2, 3, 4, 5, 6, 7, 8, 9, 11, 15, 22, 29, 36, 43, 57 and 71.

Figure 1. Study Design of FKS022-002



Source: CSR FKS022-002, Figure 1, page 25.

Clinical Pharmacology Study Endpoints

In Study FKS022-002, the primary PK endpoints were maximum concentration (C_{max}), AUC_{inf} and AUC_{last}. A margin of 80% to 125% for the 90% CI of LS GMRs of primary PK endpoints was pre-defined to assess the similarity of PK profiles.

Bioanalytical PK Method and Performance

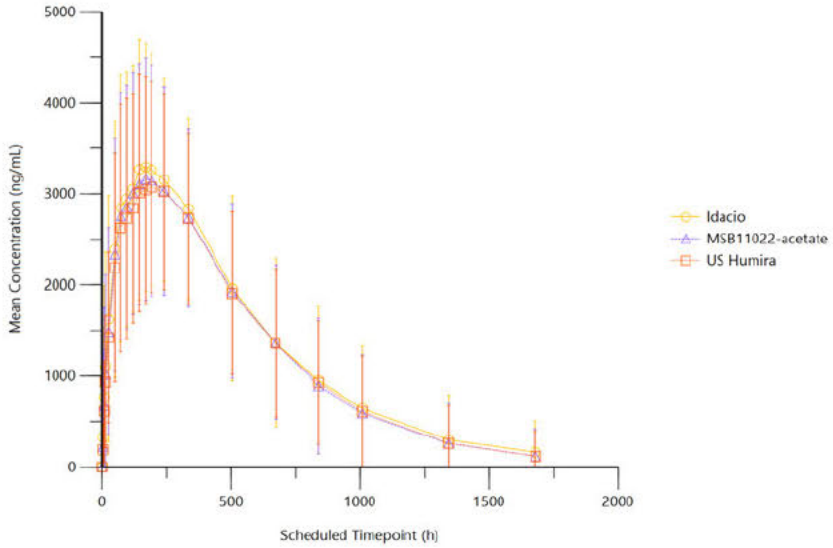
The methodology used in the analysis of biological samples was sensitive, robust and fully validated. Serum concentration of MSB11022 (A/Citrate), US-Humira and

MSB11022 (C/Acetate) were quantified using an enzyme-linked immunosorbent assay (ELISA) method. See Appendix 15.4.1 for further details on the bioanalytical method and performance in Study FKS022-002.

PK Similarity Assessment

In the PK similarity study (Study FKS022-002), the 90% CI for the GMRs for the maximum observed drug concentration (C_{max}), AUC_{inf} and AUC_{last} were contained within the prespecified criteria of 80% to 125% (Table 6). The serum concentration-time profile of the three products is shown below (Figure. 2).

Figure 2. Mean (SD) Serum Concentration-Time Profiles For MSB11022 (C/Acetate), U.S.-Humira and MSB 11022 (A/Citrate)



Source: Reviewer's analysis based on ADPC.xpt for Study FKS022-002.
Note: Idacio in this study refers to MSB11022 (A/Citrate) formulation; MSB 11022-acetate is MSB11022 (C/Acetate).

5.3.2. Study EMR200588-001: "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"

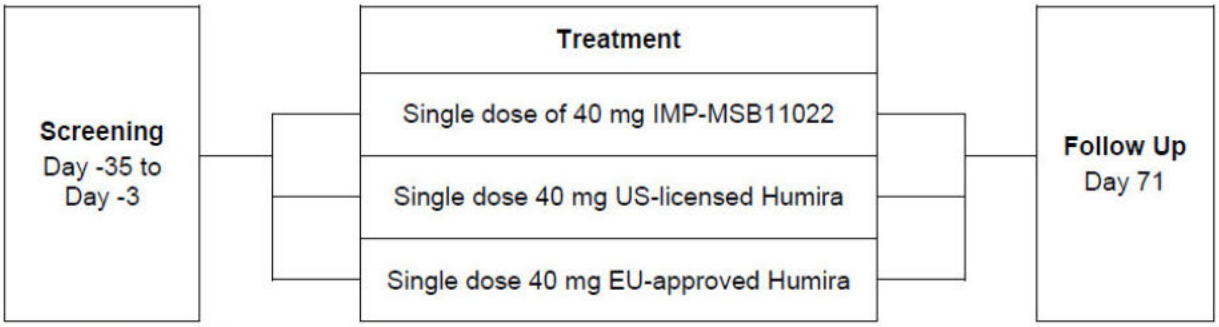
Clinical Pharmacology Study Design Features

The PK similarity study comparing MSB11022 (A/Citrate), U.S.-Humira, and E.U.-Humira was conducted in healthy subjects (Figure 3). The study was performed at 2 clinical sites in the U.K., Quintiles Drug Research Unit at Guy's Hospital and Hammersmith Medicines Research Ltd., between May 30, 2014 and Dec. 23, 2014. A total of 237 healthy subjects [78 in MSB11022 (A/Citrate), 80 in U.S.-Humira, and 79 in

E.U.-Humira] were randomized and all randomized subjects received a single dose of study drug.

Healthy subjects received a single dose of either MSB11022 (A/Citrate) 40 mg (PFS), U.S.-Humira 40 mg (PFS) or E.U-Humira (PFS) via subcutaneous injection. Serum PK samples were collected on PK: Day 1 at 0 (pre-dose), 4, 8, 12 hours post-dose and Day 2, 3, 4, 5, 6, 7, 8, 9, 11, 15, 22, 29, 36, 43, 57 and 71.

Figure 3. Study Design for Study EMR200588-001



IMP=investigational medicinal product.

Source: CSR Study EMR200588-001, Figure 1, page 22.

Clinical Pharmacology Study Endpoints

In Study EMR200588-001, the primary PK endpoints were C_{max}, AUC_{inf} and AUC_{last}. A margin of 80% to 125% for the 90% CI of LS GMRs of primary PK endpoints was pre-defined to assess the similarity of PK profiles.

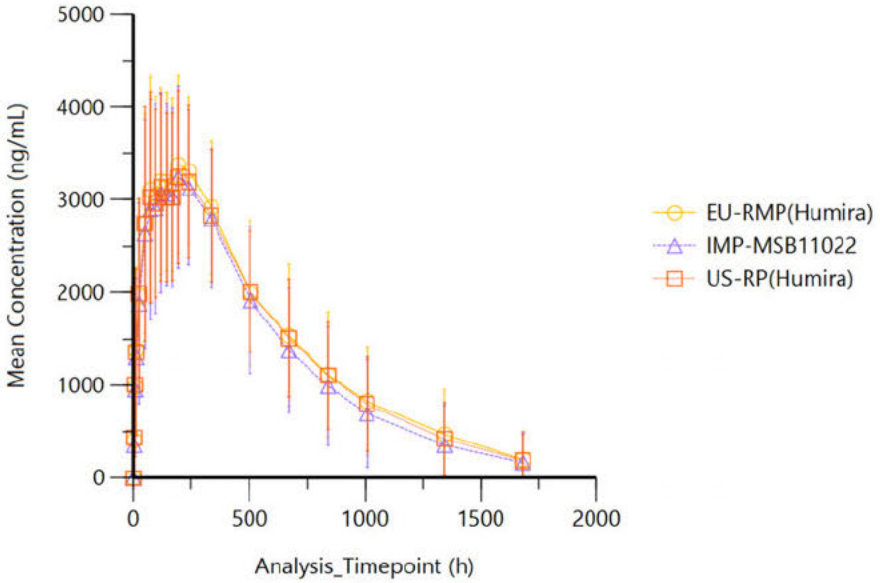
Bioanalytical PK Method and Performance

The methodology used in the analysis of biological samples was sensitive, robust, and fully validated. Serum concentrations of MSB11022 (A/Citrate), U.S.-Humira and E.U.-Humira were quantified using an enzyme-linked immunosorbent assay (ELISA). See Appendix 15.4.1 for further details on the bioanalytical method and performance in Study EMR200588-001.

PK Similarity Assessment

In the PK similarity study (Study EMR200588-001), the 90% CI for the GMRs for the C_{max}, AUC_{inf} and AUC_{last} were contained within the prespecified criteria of 80% to 125% (Table 7). The serum concentration-time profile of the three products is shown below (Figure. 4).

Figure 4. Mean (SD) Serum Concentration-Time Profiles For MSB11022 (A/Citrate), U.S.-Humira and E.U-Humira



Source: Reviewer's analysis based on ADPC.xpt for EMR200588-001.

The reviewer noted that 5 subjects in the study with ≥ 2 missing PK data. The number of missing PK data and reason for not having PK samples were listed in Table 8.

Table 8. Subjects With More Than One Missing PK Samples

Treatment Group	Subject	Number of Missing PK Samples	Reason based on ADPC.xpt and CSR Study EMR200588-001
U.S.- Humira	(b) (6)	8	Subject withdrew consent
		9	Subject did not visit
MSB11022(A/Citrate)		3	No sample received
E.U.-Humira		5	Sample not taken (subject did not visit)
		3	No sample received

Source: Reviewer's analysis based on ADPC.xpt for EMR200588-001

The reviewer conducted a sensitivity analysis excluding these subjects with multiple missing PK samples (≥ 2 missing samples) in the statistical analysis for PK similarity and the conclusion was not affected.

In addition, in the Applicant's dataset, it was noted that a total of 58 PK samples were labeled with technical issues including: centrifuge error (n=13), fridge time error (n=7), hemolyzed samples (n=14), re-assay value does not confirm original value (n=1), custom ID on tube recording different ID number (n=10), sample date updated to reflect current information from the central lab (n=13). Samples from 51 subjects were affected. One or two samples from each subject were affected. The reviewer conducted another sensitivity analysis excluding all problematic samples in the statistical analysis for PK similarity and the conclusion was not affected.

5.3.3. Study EMR200588-002: "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"

Clinical Pharmacology Study Design Features

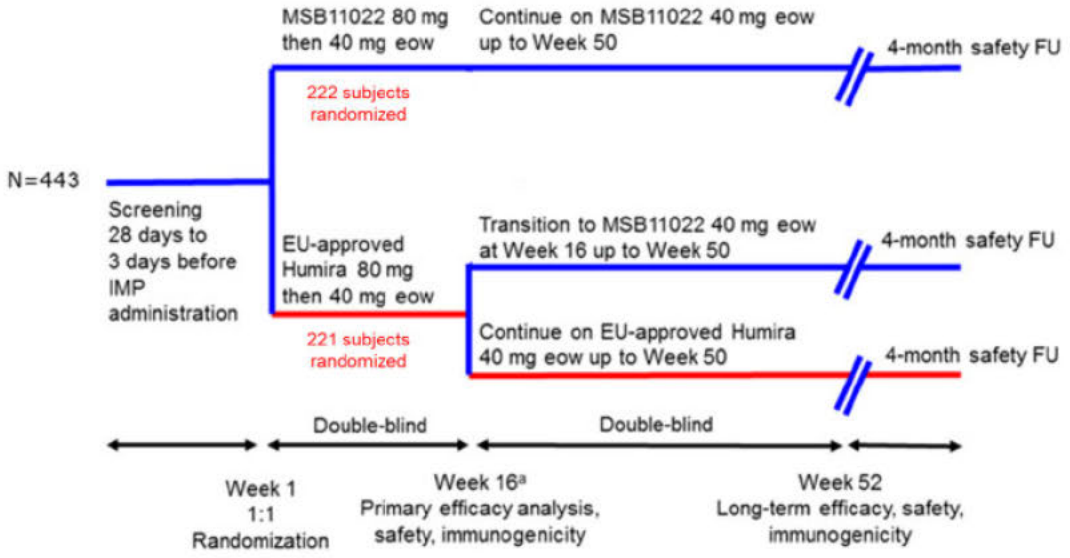
The comparative clinical safety and efficacy study compared MSB11022 (A/Citrate) 40 mg/0.8 mL and E.U.-Humira 40 mg/0.8 mL in patients with chronic plaque psoriasis. The study was performed in 76 sites in North America, South America, and Europe from 2016 to 2018. The primary efficacy endpoint in Study EMR200588-002 was the proportion of subjects with a PASI score reduction greater or equal to 75% from baseline (PASI 75) at Week 16 (Core Treatment Period). At Week 16, patients who achieved PASI 50 entered a 37-week double-blind Extended Treatment Period, in which subjects who were initially randomized to E.U.-Humira were re-randomized to receive either E.U.-Humira or MSB11022 (A/Citrate), while patients who were initially randomized to MSB11022 remained in MSB11022 throughout the entire study (Figure 5). Serum PK samples were collected pre-dose and at Week 4, 8, 12, 16, 24, 32, 40, 52 and 54 prior to each study drug administration. Additional serum PK samples were collected at Week 2, 14, 15, 25 and 33 in a subset of patients (n=77 subjects planned per group).

A total of 443 patients were randomized [222 subjects in MSB11022 (A/Citrate) and 221 subjects in E.U.-Humira] in Core Treatment Period and 441 received at least one dose of study medication [221 in MSB11022 (A/Citrate) and 220 in E.U.-Humira]. A total of 432 patients who had at least one measurable post-dose concentration were included in the PK analysis set [217 in MSB11022 (A/Citrate) and 215 in E.U.-Humira].

A total of 416 patients were re-randomized during the Extended Treatment Period [214 in MSB11022 (A/Citrate), 101 in E.U.-Humira and 101 E.U.-Humira/MSB11022 (A/Citrate)]. A total of 415 patients received at least one study medication [213 in

MSB11022 (A/Citrate), 101 in E.U.-Humira and 101 E.U.-Humira/MSB11022 (A/Citrate)]. A total 377 patients who had at least one measurable post-dose concentration in the Extended Treatment Period were included in the PK analysis set [198 in MSB11022 (A/Citrate), 87 in E.U.-Humira ad 92 E.U.-Humira/MSB11022].

Figure 5. Study Design for Study EMR200588-002



Source: CSR Study 200588-002, Figure 1

Clinical Pharmacology Study Endpoints

Trough concentrations from Week 4 to Week 54 were assessed in the study.

Bioanalytical PK Method and Performance

The methodology used in the analysis of biological samples was sensitive, robust, and fully validated. Serum concentrations of MSB11022 (A/Citrate) and E.U.-Humira were quantified using an enzyme-linked immunosorbent assay (ELISA). See Appendix 15.4.1 for further details on the bioanalytical method and performance in Study EMR200588-002.

PK Similarity Assessment

The trough concentrations were similar between MSB11022 (A/Citrate) and E.U.-Humira during the Core Treatment Period (16 weeks). After transition from E.U.-Humira to MSB11022 (A/Citrate), the trough concentrations for patients who underwent a single transition were similar to patients who remained in either MSB11022 (A/Citrate) or E.U.-Humira during Extended Treatment Period (Table 9, Figure 6 and Figure 7).

Table 9. Mean Trough Concentrations By Treatment and By Week

	MSB11022		EU-Humira		EU-Humira/MSB11022	
Week	**N**	**Concentration (ng/mL), mean (SD)**	**N**	**Concentration (ng/mL), mean (SD)**	**N**	**Concentration (ng/mL), mean (SD)**
Core Treatment Period						
1[a,b]	216	BLQ	214	BLQ	NA	NA
2[c,d,e]	66	6610 (2123)	69	6280 (2253)	NA	NA
4	189	7120 (3080)	192	7010 (2517)	NA	NA
8	188	7010 (3829)	184	6730 (3502)	NA	NA
12	190	6920 (4028)	181	6610 (3629)	NA	NA
14[c]	58	6690 (4041)	61	5910 (3670)	NA	NA
15[c,e]	65	7950 (4409)	62	7630 (4250)	NA	NA
16	192	6990 (4504)	170	6410 (4152)	NA	NA
Extended Treatment Period						
24	184	6240 (4569)	86	5870 (4516)	85	6430 (4610)
25[c,e]	67	7990 (5410)	28	6380 (4797)	25	7480 (5098)
32	182	6660 (5038)	82	6320 (4564)	81	6350 (4838)
33[c,e]	61	7980 (5724)	27	6970 (5281)	26	7850 (4772)
40	179	6630 (5308)	78	5750 (4472)	80	6310 (4751)
52	161	6910 (5750)	76	5930 (4529)	72	6600 (5394)
ET	15	4370 (4658)	15	4780 (4445)	5	822 (1399)
FU	189	3980 (3766)	96	3440 (3253)	86	3670 (3460)

Source: Refer to Module 5 Section 5.3.5.1 Study Report EMR200588-002 Table 15.3.8.1 and Table 15.3.8.2.

BLQ = below the limit of quantitation, ET = End of Treatment, FU = Follow-up collected 4 weeks after last dose of investigational product, NA = not applicable.

[a] Week 1/Day 1 predose sample.

[b] 80 mg adalimumab dose.

[c] Population-PK only subset sample.

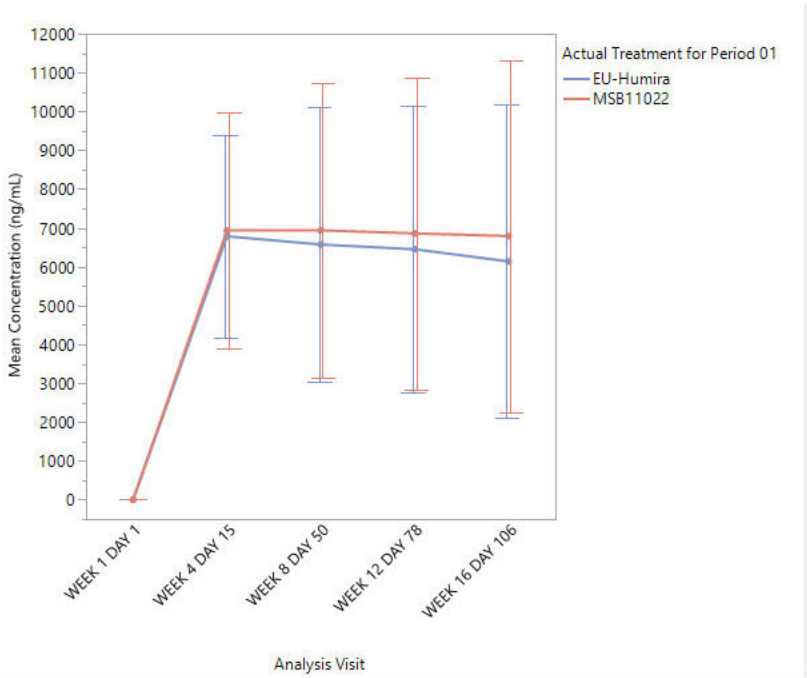
[d] Start of 40 mg every other week dosing.

[e] 1-week postdose sample.

BLQ concentrations (< 300 ng/mL) were set to zero for descriptive statistics. All visits subsequent to the Week 1 predose sample allowed for a visit window of ± 2 days. Even week visit samples subsequent to Week 2 correspond to predose/trough concentrations. Samples were excluded from descriptive statistics due to the following reasons: scheduled trough samples collected after dose; sample out of window from previous dose (± 2 days); unscheduled; PK sample excluded from analysis due to protocol deviation.

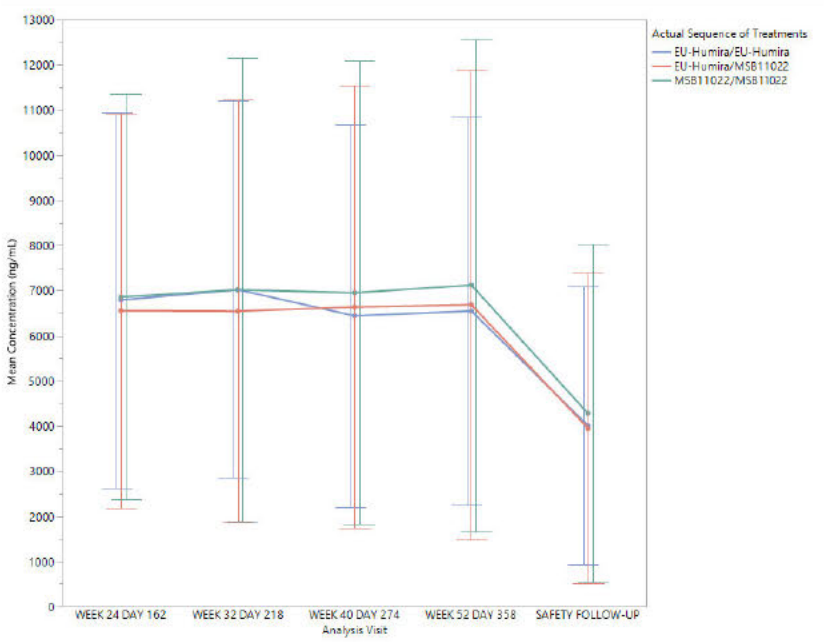
Source: Module 2.7.2 Summary Clinical Pharmacology Studies, Table 8, page 28

Figure 6. Mean (SD) Trough Concentrations By Treatment In Core Treatment Period (Week 1 to 16)



Source: Reviewer's analysis based on ADPC.xpt for Study EMR200588-002. Red: E.U.-Humira; Blue: MSB11022 (A/Citrate).
Note: Samples that were excluded by the Applicant were included in this analysis. PK sampling timepoints for the population PK subset (i.e., Week 2, 14, and 15) were not included in the graph.

Figure 7. Mean (SD) Concentrations By Treatment In Extended Treatment Period (Week 24 to Week 52)



Source: Reviewer's analysis based on ADPC.xpt for Study EMR200588-002. Blue: E.U.-Humira/E.U.-Humira; Red: E.U.-Humira/MSB11022 (A/Citrate); Green: MSB11022 (A/Citrate)/ MSB11022 (A/Citrate). Note: Samples that were excluded by the Applicant were included in this analysis. PK sampling timepoints for the population PK subset (i.e., Week 25 and 33) were not included in the graph.

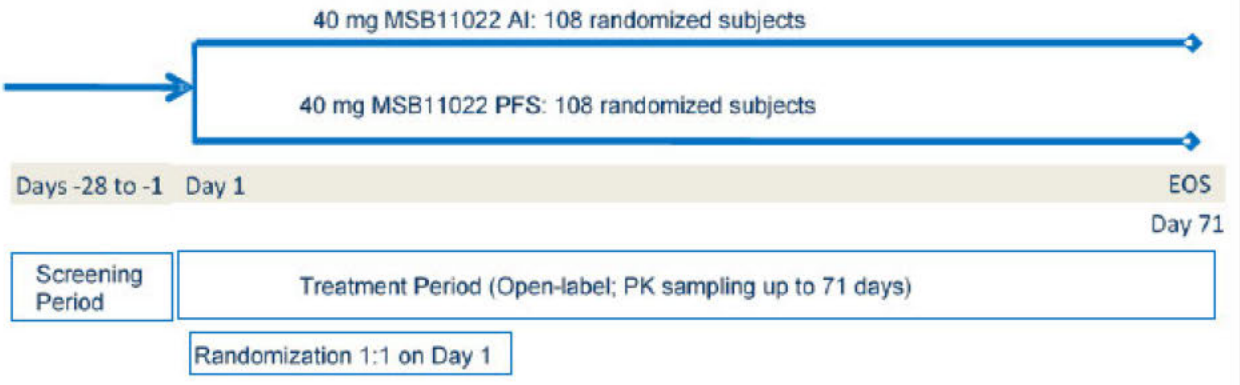
5.3.4. Study FKS022-001: "Phase I, randomized, open-label, parallel-group study to determine the pharmacokinetics, safety, and tolerability of msb11022 (proposed adalimumab biosimilar) following a single subcutaneous injection by an auto-injector or by a pre-filled syringe in healthy subjects"

Clinical Pharmacology Study Design Features

This study compared PK of two presentations of MSB11022 (C/Acetate) (i.e. AI vs. PFS) in healthy subjects (Figure 8). The study was performed in two clinical sites at PRA Health Sciences in the U.S. from July 15, 2019 to March 17, 2020. A total of 216 subjects were randomized (108 subjects in each group).

Healthy subjects were randomized in a 1:1 ratio to a single dose of either 40 mg/0.8 mL MSB11022 (C/Acetate) AI or 40 mg/0.8 mL MSB11022 (C/Acetate) PFS. Randomization was stratified by clinical site and weight categories (50 kg to ≤80 kg and >80 kg to ≤100 kg) assessed on Day -1. Randomization ensured balanced allocation of subjects between the 2 treatment groups for the baseline body weight and clinical sites factors, and ensured both injection sites (i.e., lower abdomen and thigh) were used equally for the 2 treatments. A total of 213 subjects (106 subjects from AI group and 107 subjects from PFS syringes) received the treatment. PK serum samples were taken on Day 1 (pre-does, 4, 8, 12 hours) and on Day 2 to 9, Day 11, 15, 22, 29, 36, 43, 57 and 71.

Figure 8. Study Design for Study FKS022-001



AI = auto-injector; EOS = end-of-study visit; PFS = prefilled syringe; PK = pharmacokinetic.

Source: CSR Study FKS022-001, Figure 1, page 24.

Clinical Pharmacology Study Endpoints

In Study FKS022-001, the primary PK endpoints were C_{max}, AUC_{inf} and AUC_{last}. A pre-specified margin of 80% to 125% for CI of LS GMRs was used to assess the similarity of PK profiles.

Bioanalytical PK Method and Performance

The methodology used in the analysis of biological samples was sensitive, robust and fully validated. Serum concentration of MSB11022 (C/Acetate) were quantified using an ELISA method. See Appendix 15.4.1 for further details on the bioanalytical method and performance in Study FKS022-001.

PK Similarity Assessment

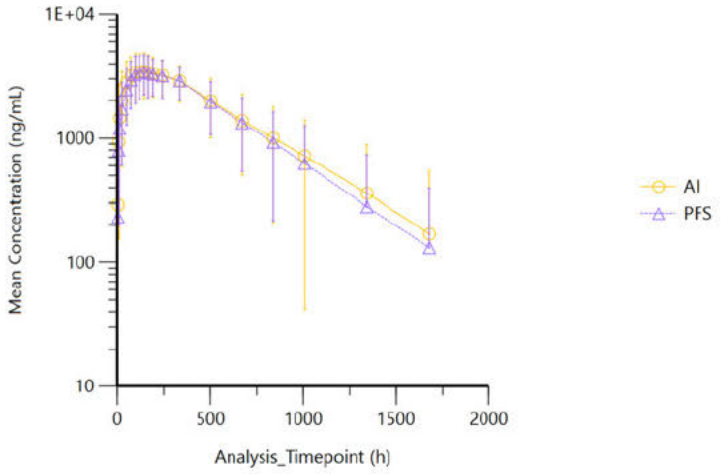
In Study FKS022-001, the 90% CI for GMR for the C_{max}, AUC_{inf} and AUC_{last} were contained within the prespecified criteria of 80% to 125% (Table 10). The serum concentration-time profile of the three products is shown below (Figure. 9).

Table 10. Summary of statistical analyses for assessment of PK similarity

	LS Geometric Mean (n)		LS GMR (90% CI)
	AI	PFS	AI vs. PFS
C_{max} (ng/mL)	3787.33 (103)	3610.02 (104)	104.91 (97.04-113.41)
AUC_{last} (h*ng/mL)	1997651.1 (103)	1902441.8 (104)	105.00 (93.19-118.32)
AUC_{inf} (h*ng/mL)	2486635.1 (96)	2286440 (102)	108.22 (97.58-120.02)

Source: Reviewer's analysis based on APDC.xpt for Study FKS022-001. Subjects who completed the study with a pre-dose concentration < 5% as well as subjects (b) (6) who discontinued from the study early were included in the analysis. Subject (b) (6) in AI who had all data BLQ and reported device failure were excluded from the analysis

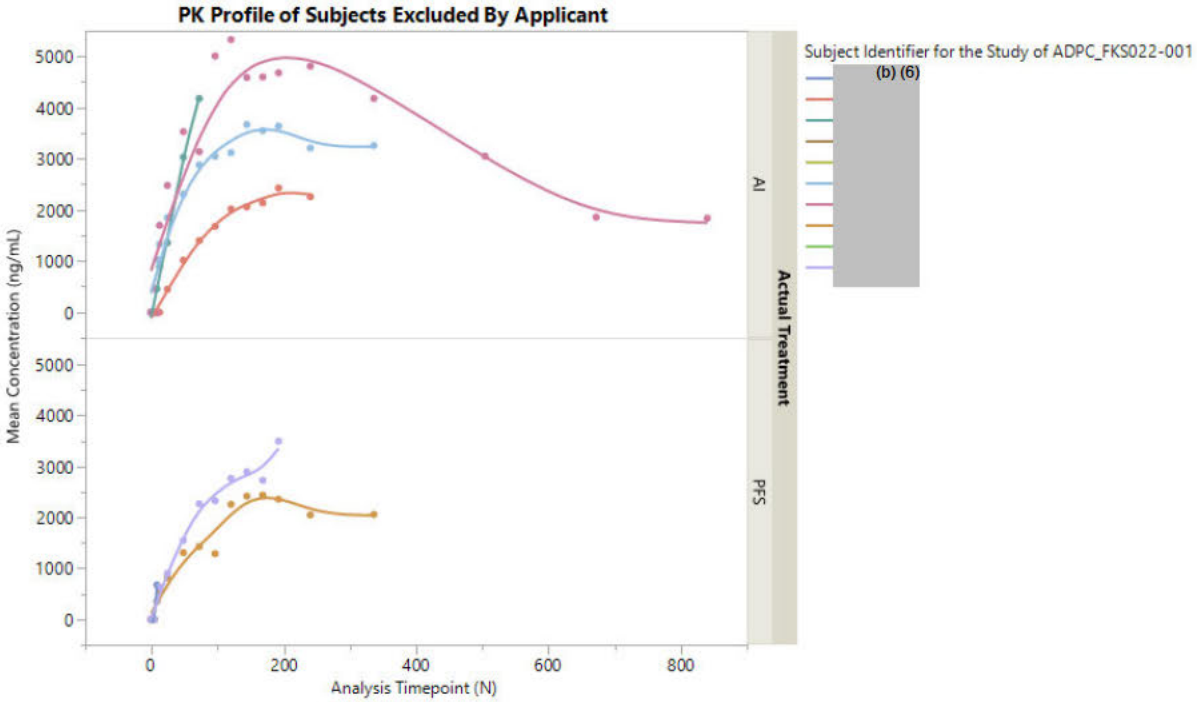
Figure 9. Mean (SD) Serum Concentration-Time Profiles For MSB11022 (C/Acetate) AI vs. PFS



Source: Reviewer's analysis based on APDC. xpt for Study FKS022-001. Subjects who completed the study with a pre-dose concentration < 5% as well as subjects (b) (6) who discontinued from the study early were included in the analysis. Subject (b) (6) in AI who had all data BLQ and reported device failure was excluded from the analysis.

The Applicant excluded 8 subjects from PK analysis based on *a prior* in a blinded fashion before data base lock. Among the 8 subjects, two of them did not receive any dose. In addition, data from another 4 subjects who discontinued from the study were not used to calculate AUC_{last} and AUC_{inf} in Applicant's analysis. The PK profile of 10 subjects who received a dose and had some PK data collected but were excluded by Applicant in PK similarity assessment is shown in Figure 10.

Figure 10. PK Profile For Subjects Excluded By Applicant

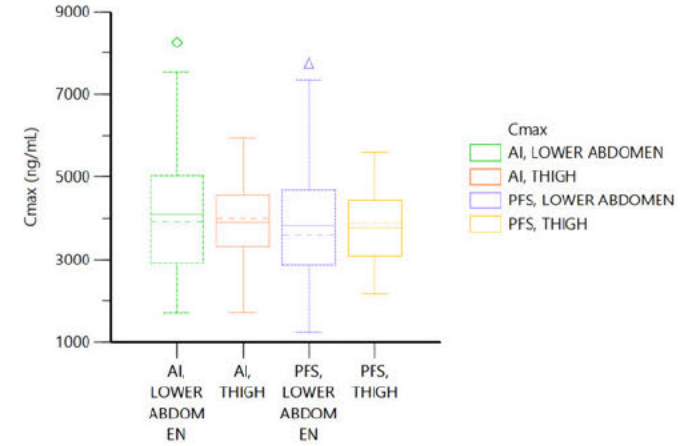


Source: Reviewer's analysis based on APDC. xpt for Study FKS022-001.

Based on the PK profile in Figure 10, subject (b) (6) (AI) had a well characterized terminal phase, while subjects (b) (6) (AI) and (b) (6) (PFS) captured C_{max} and had a few samples collected at the terminal phase. Therefore, these subjects were included in reviewer's analysis for PK similarity.

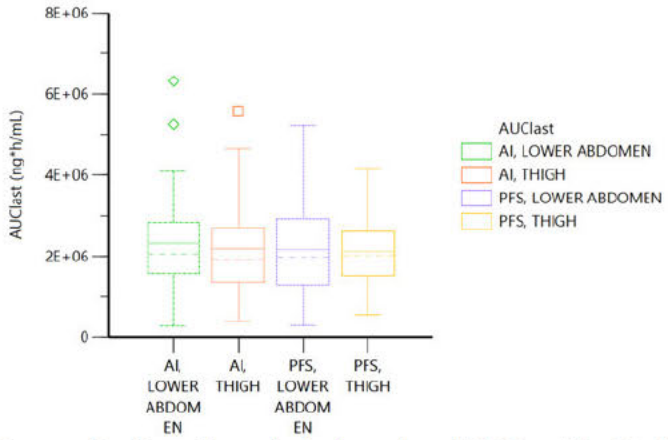
The effect of injection sites (lower abdomen vs. thigh) on PK was evaluated in the study; the PK was similar between two injection sites using either PFS and AI (Figure 11, 12, 13).

Figure 11. C_{max} By Injection Site and By Treatment



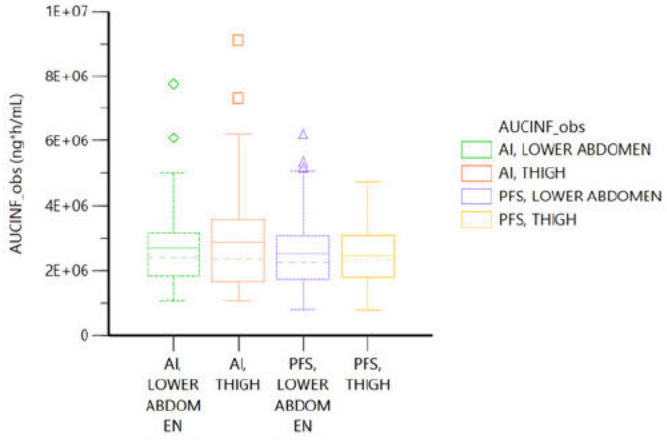
Source: Reviewer's analysis based on APDC.xpt for Study FKS022-001. Subjects who completed the study with a pre-dose concentration < 5% as well as subjects (b) (6) who discontinued from the study early were included in the analysis. Subject (b) (6) in AI who had all data BLQ and reported device failure was excluded from the analysis.

Figure 12. AUC_{last} By Injection Site and By Treatment



Source: Reviewer's analysis based on APDC.xpt for Study FKS022-001. Subjects who completed the study with a pre-dose concentration < 5% as well as subjects (b) (6) who discontinued from the study early were included in the analysis. Subject (b) (6) in AI who had all data BLQ and reported device failure were excluded from the analysis.

Figure 13. AUC_{inf} By Injection Site and By Treatment



Source: Reviewer's analysis based on APDC.xpt for Study FKS022-001. Subjects who completed the study with a pre-dose concentration < 5% as well as subjects (b) (6) who discontinued from the study early were included in the analysis. Subject (b) (6) in AI who had all data BLQ and reported device failure were excluded from the analysis.

5.4. Clinical Immunogenicity Studies

5.4.1. Clinical Immunogenicity Overview and Results

Design features of the clinical immunogenicity assessment

Immunogenicity of MSB11022 (C/Acetate) upon single dosing in healthy subjects has been evaluated in Study FKS022-002. Immunogenicity of MSB11022 (A/Citrate) upon single dosing in healthy subjects has been evaluated in both Study FKS022-002 and Study EMR200588-001. Immunogenicity of MSB11022 (A/Citrate) after repeat dosing in patients with plaque psoriasis has been evaluated in Study EMR20088-002. See Figures 1, 3 and 5 in Section 5.3 for details on the study design.

Immunogenicity endpoints

The formation of ADA and neutralizing activity of ADA were evaluated for immunogenicity assessment.

Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product, U.S.-licensed reference product, and non-U.S.-licensed comparator product (as applicable) in the study samples

The ADA assay was an electrochemiluminescence bridging immunoassay. The NAb assay was a competitive ligand-binding electrochemiluminescence assay. Refer to OBP

immunogenicity review for more details.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

The sampling plan is adequate to capture the baseline, early onset and dynamic prolife of ADA formation:

- Study FKS022-002: Serum ADA samples were collected at pre-dose and on Day 15, 29, 43 and 71
- Study EMR200588-001: Serum ADA samples were collected at pre-dose and on Day 15, 29, 43 and 71
- Study EMR200588-002: Serum ADA samples were collected at pre-dose and on Week 4, 8, 12, 16, 24, 32, 40, 52 (or early termination visit), and 4-week after last dose
- Study FKS022-001 did not assess immunogenicity.

Incidence of ADA (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

In Study FKS022-002, there was a similar incidence of pre-existing antibodies at baseline in MSB11022 (C/Acetate) (0.7% n=1/150), U.S.-Humira (1.3%, n=2/152) and MSB11022 (A/Citrate) (2%, n=3/150). Patients with pre-existing antibodies continued having positive ADA post-dose. Following a single dose of 40 mg subcutaneous injection of study drugs, 143/149 (96.0%), 144/151 (95.3%) and 139/150 (92.7%) subjects developed treatment-induced ADA at any time post-dose (Table 11).

Table 11. Immunogenicity results for binding ADA and NAb in Study FKS022-002.

	N	Anti-Drug antibody		
		Baseline [a]	Treatment-Induced [b]	Treatment-Emergent NAb [a]
MSB11022 (C/Acetate)	150	1/150 (0.7%)	143/149 [c] (96.0%)	133/149 [c] (89.3%)
U.S.-Humira	152	2/152 (1.3%)	144/151[c] (95.3%)	132/151 [c] (87.4%)
MSB11022 (A/Citrate)	150	3/150 (2%)	139/150 (92.7%)	128/150 (85.3%)

Source: [a] Adapted from CSR FKS022-002 Table 14.3.4.4.1; [b] Reviewer's analysis excluding 6 subjects with pre-existing positive ADA; [c] Subject (b) (6) [MSB11022 (C/Acetate)] and Subject (b) (6) (U.S.-Humira) discontinued early from the study on Day 2 with only ADA data from Day 1 available. Thus, they were excluded from total population.

In Study EMR200588-001, there was a similar incidence of pre-existing antibodies at baseline in MSB11022 (A/Citrate) (2.6%, n=2/78), U.S-Humira (6.3%, n=5/80) and E.U.-

Humira (0%, n=0/79), with a slightly higher rate observed in U.S.-Humira. Patients with pre-existing antibodies continued having positive ADA post-dose. Following a single dose of 40 mg of subcutaneous injection of study drugs, the treatment-induced ADA rate occurred at any-time post dose was 79.5% (n=62/78), 75% (n=60/80) and 83.5% (n=66/79) for MSB11022 (A/Citrate), U.S.-Humira and E.U-Humira, respectively (Table 12).

Table 12. Immunogenicity results for binding ADA and NAb in Study EMR200588-001

	N	Anti-Drug antibody		Treatment Emergent NAb [c]
		Baseline[a]	Treatment-Induced [b]	
MSB11022 (A/Citrate)	78	2/78 (2.6%)	62/78 (79.5%)	56/78 (71.8%)
U.S.-Humira	80	5/80 (6.3%)	60/80 (75%)	57/80 (71.3%)
E.U.-Humira	79	0 /79 (0%)	66/79 (83.5%)	54/79 (68.4%)

Source:[a] adapted from CSR Study EMR200588-001, Table 15.5.1; [b] reviewer's analysis excluding the 7 subjects with pre-existing ADA. [c] adapted from CSR Study EMR200588-001, Table 15.5.2.1, a total of 14, 15 and 13 subjects in MSB11022 (A/Citrate), U.S.-Humira and E.U.-Humira, respectively, did not have any NAb results.

In Study EMR200588-002, there was a similar incidence of pre-existing ADA at baseline in MSB11022 (A/Citrate) (1.8%, n=4/219) and E.U.-Humira (1.9%, n=4/215). The ADA incidence was similar between MSB11022 (A/Citrate) (88.1%, n=193/219) and E.U.-Humira (88.4%, n=190/215) during the Core Treatment Period throughout Week 16. After transition from E.U.-Humira to MSB11022 (A/Citrate) since Week 16, the ADA incidence was similar between patients who underwent a single transition (93.9%, n=93/99) and patients who continued being treated with either E.U.-Humira (93.9%, n=93/99) or MSB11022 (A/Citrate) (91.5%, n=195/213) (Table 13).

Table 13. Immunogenicity results for binding ADA and NAb in Study EMR200588-002.

	ADA Incidence			NAb Incidence	
	Baseline	Core Treatment Period [a]	Extended Treatment Period [b]	Core Treatment Period [a]	Extended Treatment Period [b]
MSB11022 /MSB11022	4/219 (1.8%)	193/219 (88.1%)	195/213 (91.5%)	90/219 (41.1%)	116/213 (54.5%)
E.U.-Humira	4/215 (1.9%)	190/215 (88.4%)	---	91/215 (42.3%)	---
E.U.-Humira /MSB11022	---	---	93/99 (93.9%)	---	61/99 (61.6%)
E.U.-Humira /E.U.-Humira	---	---	93/99 (93.9%)	---	52/99 (52.5%)

Source: adapted from CSR Study EMR200588-002, Table 40 and 41, page 154-155.
Note:
[a.] Over ADA and NAb Incidences in Core Treatment Period are based on number of patients who reported at least one positive ADA/ NAb value during Core Treatment Period over the total number of patients who reported ADA values during Core Treatment Period.
[b.] Overall ADA and NAb incidences in Extended Treatment Period are based on the number of patients who reported at least one positive ADA/ NAb value after Week 16 over the total number of patients who reported ADA values during Extended Treatment Period.

Incidence of NAb

In Study FKS022-002, the overall incidence of neutralizing antibodies (NAb) formation in healthy subjects following single dose was 89.3%, 87.4% and 85.3%, for MSB11022 (C/Acetate), U.S.-Humira, and MSB11022 (A/Citrate) respectively (Table 11).

In Study EMR200588-001, the overall incidence of NAb formation in healthy subjects following a single dose administration was 71.8%, 71.3% and 68.4%, for MSB11022 (A/Citrate), U.S-Humira, and E.U.-Humira, respectively (Table 12). It was noted that 14, 15 and 13 subjects in MSB11022 (A/Citrate), U.S.-Humira and E.U.-Humira, respectively, did not have any NAb results throughout the study. As the number of subjects with missing NAb values was similar among three treatment groups, the impact on assessing NAb incidence is minimal.

In Study EMR200588-002, the incidence of NAb formation was similar between MSB11022 (A/Citrate) and E.U.-Humira (41.1% and 42.3%, respectively) during the Core Treatment Period. In the Extended Treatment Period, the incidence of NAb formation was similar between patients who continued treatment with MSB11022 (A/Citrate) (54.5%) or E.U-Humira (52.5%) compared to patients who switched from E.U.-Humira to MSB11022 (61.6%) (Table 13).

5.4.2. Impact of ADA and Nab on the PK, PD, safety and clinical outcomes of the proposed product

Impact of ADA and NAb on PK

In Study FKS022-002, following a single dose, systemic exposure (AUC) for ADA positive patients was similar among treatment groups MSB11022 (C/Acetate), U.S.-Humira and MSB11022 (A/Citrate). A lower exposure was noted in ADA positive patients compared to ADA negative patients in all three treatment groups. The magnitude of AUC difference with respect to different ADA status was similar between MSB11022 (C/Acetate) and U.S.-Humira, while a slightly greater difference was noted with MSB11022 (A/Citrate), as the exposure for ADA negative subjects in MSB11022 (A/Citrate) was higher than subjects in other two treatment groups with same ADA status (Table 14). As the sample size for ADA negative patients was small (n= 5 to 8 for each group), the mean exposure data for ADA negative patients can be affected by outliers, which limits the interpretation of the exposure difference among three groups. Given that majority of subjects (>90%) in Study FKS022-002 were ADA positive in all three treatment groups and the exposure in ADA positive subjects were similar, the impact of ADA on PK is similar among three treatment groups.

Table 14. Summary of PK Parameters by Treatment and Overall ADA Status (Study FKS022-002)

	N	MSB11022 (C/Acetate)	N	U.S. Humira	N	MSB11022 (A/Citrate)
ADA Positive						
C_{max} (ng/mL)	143	3167.0 (45.9%)	146	3075.2 (44.6%)	142	3245.1 (46.3%)
T_{max} (h)	143	167.8 (4 to 504.1)	146	189.9 (48 to 456.3)	142	167.3 (4 to 505.1)
AUC_{last} (h*ng/mL)	143	1756932 (58.0%)	146	1743517 (56.9%)	142	1773299 (59.6%)
AUC_{inf} (h*ng/mL)	133	2148100 (47.7%)	134	2179092 (43.8%)	129	2187196 (48.6%)
$T_{1/2}$ (h)	133	258.3 (55.4%)	134	289.0 (52.6%)	129	262.9 (50.7%)
ADA Negative						
C_{max} (ng/mL)	5	2828.84 (34.4%)	5	3463.61 (20.2%)	8	4092.26 (29.4%)
T_{max} (h)	5	239.9 (72 to 501.9)	5	166.35 (72 to 239.5)	8	167.2 (8 to 335.1)
AUC_{last} (h*ng/mL)	5	2877889 (27.2%)	5	3100217 (24.6%)	8	3705952 (31.8%)
AUC_{inf} (h*ng/mL)	5	3814527 (23.0%)	5	3943150 (27.7%)	8	4700447 (35.8%)
$T_{1/2}$ (h)	5	780.5 (18.2%)	5	642.4 (26.1%)	8	686.9 (21.8%)

Source: reviewer's analysis based on ADPC.xpt and ADIS.xpt for Study FKS022-002. Geometric mean (CV%) was reported all PK parameters except T_{max} for which median and range were reported. Subject (b) (6) treated with MSB11022 C/Acetate with a predose concentration > 5% of C_{max} was excluded.

In Study FKS022-002, the AUC for NAb positive patients was also similar among three treatment groups. Lower exposures were also noted in NAb positive patients compare to NAb negative patients. The magnitude of AUC difference was similar across three treatment groups (Table 15).

Table 15. Summary of PK Parameters by Treatment and Overall NAb Status (Study FKS022-002)

	N	MSB11022 (C/Acetate)	N	U.S. Humira	N	MSB11022 (A/Citrate)
NAb Positive						
C_{max} (ng/mL)	132	3125.8 (45.6%)	132	3024.7 (45.6%)	128	3212.6 (46.6%)
T_{max} (h)	132	168.1 (4 to 504.1)	132	190.5 (72 to 504.3)	128	167.4 (4 to 505.1)
AUC_{last} (h*ng/mL)	132	1701707 (56.8%)	132	1655049 (56.0%)	132	1689097 (58.5%)
AUC_{inf} (h*ng/mL)	122	2082652 (45.3%)	120	2078730 (42.0%)	115	2085346 (46.2%)
$T_{1/2}$ (h)	122	244.2 (52.1%)	120	272.8 (51.3%)	115	245.9 (47.0%)
NAb Negative						
C_{max} (ng/mL)	16	3406.3 (47.0%)	19	3560.4 (27.6%)	22	3743.4 (38.9%)
T_{max} (h)	16	144 (72 to 501.9)	19	167.1 (48 to 503.6)	22	166.9 (8 to 502.5)
AUC_{last} (h*ng/mL)	16	2667838.5 (47.7%)	19	2912887.8 (29.9%)	22	3076877.4 (42.1%)
AUC_{inf} (h*ng/mL)	16	3254244.0 (50.2%)	19	3430736.9 (32.8%)	22	3706470.4 (47.4%)
$T_{1/2}$ (h)	16	559.8 (43.6%)	19	513.0 (30.2%)	22	529.2 (38.5%)

Source: Reviewer's analysis based on ADPC.xpt and ADIS.xpt for Study FKS022-002. Geometric mean (CV%) was reported all PK parameters except T_{max} for which median and range were reported. Subject (b) (6) treated with MSB11022 C/Acetate with a predose concentration > 5% of C_{max} was excluded.

In Study EMR200588-001, following a single dose, systemic exposure (AUC) for ADA positive patients was similar among treatment groups MSB11022 (A/Citrate), U.S.-Humira and E.U.-Humira. A lower exposure was noted in ADA positive patients compared to ADA negative patients in all three treatment groups. The magnitude of AUC difference was similar among these three groups (Table 16).

Table 16. Summary of PK Parameters by Treatment and ADA Status (Study EMR200588-001)

	N	MSB11022 (A/Citrate)	N	U.S. Humira	N	E.U. Humira
ADA Positive						
C_{max} (ng/mL)	64	3338.2 (38.5%)	65	3371.7 (32.1%)	66	3520.4 (31.3%)
T_{max} (h)	64	191.48 (24 to 502.9)	65	191.52 (48 to 339.90)	66	189.13 (48 to 336.60)
AUC_{last} (h*ng/mL)	64	1807070.0 (40.8%)	65	1903087.1 (53.8%)	66	1992034.9 (43.8%)
AUC_{inf} (h*ng/mL)	62	2037489.4 (38.9%)	61	2330670.9 (36.5%)	64	2331754.2 (38.9%)
$T_{1/2}$ (h)	62	254.21 (55.3%)	61	317.52 (46.7%)	64	314.44 (48.4%)
CL/F (L/h)	62	0.0196 (38.9%)	61	0.0172 (36.5%)	64	0.0172 (38.9%)
ADA Negative						
C_{max} (ng/mL)	14	3912.6 (21.9%)	14	4387.8 (26.4%)	13	4040.4 (21.6%)
T_{max} (h)	14	179.54 (96 to 506)	14	108.09 (48 to 241.8)	13	192 (72 to 503.8)
AUC_{last} (h*ng/mL)	14	3039940.9 (20.8%)	14	3025105.0 (14.6%)	13	3326201.4 (13.1%)
AUC_{inf} (h*ng/mL)	14	3716548.9 (25.7%)	14	3511374.7 (15.6%)	13	3997255.9 (15.7%)
$T_{1/2}$ (h)	14	575.07 (32.3%)	14	555.84 (23.5%)	13	579.31 (27.1%)
CL/F (L/h)	14	0.0108 (25.7%)	14	0.0114 (15.6%)	13	0.0100 (15.7%)

Source: Adapted from CSR EMR200588-001, Table 15.4.1.3. and 15.4.1.4. Geometric mean (CV%) was reported all PK parameters except T_{max} for which median and range were reported.

In Study EMR200588-001, the AUC for NAb positive patients was also similar among three treatment groups. Lower exposures were also noted in NAb positive patients compare to NAb negative patients. The magnitude of AUC difference was similar across three treatment groups (Table 17).

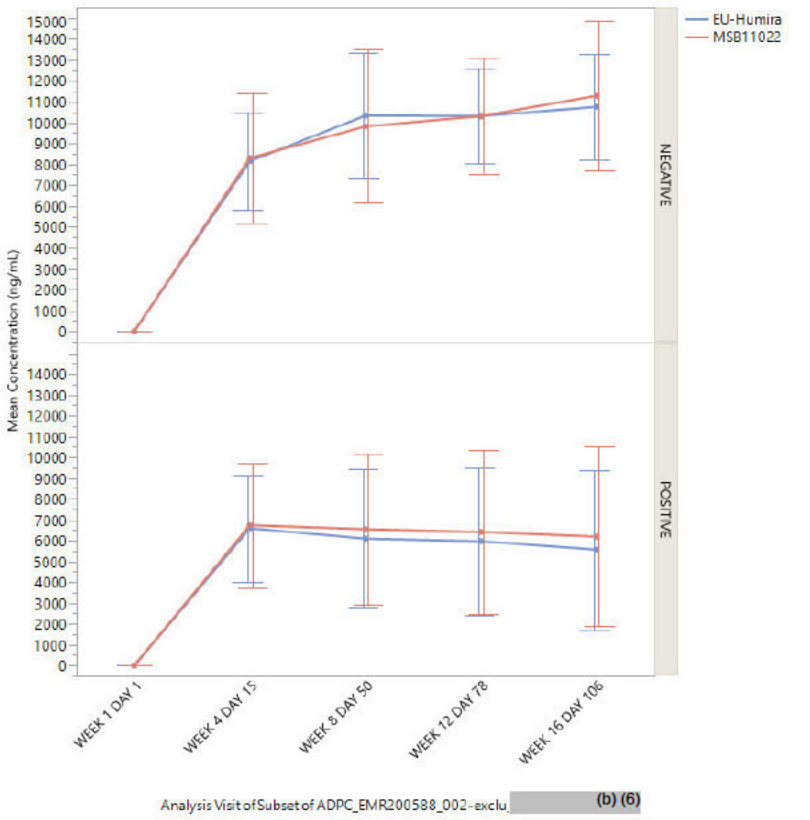
Table 17. Summary of PK Parameters by Treatment and NAb Status (Study EMR200588-001)

	N	MSB11022 (A/Citrate)	N	U.S. Humira	N	E.U. Humira
NAb Positive/ ADA Positive						
C_{max} (ng/mL)	56	3269.50 (39.7%)	57	3392.80 (30.8%)	54	3532.30 (32.7%)
T_{max} (h)	56	191.48 (24 to 502.9)	57	191.15 (48 to 339.9)	54	178.98 (48 to 336.6)
AUC_{last} (h*ng/mL)	56	1726799.0 (39.3%)	57	1823369.7 (53.8%)	54	1895134.4 (45.9%)
AUC_{inf} (h*ng/mL)	54	1949768.6 (37.1%)	53	2242879.3 (33.9%)	52	2225500.3 (40.3%)
$T_{1/2}$ (h)	54	237.46 (54.6%)	53	295.14 (43.3%)	52	288.62 (47.5%)
CL/F (L/h)	54	0.0205 (37.1%)	53	0.0178 (33.9%)		0.0180 (40.3%)
NAb Negative/ ADA Positive						
C_{max} (ng/mL)	8	3861.5 (26.6%)	8	3224.9 (42.7%)	12	3467.6 (25.6%)
T_{max} (h)	8	167.91 (72 to 335.9)	8	215.10 (120 to 336.4)	12	191.04 (72 to 241.6)
AUC_{last} (h*ng/mL)	8	2483746.1 (36.9)	8	2581482.7 (43.2%)	12	2493177.2 (22.5%)
AUC_{inf} (h*ng/mL)	8	2742227.0 (37.6%)	8	3005752.3 (44.2%)	12	2854006.4 (23.1%)
$T_{1/2}$ (h)	8	402.66 (27.8%)	8	515.27 (33.1%)	12	455.81 (28.1%)
CL/F (L/h)	8	0.0146 (37.6%)	8	0.0133 (44.2%)	12	0.0140 (23.1%)

Source: Adapted from CSR EMR200588-001, Table 15.4.1.5. and 15.4.1.6. Geometric mean (CV%) was reported all PK parameters except T_{max} for which median and range was reported.

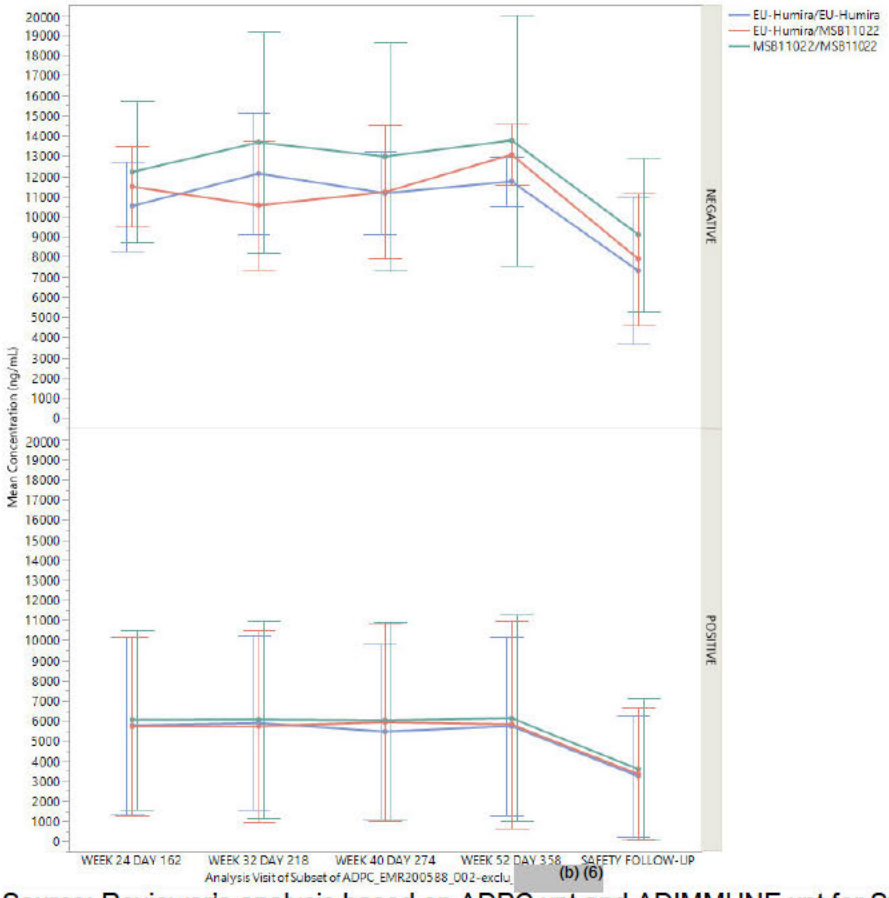
In Study EMR200588-002, the presence of ADAs was associated with decreasing mean trough concentration in both MSB11022 (A/Citrate) and E.U.-Humira. The magnitude of difference in trough concentration was similar between MSB11022 (A/Citrate) and E.U.-Humira in the Core Treatment Period (Figure 14). The magnitude was also similar in patients who switched from E.U.-Humira to MSB11022 (A/Citrate) during the Extended Treatment Period compared to those who continued with either E.U.-Humira or MSB11022 (Figure 15).

Figure 14. Mean (SD) Trough Concentrations By Treatment and ADA Status In Core Treatment Period (Study EMR200588-002)



Source: Reviewer's analysis based on ADPC.xpt for Study EMR200588-002. Subject (b) (6) whose pre-dose concentration was > 5% of C_{max} was excluded. ADA status was Core Treatment Period overall status. Top: ADA negative; Bottom: ADA positive. Red: MSB11022 (A/Citrate); Blue: E.U.-Humira.

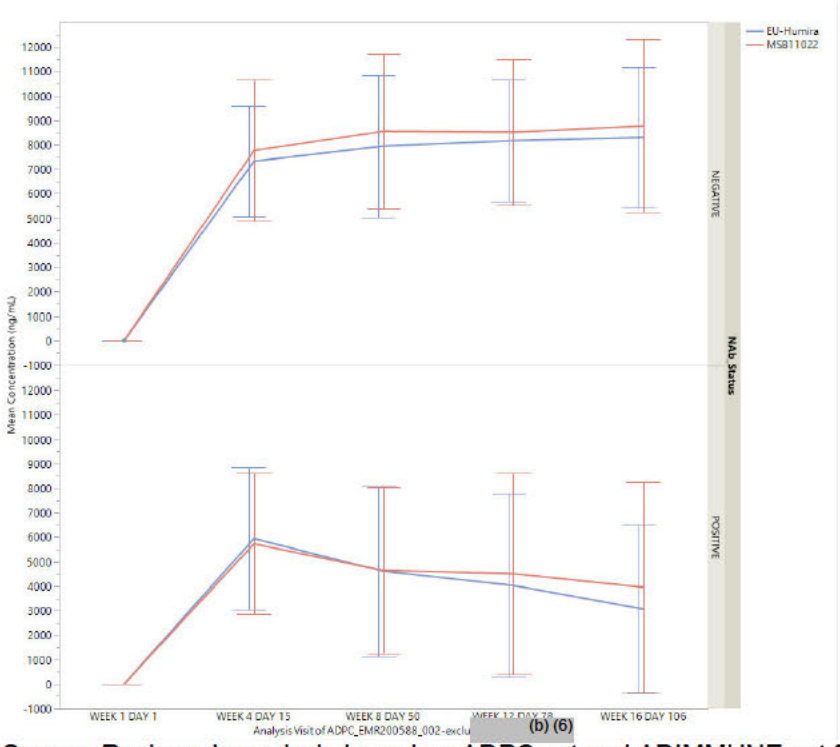
Figure 15. Mean (SD) Trough Concentrations By Treatment and ADA Status In Extended Treatment Period (Study EMR200588-002)



Source: Reviewer's analysis based on ADPC.xpt and ADIMMUNE.xpt for Study EMR200588-002. Subject (b) (6) whose pre-dose concentration was > 5% of C_{max} was excluded. ADA status was based on Extended Treatment Period overall status. Top: ADA negative; Bottom: ADA positive. Blue: E.U.-Humira/E.U.-Humira; Red: E.U.-Humira/MSB11022; Green: MSB11022/MSB11022

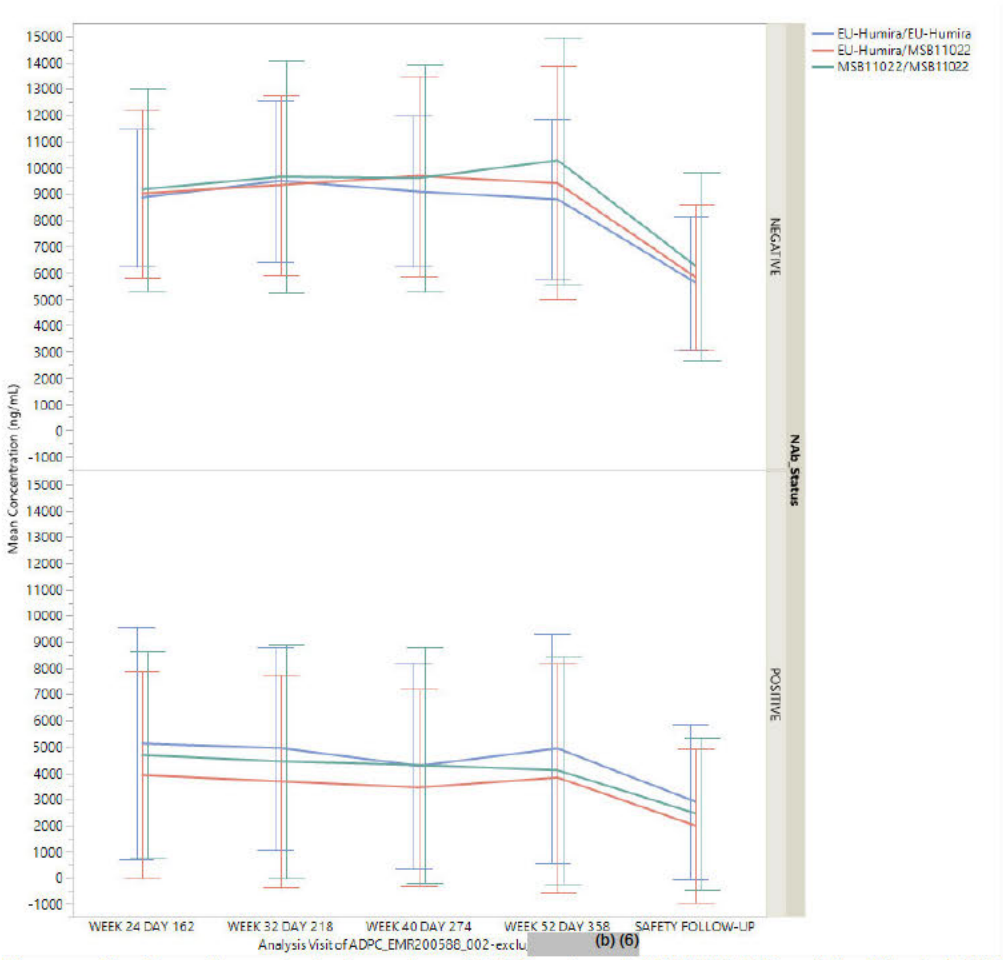
The presence of NAb also decreased the mean trough concentration. The magnitude of difference was similar between MSB11022 (A/Citrate) and E.U.-Humira during the Core Treatment Period (Figure 16). The magnitude of difference was also similar in patients who switched from E.U.-Humira to MSB11022 (A/Citrate) during the Extended Treatment Period compared to those who continued with either MSB11022 (A/Citrate) or E.U.-Humira (Figure 17).

Figure 16. Mean (SD) Trough Concentrations By Treatment and NAb Status In Core Treatment Period (Study EMR200588-002)



Source: Reviewer's analysis based on ADPC.xpt and ADIMMUNE.xpt for Study EMR200588-002. Subject (b) (6) whose pre-dose concentration was > 5% of C_{max} was excluded. NAb was based on Extended Treatment Period overall status. Patients who were ADA negative with no Nab value assessed were counted as NAb negative. Top: NAb negative; Bottom: NAb positive. Red: MSB11022 (A/Citrate); Blue: E.U.-Humira.

Figure 17. Mean (SD) Trough Concentrations By Treatment and NAb Status In Extended Treatment Period (Study EMR200588-002)



Source: Reviewer's analysis based on ADPC.xpt and ADIMMUNE.xpt for Study EMR200588-002. Subject (b) (6) whose pre-dose concentration was > 5% of C_{max} was excluded. NAb was based on Extended Treatment Period overall status. Patients who were ADA negative with no NAb value assessed were counted as NAb negative. Top: NAb negative; Bottom: NAb positive. Blue: E.U.-Humira/E.U.-Humira; Red: E.U.-Humira/MSB11022; Green: MSB11022/MSB11022

Impact of ADA and NAb on Efficacy

In Study EMR200588-002, the primary efficacy was PASI 75 at Week 16. Patients who were ADA positive had similar response rate compared to those who were ADA negative in both treatment groups during Core Treatment Period (Table 18). After switching from E.U.-Humira and MSB11022 during Extended Treatment Period, the efficacy was similar to other two treatments with the same ADA status (Table 19).

Table 18. Percent of Subjects Achieving PASI-75 at Week 2, 4, 8, 12 and 16 By ADA Status (Core Treatment Period) (Study EMR200588-002)

	ADA Negative		ADA Positive	
	E.U.-Humira (n=25)	MSB11022 (n=26)	E.U.-Humira (n=190)	MSB11022 (n=193)
Week 2	0/25 (0%) Miss: 0	0/25 (0%) Miss: 1	0/188 (0%) Miss: 2	3/193 (2%) Miss: 0
Week 4	4/25 (16%) Miss :0	2/26 (8%) Miss: 0	16/188 (9%) Miss: 2	19/190 (10%) Miss: 3
Week 8	14/23 (61%) Miss: 2	15/25 (60%) Miss: 1	95/184 (52%) Miss: 6	83/190 (44%) Miss: 3
Week 12	16/22 (73%) Miss: 3	20/24 (83%) Miss: 2	149/180 (83%) Miss: 10	139/190 (73%) Miss: 3
Week 16	21/22 (95%) Miss: 3	24/25 (96%) Miss: 1	163/180 (91%) Miss: 10	167/189 (88%) Miss: 4

Source: Reviewer's analysis based on ADQPSAI.xpt for Study EMR200588-002. A total of 434 patients from the Intent-To-Treat (ITT) population set with reported ADA data (219 in MSB11022 and 215 in E.U.-Humira) was included in the analysis. Only analysis values of "Y" for PASI 75 response was counted as a PASI 75 responder. Missing values were counted as missing and are subtracted from total patients at each Visit.

Table 19. Percent of Subjects Achieving PASI-75 at Week 24, 32, 40, 48 and 52 By ADA Status (Extended Treatment Period) (Study EMR200588-002)

	ADA Negative			ADA Positive		
	EU-Humira/EU-Humira (n=6)	EU-Humira /MSB11022 (n=6)	MSB11022 /MSB11022 (n=18)	EU-Humira /EU-Humira (n=93)	EU-Humira /MSB11022 (n=93)	MSB11022 /MSB11022 (n=195)
Week 24	5/6 (83.3%) Miss: 0	6/6 (100%) Miss: 0	18/18 (100%) Miss: 0	81/91 (89%) Miss: 2	86/91 (95%) Miss: 2	177/192 (92%) Miss: 3
Week 32	5/6 (83.3%) Miss: 0	6/6 (100%) Miss: 0	18/18 (100%) Miss: 0	78/86 (91%) Miss: 7	84/90 (93%) Miss: 3	172/186 (92%) Miss: 9
Week 40	5/6 (83.3%) Miss: 0	6/6 (100%) Miss: 0	18/18 (100%) Miss: 0	79/85 (93%) Miss: 8	80/87 (92%) Miss: 6	159/181 (88%) Miss: 14
Week 48	4/5 (80%) Miss: 1	6/6 (100%) Miss: 0	18/18 (100%) Miss: 0	79/85 (93%) Miss: 8	80/85 (94%) Miss: 8	162/178 (91%) Miss: 17
Week 52	4/4 (100%) Miss: 2	6/6 (100%) Miss: 0	18/18 (100%) Miss: 0	78/84 (93%) Miss: 9	80/86 (93%) Miss: 7	161/178 (90%) Miss: 17

Source: Reviewer's analysis based on ADQPSAI.xpt and ADIMMUNE.xpt for Study EMR200588-002. A total of 411 patients with ADA data during Extended Treatment Period were included in this analysis (213 in MSB11022/MSB11022, 99 each in EU-Humira/EU-Humira and EU-Humira/MSB11022). Only analysis values of "Y" for PASI 75 response was counted as a PASI 75 responder. Missing values were counted as missing and are subtracted from total patients at each Visit.

A decrease in efficacy was observed with NAb positive patients compared to NAb negative patients since Week 12 in both treatments during Core Treatment Period. However, the degree of decrease in efficacy was similar between two treatment groups (Table 20). With the same NAb status, the efficacy was similar between patients who switched from E.U.-Humira to MSB11022 and patients who continued with either E.U.-Humira or MSB11022 during the Extended Treatment Period (Table 20). A decrease in

efficacy was also noted with NAb positive patients compared to NAb negative patients in all three treatment groups. However, the degree of decrease in efficacy was similar (Table 21).

Table 20. Percent of Subjects Achieving PASI-75 at Week 2, 4, 8, 12 and 16 By NAb Status (Core Treatment Period) (Study EMR200588-002)

	NAb Negative		NAb Positive	
	E.U.-Humira (n=124)	MSB11022 (n=129)	E.U.-Humira (n=91)	MSB11022 (n=90)
Week 2	0/123 (0%) Miss: 1	2/128 (1.6%) Miss: 1	0/90 (0%) Miss: 1	1/90 (1.1%) Miss: 0
Week 4	13/123 (10.6%) Miss: 1	11/128 (8.6%) Miss: 1	7/90 (7.8%) Miss: 1	10/88 (11.4%) Miss: 2
Week 8	69/119 (58%) Miss: 5	64/127 (50.4%) Miss: 2	40/88 (45.5%) Miss: 3	34/88 (38.6%) Miss: 2
Week 12	102/118 (86.4%) Miss: 6	104/126 (82.5%) Miss: 3	63/84 (75%) Miss: 7	55/88 (62.5%) Miss: 2
Week 16	113/118 (95.8%) Miss: 6	118/126 (93.7%) Miss: 3	71/84 (84.5%) Miss: 7	73/88 (83%) Miss: 2

Source: Reviewer's analysis based on ADQPSAI.xpt and ADIMMUNE.xpt for Study EMR200588-002. A total of 434 patients from the Intent-To-Treat (ITT) population set with reported ADA data (219 in MSB11022 and 215 in E.U.-Humira) was included in the analysis. Only analysis values of "Y" for PASI 75 response was counted as a PASI 75 responder. Missing values were counted as missing and are subtracted from total patients at each Visit.

Table 21. Percent of Subjects Achieving PASI-75 at Week 24, 32, 40 and 52 By NAb Status (Extended Treatment Period) (Study EMR200588-002)

	NAb Negative			NAb Positive		
	E.U.-Humira/E.U.-Humira (n=38)	E.U.-Humira /MSB11022 (n=47)	MSB11022 /MSB11022 (n=97)	E.U.-Humira /E.U.-Humira (n=61)	E.U.-Humira /MSB11022 (n=52)	MSB11022 /MSB11022 (n=116)
Week 24	36/38 (95%) Miss: 0	46/47 (98%) Miss: 0	93/96 (97%) Miss: 1	50/59 (85%) Miss: 2	46/50 (92%) Miss: 2	102/114(89%) Miss: 2
Week 32	35/36 (97%) Miss: 2	46/46 (100%) Miss: 1	92/94 (98%) Miss: 3	48/56 (86%) Miss: 5	44/50 (88%) Miss: 2	98/110 (89%) Miss: 6
Week 40	35/36 (97%) Miss: 2	45/45 (100%) Miss: 2	89/92 (97%) Miss: 5	49/55 (89%) Miss: 6	41/48 (85%) Miss: 4	88/107 (82%) Miss: 9
Week 48	34/35 (97%) Miss:3	45/45 (100%) Miss: 2	88/91 (97%) Miss: 6	49/55 (89%) Miss: 6	41/46 (89%) Miss: 6	92/105 (88%) Miss: 11
Week 52	34/34 (100%) Miss: 4	45/45 (100%) Miss: 2	89/91 (98%) Miss: 6	48/54 (89%) Miss: 7	41/47 (87%) Miss: 5	90/105 (86%) Miss: 11

Source: Reviewer's analysis based on ADQPSAI.xpt for Study EMR200588-002. A total of 411 patients with ADA data during Extended Treatment Period were included in this analysis (213 in MSB11022/MSB11022, 99 each in E.U.-Humira/E.U.-Humira and E.U.-Humira/MSB11022). Only analysis values of "Y" for PASI 75 response was counted as a PASI 75 responder. Missing values were counted as missing and are subtracted from total patients at each Visit.

Impact of ADA and NAb on Safety

Safety was assessed following a single dose in FKS022-002 in healthy subjects. The incidence of treatment-emergent adverse events (TEAEs) was similar in ADA negative, ADA positive and NAb positive patients in MSB11022 (C/Acetate), U.S.-Humira and MSB11022 (A/Citrate) (Table22). Also, the incidence of general disorder and administration site reaction as well as skin and subcutaneous tissue disorder was low and similar in ADA-positive, ADA-negative and NAb-positive patients in three treatment groups (Table 22).

Table 22. TEAEs, Injection Site Reactions and Skin and Subcutaneous Tissue Disorder By ADA/NAb Status (Study FKS022-002)

	MSB11022 (C/Acetate)			**U.S.-Humira**			**MSB11022 (A/Citrate)**		
	ADA Positive N=144	ADA Negative N= 5	NAb Positive N= 133	ADA Positive N=146	ADA Negative N=5	NAb Positive N=132	ADA Positive N= 142	ADA Negative N= 8	NAb Positive N= 128
Any TEAE	93 (64.6%)	3 (60%)	87 (65.4%)	85 (58.2%)	3 (60.0%)	77 (58.3%)	85 (59.9%)	6 (75%)	79 (61.7%)
General disorder and administration site conditions	10 (6.9%)	0 (0%)	9 (6.8%)	9 (6.2%)	0 (0%)	9 (6.8%)	13 (9.2%)	0 (0%)	13 (10.2%)
Skin and subcutaneous tissue disorder	5 (3.5%)	0 (0%)	5 (3.8%)	5 (3.4%)	0 (0%)	5 (3.8%)	7 (4.9%)	0 (0%)	6 (4.7%)

Source: adapted from CSR FKS022-002 Table 14.3.1.9

Safety was assessed following multiple doses in EMR200588-002 in patients with psoriasis. The incidence of TEAEs was similar in ADA negative, ADA positive and NAb positive patients in MSB11022 (A/Citrate) and E.U.-Humira during Core Treatment Period (Table 23). The incidence of injection site reaction was low and similar between these two treatment groups during Core Treatment Period (Table 23). During the Extended Treatment Period, the incidences of TEAEs, injection site reaction and hypersensitivity in ADA negative, ADA positive and NAb positive patients were overall similar among treatment group that switched from E.U.-Humira to MSB11022 and the other two treatment groups that continued with either E.U.-Humira or MSB11022, with a slightly higher injection site reaction rate noted in ADA negative patients continuing treated with MSB11022 (A/Citrate) (Table 24). Overall, there is no evidence of impact of immunogenicity on safety observed in Study EMR200588-002.

Table 23. TEAEs, Hypersensitivity and Injection Site Reactions By ADA/NAb Status In Core Treatment Period (Study EMR200588-002)

	MSB11022 (A/Citrate)			E.U.-Humira		
	ADA Positive N=193	ADA Negative N=26	NAb Positive N=90	ADA Positive N=190	ADA Negative N=25	NAb Positive N=91
Any TEAE	100 (51.8%)	14 (53.8%)	49 (54.4%)	100 (52.6%)	16 (64%)	50 (54.9%)
Injection Site Reaction	22 (11.4%)	4 (15.4%)	7 (7.8%)	28 (14.7%)	2 (8%)	13 (14.3%)
Hypersensitivity	4 (2.1%)	1 (3.8%)	2 (2%)	5 (2.6%)	1 (4%)	2 (2%)

Source: adapted from CSR Study EMR200588-002, Table 15.3.6.26, 15.3.6.27, 15.3.6.32, 15.3.6.38, 15.3.6.39, 15.3.6.50, 15.3.6.51, 15.3.6.56, 15.3.6.68

Table 24. TEAEs, Hypersensitivity and Injection Site Reactions By ADA/NAb Status In Extended Treatment Period (Study EMR200588-002)

	MSB11022 (A/Citrate)			E.U.-Humira			E.U.-Humira/ MSB11022		
	ADA Positive N=195	ADA Negative N= 18	NAb Positive N= 116	ADA Positive N=93	ADA Negative N= 6	NAb Positive N= 61	ADA Positive N=93	ADA Negative N= 6	NAb Positive N= 52
Any TEAE	123 (63.1%)	16 (88.9%)	70 (60.3%)	60 (64.5%)	3 (50%)	38 (62.3%)	55 (59.1%)	4 (66.7%)	29 (58.8%)
Injection Site Reaction	18 (9.2%)	5 (27.8%)	10 (8.6%)	11 (11.8%)	0 (0%)	6 (9.8%)	13 (14%)	0 (0%)	7 (13.5%)
SMQ Hypersensitivity	3 (1.5%)	2 (11.1%)	2 (1.7%)	2 (2.2%)	0 (0%)	1 (1.6%)	1 (1.1%)	0 (0%)	1 (1.9%)

Source: adapted from CSR Study EMR200588-002, Table 15.3.6.28, 15.3.6.29, 15.3.6.34, 15.3.6.40, 15.3.6.41, 15.3.6.52, 15.3.6.53, 15.3.6.58, 15.3.6.70.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

Comparative Efficacy: The comparative efficacy of MSB11022 and EU-approved Humira (EU- Humira) was evaluated in Study EMR200588-002, a double-blind, randomized, multi-center, parallel-group, efficacy and safety study in subjects with moderate to severe chronic plaque psoriasis (PsO) during 52 weeks of treatment. Comparative efficacy was assessed for FDA's currently recommended primary endpoint, the percent improvement in PASI at Week 16 and the applicant's pre-specified primary endpoint, proportion of subjects achieving 75% improvement in PASI (PASI75) at Week 16. The 90% confidence interval (CI) for the treatment difference

based on the mean percent change from baseline in PASI at Week 16 for both the per-protocol (PP) Analysis Set and Intent-to-Treat (ITT) Analysis Set fall within the margins of ±10 [PP: (-0.87, 2.64), ITT: (-7.43, 0.33)]; Similarly, the 90% CI for the treatment difference based on the proportion of subjects with PASI 75 at Week 16 for both the PP and ITT Analysis Set fall within the prespecified margins of ±18 [PP: (-6.83, 3.06), ITT: (-2.89, 8.47)]. Thus, the study showed no meaningful differences between MSB11022 and EU-Humira regarding the primary efficacy endpoint.

Comparative Safety and Immunogenicity:
The comparative safety evaluation of MSB11022 reflected the known safety profile of US-Humira as described in the USPI and other published data. Given that the applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated with EU-Humira as the comparator, the submitted safety and immunogenicity data from Study EMR200588-002 in subjects with moderate to severe psoriasis supported by the data from the single-dose PK studies, EMR200588-001, FKS022-002, are adequate to support the demonstration of no clinically meaningful differences in safety and immunogenicity between MSB11022 and US-Humira. Study FKS022-001 provides support for PK comparability between the PFS and AI presentations for MSB11022 (C/Acetate).

The safety database submitted for MSB11022 includes a total of 1011 subjects who received at least one dose of study drug (689 healthy subjects and 322 subjects with psoriasis) and is adequate to provide a reliable descriptive comparison between the products. The safety risks identified are consistent with the known adverse event profile of US-Humira. There were no notable differences between MSB1102 and EU-Humira in treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, adverse events leading to discontinuation, or development of anti-drug antibodies (ADA) between the treatment groups in Study EMR200588-002. In addition, a single transition of non-treatment naïve patients to the proposed biosimilar, i.e., patients previously treated with EU-Humira to MSB1102, did not result in an increase in immunogenicity or clinically significant adverse reactions.

Overall, the collective evidence from the comparative clinical study supports a demonstration of no clinically meaningful differences between MSB1102 and US-Humira, as the Applicant provided adequate data to establish the scientific bridge between MSB1102, US-Humira, and EU-Humira to justify the relevance of data generated with EU-Humira as the comparator to the assessment of biosimilarity.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual clinical or statistical uncertainties that impact a demonstration of no meaningful differences between MSB11022 and EU-Humira.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

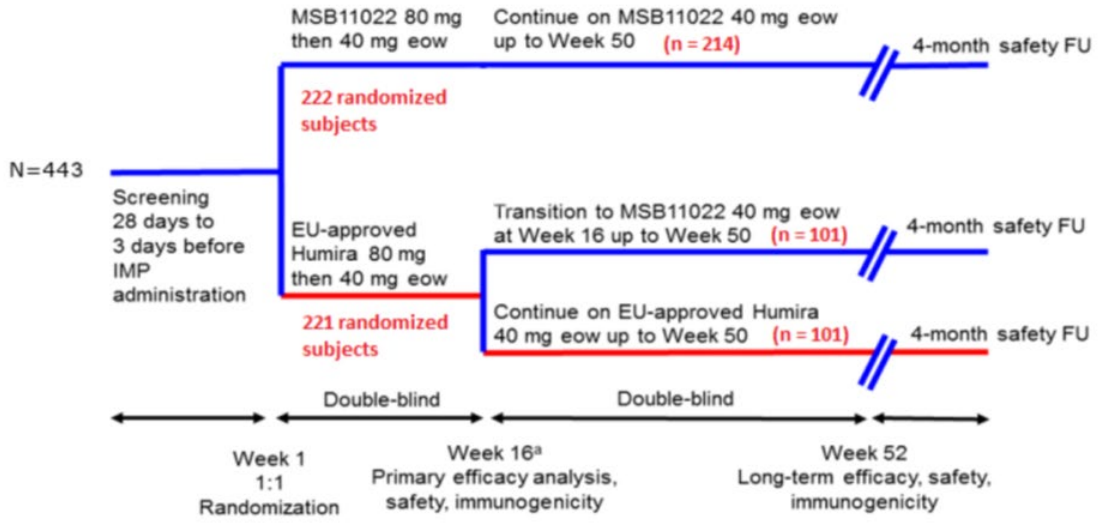
6.2.1. STUDY EMR200588-002

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Study Design and Endpoints

Figure 18. Study Design for Study EMR200588-002



Source: Refer to Module 5, Section 5.3.5.1, Study Report EMR200588-002 Week 54, Figure 1.
eow = every other week, FU = follow-up, IP = investigational product, MSB11022 = MSB11022 (A/Citrate)
a. Subjects who achieved PASI 50 at Week 16 continued into a 37-week double-blind extension period. Subjects who achieved less than PASI 50 at Week 16 were discontinued from the study. After Week 16, subjects who achieved less than PASI 50 at any scheduled visit up to Week 52 were also discontinued from the study. Subjects continued in the study at the discretion of the Investigator from Weeks 16 to 52 as long as they maintained at least PASI 50.

Study EMR200588-002 was a 2-arm, randomized, multi-center, double-blind, parallel-group equivalence study designed to demonstrate equivalence in efficacy and to compare the safety and immunogenicity of MSB11022 with EU- Humira in subjects with moderate to severe chronic plaque psoriasis during 52 weeks of treatment.

The study included a double-blind Core Treatment Period up to Week 16; an additional 37-week double-blind Extended Treatment Period (including a Safety Follow-up visit 4 weeks after the last investigational medicinal product (IMP) administration); and a 4-month Safety Evaluation Period.

In the Core Treatment Period, subjects were randomized to either subcutaneous MSB11022 or EU- Humira in a 1:1 ratio and received an initial dose of 80 mg on Day 1 of Week 1 (Baseline), followed by 40 mg every other week starting at Week 2 (1 week after the initial dose) up to and including Week 14.

After completion of the Core Treatment Period at the Week 16 visit, subjects who achieved Psoriasis Area and Severity Index 50 (PASI 50) entered a 37-week double-blind Extended Period in which a transition design was adopted. Subjects who were initially randomized to the EU-Humira group were re-randomized 1:1 to receive either MSB11022 or EU-Humira starting with the Week 16 treatment for an additional 37 weeks. Subjects who were initially randomized to the MSB11022 group remained on MSB11022 throughout the entire study. During the double-blind Extended Treatment Period, subjects received 40 mg IMP every other week from Week 16 up to and including Week 50. The overall 37-week, double-blind Extended Treatment Period allowed for the collection of long-term comparative efficacy, safety, and immunogenicity data as well as to analyze the possible impact of transitioning subjects from EU- Humira to MSB11022. Subjects who achieved less than PASI 50 at Week 16 (nonresponders) were discontinued from the study. After Week 16, subjects who worsened to a PASI score reduction < 50% at any scheduled visit up to Week 52 were also discontinued from the study.

Figure 18 above presents the study design of EMR200588-002.

The study enrolled and randomized 443 subjects aged 18 years and older, with PASI ≥ 12, Physician's Static Global Assessment (PSGA) ≥ 3 (moderate or severe) and total body surface area (BSA) ≥ 10%, from 69 sites in 12 countries in North America, South America, and Europe. Subjects were to have been diagnosed at least 6 months before randomization.

The primary efficacy endpoints considered for the analysis are:

1. FDA currently recommended endpoint: Percent change in PASI at Week 16 as recently recommended by the FDA at the BPD Type 4 meeting on October 4, 2021, where the FDA commented "Note that our recommendations for the primary endpoint in a comparative clinical study in subjects with psoriasis have evolved since 2015. We now recommend evaluating the percent change in PASI at Week 16, evaluated using a 90% confidence interval with margins of ± 10%."

- Pre-specified endpoint: The 75% improvement in PASI (PASI75) at Week 16 relative to baseline, as the primary efficacy endpoint agreed upon initially with the Agency at the study design stage in 2014.

The secondary efficacy endpoints are:

- Percentage of subjects achieving PASI 50/90/100 at Week 16
- Percentage of subjects achieving PASI 50/75/90/100 at Weeks 24 and 52
- Percent change from Baseline in PASI at Weeks 24 and 52

- Percentage of subjects achieving a static PGA score of “clear” or “almost clear” at Weeks 16compared to Baseline

Statistical Methodologies

The primary efficacy analysis population is the Per-Protocol (PP) Analysis Set, which includes all randomized and treated subjects who did not have any major protocol deviations during the Core Treatment Period with respect to factors likely to affect the efficacy of treatment. The Intent-to-treat (ITT) population is the supportive population, which includes all subjects randomized prior to the start of the Core Treatment Period.

FDA Recommended Primary Endpoint – Percent Improvement in PASI at Week 16

For assessing similarity based on the FDA recommended primary endpoint, percent change in PASI from baseline to Week 16, the primary analysis is based on the two-sided 90% confidence interval for the difference in mean percent change in PASI from baseline to Week 16 between the two treatment groups in PP Analysis Set. The difference between the two treatment groups is evaluated using an analysis of covariance model with treatment group, previous systemic therapy use, sex, and BMI as fixed factors and Baseline PASI score as covariates. If the 90% CI falls entirely within the specified margins of ± 10%, we conclude that no meaningful differences between the two products have been demonstrated.

In addition, the applicant pre-specified using nonparametric ANCOVA as a sensitivity analysis if the normality assumption is not hold for percentage changes from Baseline in PASI at Week 16.

Statistical Reviewers’ Comment:

> *We do not think the non-parametric ANCOVA model is appropriate as a sensitivity analysis for the percent improvement in PASI at Week 16 due to the following considerations.*
>
> *First, for the percent change from baseline in PASI score at Week 16, the margin ±10 was determined based on the mean value of the key secondary endpoint, not on the rank. When a non-parametric ANCOVA is used, the margin ±10 cannot be directly applied to the rank of the percent change from baseline in PASI at Week 16.*
>
> *Secondly, research has shown that the ANCOVA model is robust to the departure from normality (Jacqmin-Gadda et al 2007[1], Verbeke and Lesaffre 1996[2], Schmider et al 2010[3]). Also, the sample size (N=443) in this study is large enough for the asymptotic normality assumption based on the Central Limit*

Theory to be satisfied. Considering that Per Protocol is a post-randomization event, it may introduce selection bias and confounding effect (e.g., a subject's PP status may be impacted by the assigned treatment) to the treatment effect estimated from the primary analysis based on the PP Analysis Set. The primary analysis assumes that missing data and noncompliance (i.e., non-PP) has no impact on the unbiasedness of the treatment effect estimated from the primary analysis, i.e., the bias in the estimated treatment effect is zero.

Statistical reviewers conduct a more appropriate sensitivity analysis - the principal stratification tipping point sensitivity analysis (Low et al 2019)[4] for percent improvement in PASI at Week 16. It evaluates the impact of missing data and noncompliance on the primary analysis result and assesses the robustness of the primary analysis result based on the PP Analysis Set to any deviation from the assumed assumption that the bias introduced by the post-randomization PP analysis is zero.

[1] Jacqmin-Gadda, H., Sibillot, S., Proust, C., Molina, J. M., & Thiébaut, R. (2007). Robustness of the linear mixed model to misspecified error distribution. Computational Statistics & Data Analysis, 51(10), 5142-5154.
[2] Verbeke, G., & Lesaffre, E. (1996). A linear mixed-effects model with heterogeneity in the random-effects population. Journal of the American Statistical Association, 91(433), 217-221.
[3] Schmider, E., Ziegler, M., Danay, E., Beyer, L., & Bühner, M. (2010). Is it really robust? Reinvestigating the robustness of ANOVA against violations of the normal distribution assumption. Methodology: European Journal of Research Methods for the Behavioral and Social Sciences, 6(4), 147.
[4] Lou, Y., Jones, M. P., & Sun, W. (2019). Estimation of causal effects in clinical endpoint bioequivalence studies in the presence of intercurrent events: noncompliance and missing data. Journal of biopharmaceutical statistics, 29(1), 151-173.

Supportive analysis for percent improvement in PASI at Week 16 is conducted in the ITT Analysis Set. In order to deal with missing data in ITT, the applicant pre-specified two imputation methods:

- The primary supportive analysis is based on the same ANCOVA model as for the PP Analysis Set, except that the baseline-observation-carried-forward-like multiple imputation (BOCF-MI) approach is used to impute the missing PASI at Week 16 for those discontinued due to adverse events (AE), and the missing at random (MAR) based MI approach is used to impute all the other missing data for those not discontinued due to AE. Details are as follows.

  Multiple imputation is conducted in each randomized treatment group separately. The first step is to impute values for nonmonotonic missing data, i.e., interim missing PASI scores for subjects who had missed visits but had returned to the study. This is done to create an imputed dataset with a monotone missing pattern. Nonmonotone missing data is assumed missing at random (MAR). Imputation is achieved by the Monte Carlo Markov Chain approach, using the IMPUTE = MONOTONE option in the MCMC statement of SAS PROC MI. Once

this is achieved, Baseline PASI score values, sex, Baseline BMI and previous systemic therapy use are used to model the distribution of Baseline values that are carried forward for selected withdrawals (i.e., discontinuation due to AE). Their Baseline-distributed values are used to impute subjects' values for monotone visits missing change from Baseline PASI scores. All the other missing data for those not discontinued due to AE are imputed by the MAR-based MI approach. Percentage change from Baseline is then calculated once all missing change data from Baseline PASI scores are imputed.

- The sensitivity supportive analysis is to use the MAR-based MI approach to impute all of the missing PASIs at Week 16.

Pre-specified Primary Endpoint – PASI 75 at Week 16

For assessing similarity based on pre-specified primary endpoint, PASI 75 at Week 16, the primary analysis is based on the 2-sided 90% stratified Newcombe CI for the difference in the proportions of subjects in the two treatment groups who achieved PASI-75 at Week 16 stratified by previous systemic therapy in the PP Analysis Set. If the 90% CI falls entirely within the interval (-18%, 18%), we conclude that no meaningful differences between the two products have been demonstrated.

Statistical Reviewers' Comment:

- *The applicant originally used the 95% CI and the statistical reviewers use 90% CI instead, which is FDA's current recommended CI for comparative clinical studies. The applicant did not specify any sensitivity analysis for the primary analysis for PASI-75 at Week 16, which is based on the PP Analysis Set. As previously discussed for percentage improvement in PASI at Week 16, a similar principal stratification tipping point sensitivity analysis (Low et al 2019)[5] is used as a sensitivity analysis for the primary analysis for PASI 75 at Week 16 in the PP Analysis set.*

  [5] Lou, Y., Jones, M. P., & Sun, W. (2019). Estimation of causal effects in clinical endpoint bioequivalence studies in the presence of intercurrent events: noncompliance and missing data. Journal of biopharmaceutical statistics, 29(1), 151-173.

Supportive analysis for PASI 75 at Week 16 is conducted in the ITT Analysis Set, using the 2-sided 90% Stratified Newcombe CI. In order to handle the missing data in ITT, the sponsor pre-specified the primary supportive analysis as the nonresponder approach, where a subject with a missing PASI score at Week 16 is classified as a nonresponder at that time point.

In order to test the robustness of the primary efficacy analysis for using non-responder imputation to handle missing data in the analysis of the PASI 75 score, the applicant specified the following 3 sensitivity analyses:

1) Method 1: Imputation missing at random (MAR): This approach makes the assumption that a subject stays on treatment trajectory after discontinuation of

treatment. It is implemented as a MAR-based MI on continuous scores for PASI, followed by computing binary responses based on imputed values for PASI 75.

2) Method 2: A more conservative imputation assuming MAR: Imputed responders in the MSB11022 group only are categorized as nonresponders with a probability corresponding to the equivalence margin. This approach tests the robustness to the extent of missing data within the equivalence margin.

3) Method 3: Tipping point analysis: Data are re-analyzed for all possible combinations of the number of responders/nonresponders imputed for dropouts in each treatment group. The scenarios that "tip over" the conclusions from significant to nonsignificant are examined. A clinical interpretation is applied as to whether these "tipping point" scenarios are clinically plausible or not. These results did not require any modeling assumptions.

Statistical Reviewers' Comment:

- *The applicant's second sensitivity analysis is not appropriate to assess similarity. An Equivalence test is not a superiority test. Neither a superior nor an inferior effect is desired for similarity. Therefore, categorizing imputed responders in the test group (MSB11022) as nonresponders is only one-directional and not appropriate for assessing similarity.*
- *The applicant did not conduct the Tipping Point Analysis correctly. The applicant provided 9449 combinations of imputation scenarios in the clinical study report (Page 611-Page 2500), which is computationally unnecessarily complex.*
- *Statistical reviewers conduct the most conservative scenario of the Tipping Point Analysis, i.e., the worst case imputations.*

Worst case imputation 1: Those who missed PASI75 at Week 16 in MSB11022 are imputed as responders whereas those missed PASI75 in EU-Humira are imputed as non-responders. This is an extreme case on one end.

Worst case imputation 2: Those who missed PASI75 at Week 16 in MSB11022 are imputed as non-responders whereas those missed PASI75 in EU-Humira are imputed as responders. This is an extreme case on the other end.

No formal statistical analyses are performed for the secondary efficacy endpoints and such endpoints are analyzed descriptively. The 90% CI is reported for exploratory purpose and thus no multiplicity adjustment is considered for these analyses.

Subgroup analyses for the primary endpoint are conducted by age group (>65 years, ≥65 years), sex (male/female), race (white, non-white), BMI (<25 kg/m^2, ≥ 25 kg/m^2), and previous systemic therapy use (Biological (etanercept/infliximab), Non-biological, Treatment naïve). Descriptive statistics are reported for subgroup analyses. 90% CI is also reported for exploratory purpose.

Subject Disposition

Table 25 summarizes the subject disposition in the Core Treatment Period (Baseline to Week 16). A total of 443 subjects were randomized into the study, with 222 subjects assigned to MSB11022 and 221 subjects assigned to EU- Humira. All 443 subjects were included in the Intent-to-Treat (ITT) Analysis Set. Two subjects (1 in each treatment group) were randomized but not treated. Thus, the safety Analysis Set included 441 subjects, 221 subjects in the MSB11022 group and 220 subjects in the EU- Humira group. There were 394 subjects in the Per-Protocol (PP) Analysis Set, including 203 subjects in the MSB11022 group and 191 subjects in the EU-Humira group. Overall, there were 355 subjects from sites in Europe and 88 subjects from sites in the Americas.

During the Core Treatment Period, a total of 26 subjects (5.9%) discontinued treatment prior to Week 16. The proportions of subjects with treatment or study discontinuation before Week 16 was slightly lower for the MSB11022 group (3.6% and 3.6%, respectively) compared with the EU- Humira group (8.1% and 8.6%, respectively). The most common reason for discontinuation from IMP before Week 16 was AE (2.5%). The most common reasons for premature discontinuation from the study before Week 16 were AE (2.3%) and withdrawal of consent (2.3%).

Table 2 summarizes subject disposition in the Extended Treatment Period. A total of 416 subjects were re-randomized for the Extended Treatment Period. After re-randomization at Week 16, 40 subjects (9.6%) discontinued treatment: 18 (8.4%) in the MSB11022 group, 11 (10.9%) in the EU- Humira group, and 11 (10.9%) in the EU-Humira/MSB11022 group. The most common reason for treatment discontinuation after re-randomization was AE (overall 3.5%: 3.7%, 5.9%, and 4.0% in the MSB11022, EU-Humira, and EU- Humira/MSB11022 groups, respectively). There was no notable difference in the incidence of treatment discontinuations after re-randomization across the 3 treatment groups (Table 26).

Table 25. Subject Disposition in Core Treatment Period (Baseline to Week 16)

Characteristics	MSB11022 (N=222) n (%)	EU- Humira (N=221) n (%)	Total (N=443) n (%)
Randomized subjects, n (%)	222 (100.0)	221 (100.0)	443 (100.0)
Received no treatment, n (%)	1 (0.5)	1 (0.5)	2 (0.5)
Treatment ongoing at Week 16[a], n(%)	213 (95.9)	202 (91.4)	415 (93.7)
Reason for discontinuation of treatment prior to Week 16[b], n(%)	8 (3.6)	18 (8.1)	26 (5.9)

Characteristics	MSB11022 (N=222) n (%)	EU- Humira (N=221) n (%)	Total (N=443) n (%)
Adverse event, n (%)	2 (0.9)	9 (4.1)	11 (2.5)
Lost to follow-up, n (%)	1 (0.5)	2 (0.9)	3 (0.7)
Protocol noncompliance, n (%)	3 (1.4)	1 (0.5)	4 (0.9)
Lack of efficacy, n (%)	0 (0.0)	2 (0.9)	2 (0.5)
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrew consent, n (%)	1(0.5)	4 (1.8)	5 (1.1)
Other, n (%)	1 (0.5)	0 (0.0)	1 (0.2)
Reason for discontinuation of the study during the Core Period without being re-randomized[c], n (%)	8 (3.6)	19 (8.6)	27 (6.1)
Adverse event, n (%)	3 (1.4)	7(3.2)	10 (2.3)
Lost to follow-up, n (%)	1 (0.5)	2 (0.9)	3 (0.7)
Protocol noncompliance, n (%)	1 (0.5)	1 (0.5)	2 (0.5)
Lack of efficacy, n (%)	0 (0.0)	1 (0.5)	1 (0.2)
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrew consent, n (%)	2 (0.9)	8 (3.6)	10 (2.3)
Other, n (%)	1 (0.5)	0 (0.0)	1 (0.2)

Source: Table 3 in EMR200588-002 Clinical Study Report and reviewer analysis
a Subject re-randomized and received extended treatment.
b This refers to the “Primary reason for permanent treatment termination” on the “Treatment termination” eCRF page. It includes all subjects whose last dose on the “Treatment termination” eCRF page was core IMP administered ≤ Week 14, including subjects who were re-randomized but never received extended treatment.
c This refers to the “Primary reason for study discontinuation” on the “Study termination” eCRF page, up to and including the Week 54 analysis cutoff date.

Table 26. Subject Disposition Status in Extended period (Week 16 – 52), ETP-ITT Analysis Set

	MSB11022	EU-Humira	EU-Humira/ MSB11022	Total
Re-randomized subjects (ETP-ITT), n (%)	214 (100.0)	101 (100.0)	101 (100.0)	416 (100.0)
Received no treatment after re-randomization, n (%)	1 (0.5)	0 (0.0)	0 (0.0)	1(0.2)
Treatment completed[a], n (%)	195 (91.1)	90 (89.1)	90 (89.1)	375 (90.1)
Reason for discontinuation of treatment after re-randomization[b], n (%)	18 (8.4)	11 (10.9)	11 (10.9)	40 (9.6)
Adverse event, n (%)	8 (3.7)	6 (5.9)	4 (4.0)	10 (2.4)
Lost to follow-up, n (%)	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.5)
Protocol noncompliance, n (%)	2 (0.9)	0 (0.0)	1 (1.0)	3 (0.7)
Lack of efficacy, n (%)	4 (1.9)	2 (2.0)	2 (2.0)	8 (1.9)
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrew consent, n (%)	3 (1.4)	2 (2.0)	2 (2.0)	7 (1.7)
Other, n (%)	1 (0.5)	0 (0.0)	1 (1.0)	2 (0.5)

Source: Table 4 in EMR200588-002 Clinical Study Report and reviewer analysis
EU-Humira = EU-approved Humira.
a Treatment completed as per the 'Treatment Termination' page.
b This refers to the "Primary reason for permanent treatment termination" on the "Treatment termination" eCRF page. It includes all subjects whose last dose on the "Treatment termination" eCRF page was extended IMP administered ≥ Week 16 and "Treatment discontinuation" is ticked.
c This refers to the "Primary reason for study discontinuation" on the "Study termination" eCRF page up to and including the Week 54 analysis cutoff date.

Table 27 summarizes the PP Analysis Set during the Core Treatment Period. Overall, 11.1% of subjects reported important (defined as nonminor, subject-level deviations) deviations leading to exclusion from the PP Analysis Set, with a slightly higher proportion reported in the EU- Humira group (13.6%) compared with the MSB11022 group (8.6%). The most common protocol deviation was that 31 (7.0%) subject received ≤ 7 injections of IMP during the Core Treatment Period, including 11 (5%) from MSB11022 and 20 (9%) from EU-Humira, which contributed to the slight difference in the proportion of PP between MSB11022 (8.6%) and EU-Humira (13.6%). Other minor deviations are body weight > 120 kg or BMI ≥ 30 kg/m2 (5 (1.1%)) and subject used prohibited medication(s) and/or therapies at any time during the study (4 (0.9%)). All other important deviations were reported in no more than 2 subjects per treatment group.

Table 27. Per Protocol Population in the Core Treatment Period (Baseline to Week 16)

		MSB11022 (N=222) n (%)	EU-Humira (N=221) n (%)	Total N=443
Total PP Analysis Set through week 16		203	191	394
Number of subjects excluded from the PP Analysis Set [a]		19 (8.6)	30 (13.6)	49(11.1%)
Reason for Exclusion:	Deviation Code			
Subject did not meet inclusion criteria 6, 7, and/or 8: BSA, PASI, PGA	PDEV02	1 (0.5)	0 (0.0)	1 (0.2)
Subject met exclusion criterion 7: prior use of other biologics	PDEV06	1 (0.5)	0 (0.0)	1 (0.2)
Body weight > 120 kg (per Amendment 5) or BMI ≥ 30 (exclusion criterion 16)	PDEV07	2 (0.9)	3 (1.4)	5 (1.1)
Subject met exclusion criterion 13 (infection)	PDEV08	2 (0.9)	0 (0.0)	2 (0.5)
Subject assigned to incorrect randomization stratum with respect to previous biological treatment	PDEV11	1 (0.5)	1 (0.5)	2 (0.5)
Wrong IMP kit (other than assigned by IWRS) dispensation/administration to subject	PDEV14	0 (0.0)	1 (0.5)	1 (0.2)
Subject received ≤ 7 injections of IMP administration within Core Treatment Period [b]	PDEV16	11 (5.0)	20 (9.0)	31 (7.0)
Incorrect amount of subcutaneous IMP administered [c]	PDEV19	0 (0.0)	1 (0.5)	1 (0.2)
Week 16 visits not performed	PDEV20	1 (0.5)	2 (0.9)	3 (0.7)
Subject developed withdrawal criteria and was not subsequently discontinued from the study according to protocol requirements	PDEV21	0 (0.0)	1 (0.5)	1 (0.2)
Subject used prohibited medication(s) and/or therapies at any time during the study	PDEV22	2 (0.9)	2 (0.9)	4 (0.9)
Exclusion of subject at Sponsor discretion due to technical issues with IMP assignment	PDEV99	0 (0.0)	1 (0.5)	1 (0.2)

Source: Table 5 in EMR200588-002 Clinical Study Report and reviewer analysis
BMI = body mass index; BSA = body surface area; EU-Humira = EU-approved Humira; IMP = investigational medicinal product; ITT = Intent-to-Treat; IWRS = interactive web response system; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PP = Per-protocol.

a. Subjects may have more than 1 reason for exclusion from the PP Analysis Set.
b. Corresponds to less than 80% study treatment compliance within the Core Treatment Period.
c. Two kits of IMP were administered in error to 1 subject at Week 4; this was reported as a nonserious AE of accidental overdose. This AE was considered resolved on the day of onset and there was no change in study treatment as a result. No toxicity grade was reported.

Demographics and Baseline Characteristics

Table 28 reports the demographic characteristics for the ITT Analysis Set. Sex, race, ethnicity, and age were generally balanced between the treatment groups in Study

EMR200588-002. Among the 443 subjects, the mean age was about 43 years and 95.3% were younger than 65 years old. The majority of subjects were male (66.6%) and white (91.8%).

Table 29describes the baseline disease characteristics for the ITT Analysis Set. The baseline characteristics were similar between treatment groups in ITT. Overall, the mean PASI score was 20.7, with 70.1% of the subjects having moderate psoriasis severity vs 29.9% having severe psoriasis severity. Fifty-one subjects (11.5%) had psoriatic arthritis (PsA), including 26 (11.7%) in the MSB11022 group and 25 (11.3%) in the EU-Humira group. The mean of percent of body surface area affected was 29%. Median time since diagnosis of plaque-type psoriasis (ITT Analysis Set) was comparable between treatment groups (MSB11022: 185.1 months, EU- Humira: 176.3 months). Most subjects (86.7%) had a history of systemic therapy (stratification factor), including previous biological therapy with either etanercept (11.3%) or infliximab (0.7%).

Demographic characteristics (Table 30) and baseline disease characteristics (Table 31) for the PP Analysis Set were consistent with those of the ITT Analysis Set.

Table 28. Demographic Characteristics in ITT Analysis Set

Characteristics	MSB110222 (N=222) n (%)	EU-Humira (N=221) n (%)	Overall (N=443) n (%)
Age (years)			
Mean (SD)	43.96 (12.87)	42.17 (12.05)	43.07 (12.48)
Median	44	41	42
Min, Max	19,72	21,74	19,74
Age group - n (%)			
<65 years	210 (94.6)	212 (95.9)	422 (95.3)
≥65 years	12 (5.4)	9 (4.1)	21 (4.7)
Sex - n (%)			
Male	147 (66.2)	148 (67.0)	295 (66.6)
Female	75 (33.8)	73 (33.0)	148 (33.4)
Ethnicity – n (%)			
Hispanic or Latino	23 (10.4)	23 (10.5)	46 (10.4)
Not Hispanic or Latino	199 (89.6)	196 (89.5)	395 (89.6)
Race – n (%)			
White	205 (92.3)	200 (90.5)	405 (91.8)
Black or African American	2 (0.9)	1 (0.5)	3 (0.6)
Asian	5 (2.3)	9 (4.1)	14 (3.2)
American Indian or Alaska Native	10 (4.5)	8 (3.6)	18 (4.1)
Other	0 (0.0)	1 (0.5)	1 (0.2)
Missing/Not collected at this site	0 (0.0)	2 (0.9)	2 (0.5)

Source: Table 8 in Clinical Study Report and reviewer analysis
EU-Humira = EU-approved Humira; ITT = Intent-to-Treat; SD = standard deviation.

Table 29. Baseline Disease Characteristics in ITT Analysis Set

Characteristics	MSB11022 N=222 n (%)	EU-Humira N=221 n (%)	Overall N=443 n(%)
Time since first diagnosis of plaque-type psoriasis (months)			
Mean ± SD	207.20 ± 141.75	200.31 ± 141.16	203.76 ± 141.34
Median	185.1	176.3	183.5
Min; Max	8.0; 651.8	7.3; 772.3	7.3; 772.3
Psoriatic arthritis, n (%)			
Yes	26 (11.7)	25 (11.3)	51 (11.5)
No	196 (88.3)	196 (88.7)	392 (88.5)
Time since diagnosis of psoriatic arthritis (months)			
n (%)	26 (11.7)	25 (11.3)	51 (11.5)
Mean ± SD	87.93 ± 86.57	80.03 ± 106.16	84.06±95.76
Previous biologic or other therapy for psoriasis, n (%)			
Yes	192 (86.5)	192 (86.9)	384 (86.7)
No	30 (13.5)	29 (13.1)	59 (13.3)
Previous biologics and other therapies, n (%)			
Etanercept	24 (10.8)	26 (11.8)	50 (11.3)
Infliximab	2 (0.9)	1 (0.5)	3 (0.7)
Other	189 (85.1)	190 (86.0)	379 (85.6)
Previous phototherapy/photochemotherapy, n (%)			
Yes	100 (45.0)	116 (52.5)	216 (48.8)
No	122 (55.0)	105 (47.5)	227 (51.2)
PASI score			
Mean ± SD	20.51 ± 8.65	21.02 ± 8.20	20.74 ± 8.42
Median	17.4	18.3	17.6
Min; Max	12.0; 61.8	12.1; 53.5	12.0; 61.8
Percent of body surface area affected [a]			
Mean ± SD	28.25 ± 14.08	29.65 ± 13.72	28.93 ± 13.92
Median	24.9	27.0	26.0
Min; Max	11.0; 86.0	10.0; 76.5	10.0; 86.0
PGA, n (%)			
Almost clear	0 (0.0)	0 (0.0)	0 (0.0)
Clear	0 (0.0)	0 (0.0)	0 (0.0)
Mild	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	159 (71.6)	151 (68.3)	310 (70.1)
Severe	63 (28.4)	69 (31.4)	132 (29.9)

Source: Table 9 in Clinical Study Report and reviewer analysis
BSA = body surface area; eCRF = electronic case report form; EU-Humira = EU-approved Humira; ITT = Intent-to-Treat; Max = maximum; Min = minimum; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment.
a BSA (%) is based on data collected in the PASI eCRF page.

Table 30. Demographic Characteristics in PP Analysis Set

Characteristics	MSB110222 (N=203) n (%)	EU-Humira (N=191) n (%)	Overall (N=394) n (%)
Age (years)			
Mean (SD)	44.23 (12.72)	41.84 (11.80)	43.07 (12.32)
Median	44.0	40.0	42.0
Min, Max	19.0, 72.0	21.0, 74.0	19.0, 74.0
Age group - n (%)			
<65 years	192 (94.6)	184 (96.3)	376 (95.4)
≥65 years	11 (5.4)	7 (3.7)	18 (4.6)
Sex - n (%)			
Male	136 (67.0)	130 (68.1)	266 (67.5)
Female	67 (33.0)	61 (31.9)	128 (32.5)
Ethnicity – n (%)			
Hispanic or Latino	18 (8.9)	15 (7.9)	33 (8.4)
Not Hispanic or Latino	185 (91.1)	176 (92.2)	361 (91.6)
Race – n (%)			
White	192 (94.6)	179 (93.7)	371 (94.2)
Black or African American	1 (0.5)	0 (0.0)	1 (0.3)
Asian	3 (1.5)	8 (4.2)	11 (2.8)
American Indian or Alaska Native	7 (3.5)	4 (2.1)	11 (2.8)

Source: Reviewer analysis
EU-Humira = EU-approved Humira; ITT = Intent-to-Treat; SD = standard deviation.

Table 31. Baseline Characteristics in PP Analysis Set

Characteristics	MSB11022 N=203 n (%)	EU-Humira N=191 n (%)	Overall N=394 n(%)
Time since first diagnosis of plaque-type psoriasis (months)			
Mean (SD)	209.98 (142.87)	198.87 (143.99)	204.59 (143.34)
Median	185.6	171.9	183.5
Min; Max	7.9; 651.8	7.3, 772.3	7.3, 772.3
Psoriatic arthritis, n (%)			
Yes	21 (10.3)	22 (11.5)	43 (10.9)
No	182 (89.7)	169 (88.5)	351 (89.1)
Time since diagnosis of psoriatic arthritis (months)			
n (%)	21 (10.3)	22 (11.5)	43 (10.9)
Mean (SD)	88.36 (91.85)	66.63 (58.71)	77.24 (76.56)
Previous biologic or other therapy for psoriasis, n (%)			
Yes	177 (87.2)	168 (88.0)	345 (87.6)
No	26 (12.8)	23 (12.0)	49 (12.4)
Previous biologics and other therapies, n (%)			
Etanercept	22 (10.8)	24 (12.6)	46 (11.7)
Infliximab	2 (1.0)	1 (0.5)	3 (0.8)
Other	175 (86.2)	166 (86.9)	341 (86.5)
Previous phototherapy/photochemotherapy, n (%)			
Yes	89 (43.8)	101 (52.9)	190 (48.2)
No	114 (56.2)	90 (47.1)	204 (51.8)
PASI score			
Mean (SD)	20.64 (8.80)	21.18 (8.08)	20.90 (8.45)
Median	17.4	18.4	18.0
Min; Max	12.0; 61.8	12.1; 61.8	12.0; 61.8
Percent of body surface area affected a			
Mean (SD)	28.56 (14.27)	29.85 (13.62)	29.18 (13.96)
Median	25.9	27.1	26.9
Min; Max	11.0; 86.0	10.0; 72.0	10.0; 86.0
PGA, n (%)			
Almost clear	0 (0.0)	0 (0.0)	0 (0.0)
Clear	0 (0.0)	0 (0.0)	0 (0.0)
Mild	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	146 (71.9)	128 (67.0)	274 (69.5)
Severe	57 (28.1)	63 (33.0)	120 (30.5)

Source: Table 15.1.6.4 in Clinical Study Report and reviewer's analysis

Analysis of Primary Clinical Endpoint(s)

FDA-recommended Primary Endpoint: Percent Improvement in PASI at Week 16

Table 32 presents results of the primary analysis for the FDA recommended primary endpoint, percentage change in PASI from baseline to Week 16, by randomization stratum and the overall population in the PP Analysis Set. Overall, the mean percent change from baseline in PASI at Week 16 was -92.14% for the MSB11022 group and -93.02% for the EU-Humira group, with an estimated treatment difference of 0.88%. The 90% CI for treatment differences was (-0.87%, 2.64%), which is fully contained within the FDA recommended margin of -10% to +10%. The three previous systemic therapy strata showed similar results. Thus, no meaningful differences between treatment groups for the FDA recommended primary efficacy endpoint is demonstrated based on the primary analysis.

Table 32. Results of Primary Analysis for the FDA-recommended Endpoint, Mean Percent Change from Baseline in PASI Score at Week 16, by Previous Systemic Therapy and Overall, in PP

		MSB11022		EU-Humira	
		Value	% Change from Baseline	Value	% Change from Baseline
Overall					
Baseline	n Mean (SD)	203 20.63 (8.79)		191 21.18 (8.08)	
Week 16	n Mean (SD)	203 1.84 (2.29)	203 -90.67 (11.36)	191 1.67 (2.17)	191 -91.75 (9.96)
	LS Mean (SE)		-92.14 (0.86)		-93.02 (0.87)
	Difference LS Mean (MSB11022 – EU-Humira) 90% CI of the difference*	0.88 (-0.87, 2.64)			
By Strata					
Previous Biological Systemic Therapy					
	n Mean (SD)		25 -95.16 (6.98)		25 -94.44 (10.24)
Previous Nonbiological Systemic Therapy					
	n Mean (SD)		74 -90.02 (10.76)		67 -89.87 (10.97)
Treatment-Naïve					
	n Mean (SD)		104 -90.05 (12.41)		99 -92.35 (9.00)

Source: Table 16 in Clinical Study Report, and reviewer analysis.
An ANCOVA model was fitted with treatment group, previous systemic therapy use, sex, and BMI category as fixed factors and baseline PASI score as a covariate.
*95% CI of the mean difference is (-1.21, 2.98) for the PP Analysis Set

Table 33 shows the results of the supportive analysis for percent improvement in PASI at Week 16 in the ITT Analysis Set, where BOCF-like MI Approach is used to impute the missing PASI at Week 16 for those discontinued due to AE; MAR-based MI Approach is used to impute all the other missing PASI at Week 16 for those not discontinued due to AE. Table 9 shows that a small proportion of subjects (3.6% of MSB11022 vs. 8.6% of EU-Humira) missed PASI assessment at Week 16. The 90% CI for treatment differences was (-7.43%, 0.33%), which is also contained within the FDA recommended margin of -10% to +10%. Therefore, the supportive analysis results using the ITT Analysis Set (Table 33) are consistent with that of the primary analysis in the PP Analysis Set (Table 32).

Table 33. Results of Supportive Analysis for the FDA-recommended Endpoint, Mean Percent Change from Baseline in PASI Score at Week 16 in ITT

	MSB11022 N=222 LSMean (SE)	**U.S.- Humira N=221 LSMean (SE)**	**LSMean Difference (90% Confidence Interval)**
Missing data rate at Week 16	8 (3.6%)	19 (8.6%)	
BOCF-like MI *	-89.41 (1.89)	-85.86 (2.04)	-3.55 (-7.43,0.33)**

Source: Table 15.2.1.5 in additional analyses and reviewer analysis
An ANCOVA model was fitted with treatment group, previous systemic therapy use, sex, and BMI category as fixed factors and baseline PASI score as a covariate.
* BOCF-like MI Approach is used to impute the missing PASI at Week 16 for those discontinued due to AE; MAR-based MI Approach is used to impute all the other missing PASI at Week 16 for those not discontinued due to AE.
** 95% CI is (-8.18, 1.08)

Pre-specified Primary Efficacy Endpoint

Table 34 summarizes the primary analysis result for the protocol-specified primary efficacy endpoint, the PASI 75 response rate at Week 16, in the PP Analysis Set. In PP, the proportion of subjects achieving PASI-75 at Week 16 was 89.7% for the MSB11022 group and 91.6% for the EU-Humira group, with an estimated proportion difference of -1.9%. The 90% CI for treatment differences was (-6.83%, 3.06%), which is contained within the pre-specified margin of -18% to 18%; thus, no meaningful differences between MSB11022 and EU-Humira based on PASI 75 at Week 16 is demonstrated based on the primary analysis.

Table 34. Results of Primary Analysis for the Pre-specified Primary Endpoint, PASI 75 Response Rates at Week 16, by Previous Systemic Therapy and Overall, in PP

	MSB11022	EU-Humira
Overall	**N=203**	**N=191**
Subjects with PASI 75 at Week 16, n (%)	182 (89.7)	175 (91.6)
Proportion Difference	-1.9	
90% stratified Newcombe CI (%)*	[-6.83, 3.06]	
By Strata		
Previous Biological Systemic Therapy	N=25	N=25
Subjects with PASI 75 at Week 16, n (%)	24 (96.0)	24 (96.0)
Previous Nonbiological Systemic Therapy	N=74	N=67
Subjects with PASI 75 at Week 16, n (%)	68 (91.9)	57 (85.1)
Treatment-Naïve	N=104	N=99
Subjects with PASI 75 at Week 16, n (%)	90 (86.5)	94 (95.0)

Source: Table 14 in Clinical Study Report, and reviewer analysis.
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.
*95% stratified Newcombe CI is [-7.82, 4.07] for the PP Analysis Set.

Table 35 reports the supportive analysis result for PASI at Week 16 in the ITT Analysis Set, where the nonresponder method is used to impute any missing data. The supportive analysis result using the ITT Analysis Set (Table 11) is consistent with that of the primary analysis in the PP Analysis Set (Table 10): the 90% CI for treatment differences was (-2.89%, 8.47%) for the ITT Analysis Set, which is also contained within the pre-specified margin of -18% to 18%.

Table 35. Results of Supportive Analysis for the Pre-specified Primary Endpoint, PASI 75 Response Rates at Week 16, by Stratum and Overall, in ITT (Non-Responder Imputation)

	MSB11022	EU-Humira
Overall	**N=222**	**N=221**
Subjects with PASI 75 at Week 16, n (%)	191 (86.0)	184 (83.3)
Proportion Difference	2.79	
90% stratified Newcombe CI (%)*	[-2.89, 8.47]	
By Strata		
Previous Biological Systemic Therapy	N=28	N=27
Subjects with PASI 75 at Week 16, n (%)	27 (96.4)	24 (88.9)
Previous Nonbiological Systemic Therapy	N=82	N=79
Subjects with PASI 75 at Week 16, n (%)	70 (85.4)	61 (77.2)
Treatment-Naïve	N=112	N=115
Subjects with PASI 75 at Week 16, n (%)	94 (83.9)	99 (86.1)

Source: Table 14 in Clinical Study Report, and reviewer analysis.
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.
All subjects in the ITT Analysis Set without a Week 16 assessment had been assumed to be nonresponders.
*95% stratified Newcombe CI is [-4.00, 9.57] for the ITT Analysis Set.

Potential Effects of Missing Data

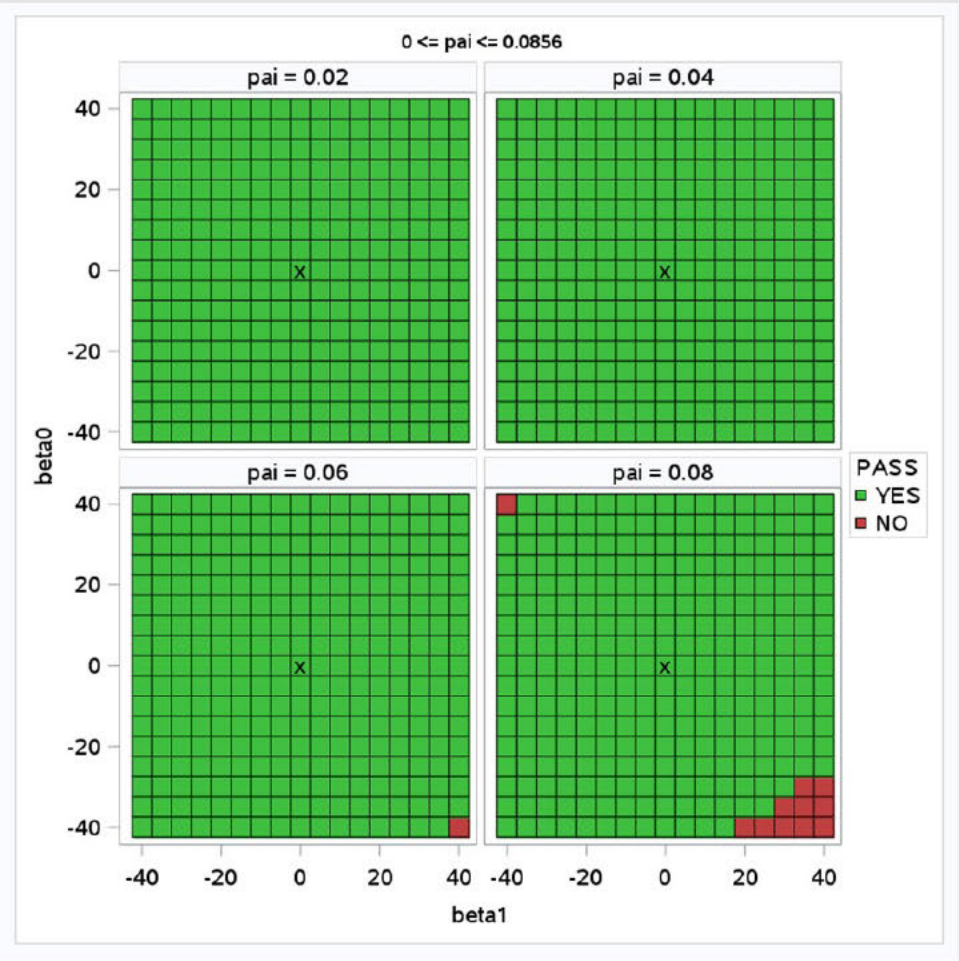
Sensitivity Analysis for FDA-recommended Primary Efficacy Endpoint in PP

As discussed in Table 27, the proportion of PP was generally balanced between the two treatment groups (MSB11022: 91.4%; EU-Humira: 86.4%). The figure below shows the tipping point sensitivity analysis for the FDA-recommended primary endpoint, percent improvement in PASI at Week 16, in the PP Analysis Set. It evaluates the impact of missing data and noncompliance (i.e., non-PP) on the result of the primary analysis for percent improvement in PASI at Week 16. The green zone is when similarity between MSB11022 and EU-Humira passes whereas the red zone is when similarity fails to pass. The 'x' is the similarity passing status based on the primary analysis which assumes that missing data and noncompliance have no impact on the unbiasedness of the treatment effect based on the primary analysis, i.e., the bias of the estimated treatment effect is zero. The rest of the area is when this assumption is deviated at different levels under different sensitivity scenarios (Lou et al 2019)[6]. The figure below

shows that the passing of similarity based on the primary analysis for the percent improvement in PASI at Week 16 was robust to the deviation from the no bias assumption, which validates the result of the primary analysis.

[6] Lou, Y., Jones, M. P., & Sun, W. (2019). Estimation of causal effects in clinical endpoint bioequivalence studies in the presence of intercurrent events: noncompliance and missing data. Journal of biopharmaceutical statistics, 29(1), 151-173.

Figure 19. Principal Stratification Tipping Point Sensitivity Analysis for the FDA-recommended Primary Endpoint, Percent Improvement in PASI at Week 16, in PP



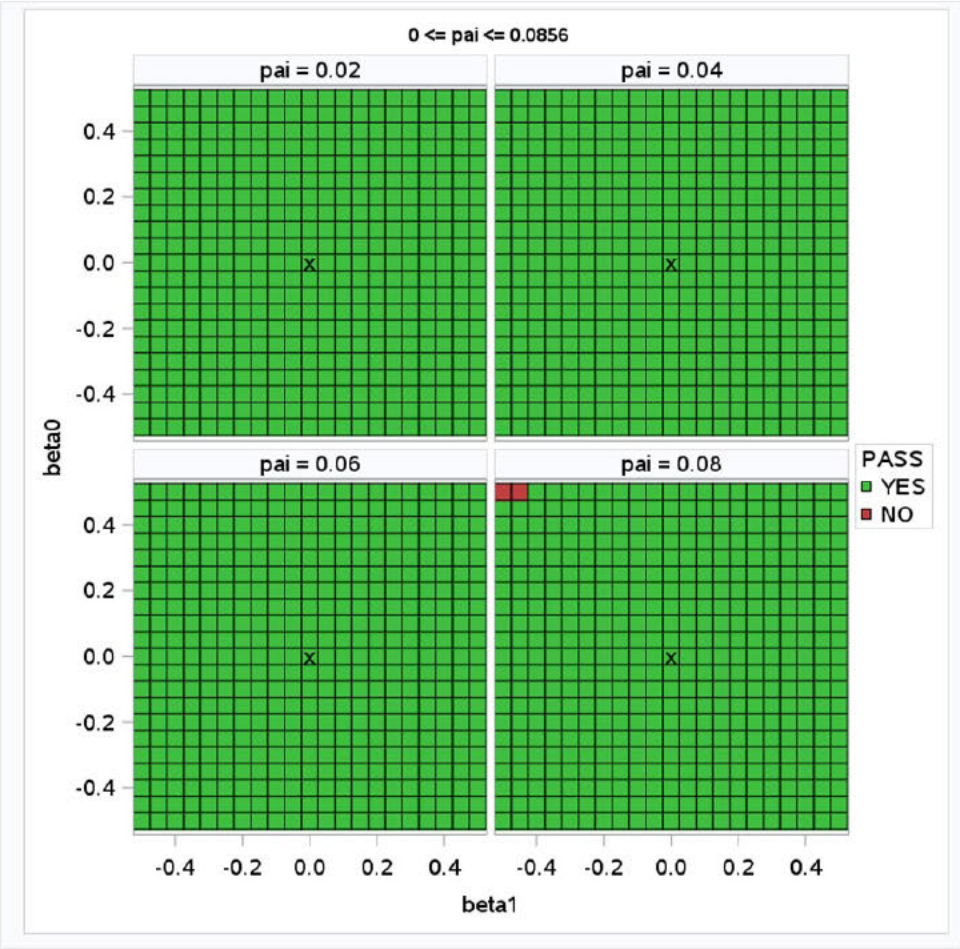
Source: reviewer analysis

Sensitivity Analysis for Pre-specified Primary Efficacy Endpoint in PP

Figure 20 shows the principal stratification tipping point sensitivity analysis for the pre-specified primary endpoint, PASI 75 at Week 16, in the PP Analysis Set. Similarly, the passing of similarity based on the primary analysis for PASI 75 at Week 16 was also

robust to the different degrees of deviation from the no bias assumption under various scenarios, which confirms the result of the primary analysis.

Figure 20. Principal Stratification Tipping Point Sensitivity Analysis for the Pre-specified Primary Endpoint, PASI 75 Response Rates at Week 16, in PP



Source: reviewer analysis

Sensitivity Analysis for the FDA Recommended Primary Endpoint in ITT

As previously discussed, a small proportion of subjects (3.6% of MSB11022 vs. 8.6% of EU-Humira) missed PASI assessment at Week 16. To evaluate the potential impact of missing data on the results of the primary supportive analysis for percent improvement in PASI at Week 16 in the ITT Analysis Set (Table 33), which uses the BOCF-like MI approach for those discontinued due to AE and the MAR-baseline MI approach for other missing data, the applicant conducted a sensitivity analysis using the MAR-based MI approach for all the missing data. Table 34 shows that the 90% CI of the mean difference (-1.93%, 1.91%) still falls within the margin of ± 10% based on the MAR-based MI approach. Thus, no meaningful differences between treatment groups for the FDA recommended primary efficacy endpoint in ITT is demonstrated by the sensitivity

analysis. This confirms the finding from the primary supportive analysis for percent improvement in PASI at Week 16 (Table 33).

Table 36. Sensitivity Analysis for Handling Missing data for the FDA Recommended Efficacy Endpoint, Percent Improvement in PASI from Baseline to Week 16, in ITT

	MSB11022 N=222	U.S.- Humira N=221	LSMean Difference (90% Confidence Interval)
Missing data rate at Week 16 N(%)	8 (3.6%)	19 (8.6%)	
Sensitivity Analysis:			
MAR-based MI LSMean(SE)	-91.48 (0.94)	-91.47 (0.97)	-0.01 (-1.93, 1.91)*

Source: Table 15.2.1.38 in Clinical Study Report, and reviewer analysis.
* 95% CI is (-2.30, 2.27) for the ITT Analysis Set.

Sensitivity Analysis for the Pre-specified Primary Efficacy Endpoint in ITT

Table 37 summarizes the results of different sensitivity analyses to test the robustness of the primary supportive analysis by using non-responder imputation to handle missing data in the analysis of the PASI 75 score at Week 16 (Table 34). Same as the percent improvement in PASI at Week 16, there was a small missing data rate in PASI 75 at Week 16: 8 (3.6%) in MSB11022 and 19 (8.6%) in EU-Humira. For all the sensitivity analyses including the sponsor's MAR-based MI method and statistical reviewers' Worst Case Imputations 1 and 2, the 90% CI of the proportion difference in PASI-75 at Week 16 between the two treatment groups all falls within the margin of ± 18%. Hence, this confirms the study finding from the primary supportive efficacy analysis using the non-responder imputation in Table 34.

Table 37. Sensitivity Analysis for Handling Missing Data for the Pre-specified Primary Efficacy Endpoint, PASI-75 at Week 16, in ITT

	MSB11022 N=222	EU-Humira N=221	90% CI for Proportion Difference
Missing data rate at Week 16	8 (3.6%)	19 (8.6%)	
Sensitivity Analysis:			
MAR-based MI Method	191 (86.0%)	184 (83.3%)	0.65 (-6.76,5.45)*
Worst Case Imputation 1: Non-responder in MSB11022 group + responder in EU-Humira	191 (86.0%)	203 (91.7%)	-5.80 (-10.80, -0.86)
Worst Case Imputation 2: Responder in MSB11022 + non-responder in EU-Humira	199 (89.6%)	184 (83.3%)	6.39 (1.01, 11.79)

Source: Table 15.2.1.37 in Clinical Study Report, and Reviewer analysis
*95% CI is (-6.80, 5.49) for MAR-based MI Method.

Assay Sensitivity and Constancy

Study EMR200588-002 was a comparative clinical study of MSB11022 and EU-Humira and it did not include a placebo arm. One Phase II placebo-controlled trial of "Humira" has been published (Gordon (2006), and the US-Humira label includes the results from the two pivotal Phase III placebo-controlled trials of "Humira" (BLA125057 Study Ps-I and Study Ps-II). Each of these studies presented the percent improvement in PASI at either Week 16 or 16 as a secondary endpoint. The key design criteria and results for the Humira studies in label and publication are presented in Table 38. The Gordon study had less restrictive inclusion criteria (BSA ≥ 5, no requirement on PASI), but Study Ps-I and Ps-II had similar inclusion criteria to Study EMR200588-002 (BSA ≥ 10, PASI ≥ 12, and PSGA ≥ Moderate). The percent improvement in PASI on the EU-Humira arm in Study EMR200588-002 is generally consistent with the results from the previous "Humira" studies at Week 16. The proportion of subjects achieving PASI-75 at Week 16 in Study EMR200588-002 is also consistent with the previous "Humira" studies. Because of the low placebo response rate in the previous studies and the consistency of response across studies, the assumption of assay sensitivity appears reasonable for Study EMR200588-002.

Table 38. Characteristics and Results of Published "Humira" Studies on Psoriasis and of Study EMR200588-002

	Gordon (2006)	BLA125057 Study Ps-I [Menter (2008)]	BLA125057 Study Ps-II [Saurat (2008)]	Study EMR200588-002
Selected inclusion criteria	BSA ≥ 5	BSA ≥ 10 PASI ≥ 12 PSGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 PSGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 PSGA ≥ Mod
Region/Country	US, Canada	US, Europe, Canada	US, Canada	North America, South America, Europe,
Baseline PASI Mean *(Humira)*	PASI = 16.7	PASI = 19.0	PASI = 21.0	PASI = 20.7
% Imp. in PASI *Humira*	(Week 12) 70	(Week 12) 76	(Week 16) 81	(Week 16) 92
Placebo	14	15	22	--
PASI-75 *Humira*	(Week 12) 53% (n=50)	(Week 16) 71% (n=814)	(Week 16) 78% (n=99)	(Week 16) 83% (n=221)
Placebo	4% (n=52)	7% (n=398)	19% (n=48)	--

Source: Reviewer analysis

[1] Lou, Y., Jones, M. P., & Sun, W. (2019). Estimation of causal effects in clinical endpoint bioequivalence studies in the presence of intercurrent events: noncompliance and missing data. Journal of biopharmaceutical statistics, 29(1), 151-173.

Analysis of Secondary Clinical Endpoint(s)

Table 39 summarizes the secondary clinical endpoint, percentage of subjects who achieved PASI 50/90/100 at Week 16, in the PP and ITT Analysis Sets. Non-responder imputation is used to handle missing PASI assessments in the ITT Analysis Set. The response rate was similar between the two treatment groups in the PP Analysis Set and the ITT Analysis Set. The 2-sided 90% stratified Newcombe CIs for the difference in PASI 50, PASI 90, and PASI 100 response rates are reported for exploratory purpose. The response rates were generally similar between the two arms.

Table 39. Secondary Endpoint, PASI 50/90/100 at Week 16, in PP and ITT

	MSB11022	EU-Humira	Proportion Difference (90% Stratified Newcombe CI*)
PP Analysis Set	**N=203 n (%)**	**N=191 n (%)**	
PASI 50	203 (100.0)	191 (100.0)	n/a
PASI 90	129 (63.6)^	126 (66.0)	-2.25 (-10.09, 5.66)
PASI 100	67 (33.0)	71 (37.2)	-4.03 (-11.88, 3.86)
ITT Analysis Set (nonresponder imputation)	**N=222 n (%)**	**N=221 n (%)**	
PASI 50	214 (96.4)	201 (91.0)	5.44 (1.55, 9.45)
PASI 90	134 (60.4)^	132 (59.7)	0.61 (-7.01, 8.23)
PASI 100	71 (32.0)	75 (33.9)	-2.02 (-9.32, 5.30)

Source: Table 17 in Clinical Study Report and Reviewer Analysis
* The 90% CI for the treatment difference between treatment is for exploratory purpose
PASI 50/90/100 is a reduction since Baseline in PASI score of ≥ 50%, ≥ 90% and = 100%, respectively.
^ PASI 90 in MSB11022 is 130 (64.0%) in the PP Analysis Set and 135 (66.5%) in the ITT Analysis Set in Table 17 in Clinical study report.

Table 40 reports the PASI 50/75/90/100 response rates at Weeks 24 and 52 (extended treatment period) in three treatment groups (MSB11022, EU-Humira, and EU-Humira to MSB11022) at Weeks 24 and 52 in the ETP-PP and ETP-ITT Analysis Set. The response rates were generally similar among the three treatment groups in both the ETP-PP and ETP-ITT Analysis Sets.

Table 40. Secondary Endpoint, PASI 50/75/90/100 Response Rates at Weeks 24 and 52 (Extended Treatment Period), in ETP-PP and ETP-ITT

PASI Score	MSB11022	EU-Humira	EU-Humira to MSB11022
ETP-PP Analysis Set Reduction Since Core Baseline	**N=203** n (%)	**N=95** n (%)	**N=96** n (%)
Week 24			
PASI 50	200 (100.0)	93 (98.9)	92 (100.0)
PASI 75	185 (92.5)	83 (88.3)	87 (94.6)
PASI 90	148 (74.0)	74 (78.7)	74 (80.4)
PASI 100	85 (42.5)	35 (37.2)	33 (35.9)
Week 52			
PASI 50	182 (97.8)	85 (100.0)	87 (100.0)
PASI 75	169 (90.9)	79 (92.9)	81 (93.1)
PASI 90	142 (76.3)	67 (78.8)	74 (85.1)
PASI 100	100 (53.8)	46 (54.1)	50 (57.5)
ETP-ITT Analysis Set Reduction Since Core Baseline	**N=214** n (%)	**N=101** n (%)	**N=101** n (%)
Week 24			
PASI 50	210 (100.0)	96 (99.0)	97 (100.0)
PASI 75	195 (92.9)	86 (88.7)	92 (94.8)
PASI 90	155 (73.8)	77 (79.4)	78 (80.4)
PASI 100	89 (42.4)	36 (37.1)	37 (38.1)
Week 52			
PASI 50	192 (98.0)	88 (100.0)	92 (100.0)
PASI 75	179 (91.3)	82 (93.2)	86 (93.5)
PASI 90	150 (76.5)	70 (79.5)	78 (84.8)
PASI 100	103 (52.6)	47 (53.4)	54 (58.7)

Source: Table 15.2.1.8, Table 15.2.1.9. in Clinical Study Report, and Reviewer analysis
Core baseline was defined as the last nonmissing assessment on or prior to Day 1.
PASI 50/75/90/100 was a reduction since Baseline in PASI score of ≥ 50%, ≥ 75%, ≥ 90% and = 100%, respectively.
ETP-ITT = Extended Treatment Period Intent-to-Treat; ETP-PP = Extended Treatment Period Per-protocol; EU-Humira = EU-approved Humira; PASI = Psoriasis Area and Severity Index.

Table 41 summarizes the percent change from baseline in PASI score at Weeks 24 and 52 in three treatment groups (MSB11022, EU-Humira, and EU-Humira to MSB11022) in the ETP-PP Analysis Set. There were no discernible differences across the treatment groups regarding the mean percent change in PASI from Core Baseline to Weeks 24 and 52 based on the ETP-PP Analysis Set. The improvement in PASI that had been achieved during the first 16 weeks of treatment was maintained over time and was similar among treatment groups.

Table 41. Secondary Endpoint, Percent Change from Core Baseline in PASI Score at Weeks 24 and 52 (Extended Treatment Period), in ETP-PP Analysis Set

Visit	Statistics	MSB11022 to MSB11022 N=203	EU-Humira to EU-Humira N=95	EU-Humira to MSB11022 N=96
Core Baseline	Number of subjects, N1	203	95	96
	PASI, mean (SD)	20.63 (8.79)	21.26 (7.78)	21.11 (8.40)
Week 24	Number of subjects, N1	200	94	92
	PASI, mean (SD)	1.43 (2.10)	1.88 (3.46)	1.16 (1.74)
	% Change from Core Baseline, mean (SD)	-92.92 (9.98)	-91.39 (12.73)	-94.22 (8.23)
Week 52	Number of subjects, N1	188	85	87
	PASI, mean (SD)	1.40 (2.82)	1.25 (2.01)	1.09 (2.11)
	% Change from Core Baseline, mean (SD)	-92.88 (13.64)	-93.98 (9.68)	-94.83 (9.72)

Source: Table 15.2.1.10 in Clinical Study Report.
Core Baseline was defined as the last nonmissing assessment on or prior to Study Day 1. N1 is the number of subjects who were considered to have had the visit.
ETP-PP = Extended Treatment Period Per-protocol; EU-Humira = EU-approved Humira; PASI = Psoriasis Area and Severity Index.

Table 42 reports the PGA responder rate, i.e., percentage of subjects achieving a static PGA score of “clear” or “almost clear” at Week 16 compared to baseline, in the PP and ITT Analysis Sets. The responder rates were similar between the two treatment groups in the PP Analysis: 84.2% in MSB11022 and 81.7% in EU-Humira, with 90% stratified Newcombe CI: (-3.63, 8.91) (for exploratory purpose). The results in the ITT Analysis Set were consistent with the PP analysis.

Table 42. Secondary Endpoint, PGA Responders at Week 16, in PP and ITT Analysis Sets

	MSB11022	EU-Humira	90% Stratified Newcombe CI*
PP Analysis Set	**N=203**	**N=191**	
PGA responders, n (%) PGA nonresponders, n (%)	171 (84.2) 32 (15.8)	156 (81.7) 35 (18.3)	(-3.63, 8.91)
ITT Analysis Set	**N=222**	**N=221**	
PGA responders, n (%) PGA nonresponders, n (%)	180 (84.1) 34 (15.9)	163 (80.7) 39 (19.3)	(-2.71, 9.40)

Source: Table 15.2.2.1, Table 15.2.2.2 in Clinical Study Report, and reviewer analysis
* The 90% CI for the treatment difference between treatment is for exploratory purpose

Additional Analyses

No exploratory endpoints were analyzed. The primary and secondary endpoints are adequate to determine biosimilarity.

Table 43 presents the subgroup analyses for the percentage of subjects achieving PASI75 at Week 16 by treatment among the PP Analysis Set. Overall, there were no meaningful differences between treatment groups in the percentage of subjects achieving PASI75 at Week 16 by the various subgroups of subjects analyzed. The impact of age, gender, weight, BMI, race, ethnicity, and previous systemic therapy use was in general similar for subjects treated with MSB11022 and EU-Humira.

Table 43. Subgroup Analyses for the Pre-specified Primary Efficacy Endpoint, PASI 75 at Week 16, in PP

Subgroup	PASI 75	MSB11022 N=203 n (%)	EU-Humira N=191 n (%)	Risk Difference (90% CI*)
Age				
< 65 years	Yes	174 (90.6)	169 (91.9)	-0.99 (-5.99, 3.97)
	No	18 (9.4)	15 (8.2)	
≥ 65 years	Yes	8 (72.7)	6 (85.7)	n/a
	No	3 (27.3)	1 (14.3)	
Sex				
Male	Yes	120 (88.2)	118 (90.8)	-2.43 (-8.78, 3.96)
	No	16 (11.8)	12 (9.2)	
Female	Yes	62 (92.5)	57 (93.4)	-1.10 (-9.36, 7.44)
	No	5 (7.5)	4 (6.6)	
Weight				
< 90 kg	Yes	131 (91.6)	135 (93.1)	-1.69 (-7.18, 3.73)
	No	12 (8.4)	10 (6.9)	
≥ 90 kg	Yes	51 (85.0)	40 (87.0)	-1.36 (-12.69, 10.82)
	No	9 (15.0)	6 (13.0)	
BMI				
< 25 kg/m2	Yes	58 (93.5)	64 (94.1)	-0.08 (-9.02, 7.03)
	No	4 (6.5)	4 (5.9)	
≥ 25 kg/m2	Yes	124 (87.9)	111 (90.2)	-2.09 (-8.49, 4.50)
	No	17 (12.1)	12 (9.8)	
Race				
White	Yes	172 (89.6)	163 (91.1)	-1.44 (-7.32, 3.75)
	No	20 (10.4)	16 (8.9)	
Other	Yes	10 (90.9)	12 (100.0)	n/a
	No	1 (9.1)	0 (0.0)	
Ethnicity				

Subgroup	PASI 75	MSB11022 N=203 n (%)	EU-Humira N=191 n (%)	Risk Difference (90% CI*)
Hispanic or Latino	Yes	15 (83.3)	13 (86.7)	1.32 (-21.24, 26.61)
	No	3 (16.7)	2 (13.3)	
Not Hispanic or Latino	Yes	167 (90.3)	162 (92.0)	-1.84 (-6.91, 3.24)
	No	18 (9.7)	14 (8.0)	
Previous systemic therapy use**				
Biological (etanercept/infliximab)	Yes	24 (96.0)	24 (96.0)	0.00 (-12.48, 12.48)
	No	1 (4.0)	1 (4.0)	
Nonbiological	Yes	68 (91.9)	57 (85.1)	6.82 (-2.12, 16.16)
	No	6 (8.1)	10 (14.9)	
Treatment Naïve	Yes	90 (86.5)	94 (95.0)	-8.41 (-15.34, -1.65)
	No	14 (13.5)	5 (5.1)	
Region				
Americas	Yes	32 (91.4)	29 (87.9)	7.10 (-6.25, 20.91)
	No	3 (8.6)	4 (12.1)	
Europe	Yes	150 (89.3)	146 (92.4)	-3.09 (-8.46, 2.29)
	No	18 (10.7)	12 (7.6)	

Source: Reviewer analysis
*90% stratified Newcombe CI for the difference in PASI 75 response rate stratified by the previous systemic therapy use for exploratory purpose
**90% Unstratified Newcombe CI for the difference in PASI 75 response rate is reported for the previous systemic therapy use for exploratory purpose

Table 44 reports the subgroup analysis for the FDA recommended primary efficacy endpoint, percent improvement from baseline in PASI at Week 16, among subgroups: age group, sex, BMI, race, and previous systemic therapy use. In summary, there were no meaningful differences between treatment groups in the percent change of PASI at Week 16 from baseline by the various subgroups of subjects analyzed. The impact of age group, sex, BMI, race, and previous systemic therapy use was in general similar for MSB11022 and EU-Humira.

Table 44. Subgroup Analysis for the FDA Recommended Primary Efficacy Endpoint, Percent Change from Baseline in PASI at Week 16, in PP

Subgroup	MSB11022 (N=203)		EU-Humira (N=191)		LS Mean Difference (90% CI)*
	n	Mean (Std Dev)	n	Mean (Std Dev)	
Age					
<65 years	192	-90.88 (11.12)	184	-91.93 (9.85)	0.79 (-1.32, 2.90)
≥ 65 years	11	-86.92 (15.13)	7	-87.09 (12.50)	n/a
Sex					
Female	67	-92.87 (11.45)	61	-92.12 (8.93)	-0.50 (-3.46, 2.50)
Male	136	-89.58 (11.20)	130	-91.58 (10.43)	1.65 (-0.55, 3.85)
BMI					
< 25 kg/m^2	62	-93.50 (10.06)	68	-92.43 (9.57)	-0.71 (-3.61, 2.18)
≥ 25 kg/m^2	141	-89.42 (11.70)	123	-91.38 (10.18)	1.83 (-0.40, 4.07)
Race					
White	192	-90.69 (11.51)	179	-91.76 (10.08)	0.95 (-0.89, 2.78)
Non-white	11	-90.26 (8.68)	12	-91.70 (8.30)	2.14 (-5.56, 9.84)
Previous systemic therapy use**					
Biological (etanercept /infliximab)	25	-95.16 (6.99)	25	-94.44 (10.24)	-0.68 (-4.83, 3.47)
Non-biological	74	-90.02 (10.76)	67	-89.87 (10.97)	-0.30 (-3.38, 2.77)
Treatment naive	104	-90.05 (12.41)	99	-92.35 (9.00)	2.20 (-0.30, 4.69)
Region					
Americas	35	-91.78 (8.53)	33	-90.19 (11.87)	-2.44 (-6.70, 1.83)
Europe	168	-90.44 (11.87)	158	-92.08 (9.48)	1.39 (-0.55, 3.34)

Source: Reviewer analysis
*An ANCOVA model was fitted for each subgroup with treatment group, previous systemic therapy, sex, and BMI category as fixed factor and baseline PASI score as a covariate.
**AN ANCOVA model was fitted for each subgroup with treatment group, sex, and BMI category as fixed factor and baseline PASI score as a covariate.

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6.3. Review of Safety Data

Study EMR200588-002 enrolled subjects with moderate to severe plaque psoriasis and provided the primary data for comparisons of safety between EU-HUMIRA and MSB11022 (A/Citrate). The primary timepoint for the safety assessments was Week 16. Subsequently, a portion of subjects who received EU-HUMIRA were transitioned to MSB11022 (A/Citrate) in order to assess for potential safety issues after switching from EU-HUMIRA to MSB11022 (A/Citrate) for an additional 37 weeks. Comparative safety analyses were performed of treatment emergent adverse events and adverse reactions, serious adverse events, laboratory parameters, vital signs, hypersensitivity reactions, and immunogenicity.

Safety analyses were also performed for the single-dose clinical pharmacology studies FKS022-022 and EMR200588-001.

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

The Applicant provided safety data from three clinical studies: EMR200588-001, FKS022-002 and EMR200588-002, as listed in Section 2.2. All subjects received at least one 40 mg dose of either MSB11022, US-HUMIRA or EU-HUMIRA SC. The safety analyses were performed on the 'as treated' populations. The primary safety data was derived from the comparative clinical Study EMR200588-002 that evaluated subjects with moderate to severe plaque psoriasis. The other two studies (EMR200588-001 and FKS022-002) were PK studies conducted in healthy subjects.

Study EMR200588-001 was a randomized, double-blind, parallel-group, single-dose study comparing the pharmacokinetics, safety, tolerability, and immunogenicity of MSB11022, US-Humira, and EU-Humira in healthy volunteers. Briefly, 237 healthy subjects were randomized to receive MSB11022 (n=78), US-Humira (n=80) or EU-Humira (n=79). Healthy subjects received a single dose of either MSB11022 (A/Citrate) 40 mg (PFS), US-Humira 40 mg (PFS) or EU-Humira (PFS) via subcutaneous injection. Serum PK samples were collected on PK: Day 1 at 0 (pre-dose), 4, 8, 12 hours post-dose and Day 2, 3, 4, 5, 6, 7, 8, 9, 11, 15, 22, 29, 36, 43, 57 and 71. All randomized subjects received a single dose of study drug. The reader is referred to Section 5.3.1 for further details of the overall study design. The safety database of study EMR200588-001 was sufficient to show no meaningful differences between MSB11022 (A/Citrate), US-Humira, and EU-Humira.

Study FKS022-022 was a randomized, double-blind, parallel group, single-dose study designed to compare the pharmacokinetics, safety, tolerability, and immunogenicity of MSB11022 (C/Acetate) compared to US-Humira and MSB11022 (A/Citrate). A total of 452 healthy subjects who were randomized received a single dose subcutaneous injection of either MSB11022 (C/Acetate) 40 mg (n=150), US-Humira 40 mg (n=152) or MSB11022 (A/Citrate) 40 mg (n=150). Serum PK samples were collected on PK: Day 1

at 0 (pre-dose), 4, 8, 12 hours post-dose and Day 2, 3, 4, 5, 6, 7, 8, 9, 11, 15, 22, 29, 36, 43, 57 and 71. The reader is referred to Section 5.3.2 for further details of the overall study design. The safety database of study FKS022-022 was adequate to demonstrate no clinically meaningful differences between MSB11022 (A/Citrate), US-Humira, and MSB11022 (C/Acetate).

Study EMR200588-002 was a randomized, double-blind, parallel group, active-controlled study in subjects with moderate to severe plaque psoriasis that provided the primary safety data. The safety population (defined as the population of subjects who received at least one dose of the investigational product) included 441 subjects, 221 initially randomized to MSB11022 (A/Citrate) and 220 initially randomized to EU-HUMIRA. At Week 16, all subjects who achieved <PASI 50 response withdrew from the study. Subjects who achieved ≥PASI 50 response who were initially randomized to MSB11022 (A/Citrate) continued on MSB11022 (A/Citrate), while subjects who were initially randomized to EU-HUMIRA were re-randomized to continue on EU- HUMIRA or transition to MSB11022 (A/Citrate). The transition period was used to assess potential risks related to safety and immunogenicity that resulted from switching from EU-HUMIRA to MSB11022 (A/Citrate). Additional details of the study design are described in Section 6.2.1.

The size of the safety database of EMR200588-002 was adequate to demonstrate findings of no meaningful differences between MSB11022 (A/Citrate) and EU-HUMIRA.

Categorization of Adverse Events

Adverse events (AEs)[4] were evaluated throughout Study EMR200588-002 and coded using MedDRA Version 20.1. Study EMR200588-002 used the following standard categorization of AEs:

A Serious Adverse Event (SAE) was defined as any untoward medical occurrence that at any dose:

- Resulted in death
- Was life-threatening (The term “life-threatening” referred to an event in which the subject was at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe)
- Required inpatient hospitalization or prolonged an existing hospitalization
- Resulted in persistent or significant disability or incapacity
- Was a congenital anomaly or birth defect
- Was otherwise considered to be medically important. (Note: Important medical events that may not have resulted in death, be life-threatening, or required hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may have jeopardized the subject or may have required medical or surgical intervention to prevent one of the outcomes listed above.

[4] 21 CFR § 312.32(a): Adverse event refers to any untoward medical event associated with the use of a drug in humans, whether or not it is considered drug related.

Examples of such events included allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Investigators graded the severity or toxicity of each AE by utilizing the National Cancer Institute – Common Terminology Criteria for AEs ([NCI-CTCAE], Version 4.03, publication date: 14 June 2010). The following five grades were used:

- Grade 1 or Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 or Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 3 or Severe; medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
- Grade 4 or Life-threatening consequences; urgent intervention indicated.
- Grade 5 or Death related to AE.

Any clinical AE with severity of Grade 4 or 5 was reported as an SAE.

Investigators assessed the causal relationship of AEs to IMPs using the following definitions.

Unrelated: Not reasonably related to the IMPs. AE could not medically (pharmacologically/clinically) be attributed to the IMPs under study. A reasonable alternative explanation must have been available.

Related: Reasonably related to the IMPs. AE could medically (pharmacologically/clinically) be attributed to the IMPs under study.

Treatment-emergent adverse events (TEAEs were those events that started on or after the day of first administration of study treatment up to the 4-month Safety Evaluation assessment. A “worst case approach” was used (i.e., if time was missing or if the AE occurred at the same time as the first administration of the first study treatment given, then the AE was to be classified as treatment emergent).

The following were predefined **Adverse Events of Special Interest** (AESIs) for this study:

- Serious infections (those requiring hospitalization, those with fatal outcome or sepsis, or those requiring intravenous antibiotics/antimicrobials)
- Latent tuberculosis infection (LTBI)
- Active tuberculosis (TB).

Based on labeled risks associated with US-Humira and other TNF inhibitors, the Applicant submitted an assessment of the following additional AESIs (4-month safety

update report submitted 4/6/22) as requested by the FDA during a BPD Type 4 meeting (held on 10/4/2021):

- New onset of Lupus-like syndrome
- Malignancies including lymphoma and leukemia
- Elevations in liver enzymes

Safety Analyses

The analyses of the safety of MSB11022 were conducted on the safety population comprised of all subjects randomized and treated with at least 1 dose of study drug. By agreement with the Agency, the application did not include integrated (pooled) analyses of the AE data across the three clinical studies due to differences in the study designs, study populations and treatment durations.

Treatment-emergent adverse events (TEAEs), treatment-related TEAEs, and SAEs were summarized by SOC and PT according to MedDRA terminology with descriptive comparisons between MSB11022 and EU-HUMIRA (and, where applicable, US-HUMIRA).

In Study EMR200588-002, the Applicant pre-specified the following safety endpoints and analyses:

- The nature, occurrence, severity, and outcome of AEs, SAEs, and AESIs, including overall deaths.
- Frequency and severity of injection site reactions (ISRs).
- Routine safety parameters, including laboratory values (including hematology, chemistry, urinalysis, anti-double-stranded DNA, and antinuclear antibodies), vital sign measurements, 12-lead ECG results, tuberculosis assessments, and physical examination findings.

The review of the safety of MSB11022 in Study EMR200588-002 focused on the comparison of the data from subjects who received MSB11022 (A/Citrate) versus EU-HUMIRA during the Core Treatment Period (Weeks 1 to 16). In addition, data from subjects who received continuous MSB11022 was compared with data from subjects who received continuous EU-HUMIRA from the Overall Treatment Period (Weeks 1 to 54). An analysis was also performed of the effects of switching from EU-Humira to the proposed biosimilar in terms of hypersensitivity, immunogenicity, or other reactions. At Week 16, the protocol specified that subjects who received EU-HUMIRA were re-randomized to either continue on EU-HUMIRA or switch to MSB11022 (A/Citrate). A single transition was used to specifically assess potential differences in safety and immunogenicity risk as a result of switching from EU-HUMIRA to MSB11022 (A/Citrate).

Refer to Section 5.4 Clinical Immunogenicity Studies and Section 6.4 Clinical Conclusions on Immunogenicity for the discussion of the safety analyses pertaining to immunogenicity assessments.

6.3.2. Major Safety Results

EMR200588-001 and FKS022-022
Analysis of the safety data from the single-dose pharmacology studies EMR200588-001 and FKS022-022 were performed and no clinically significant differences regarding deaths, SAEs, TEAEs, AEs leading to discontinuation or AESIs were seen between treatment arms. Due to the nature of these study designs, clinically relevant safety information is limited and will not be further discussed in this review. The review of safety of MSB11022 will focus on the data derived from study EMR200588-002.

EMR200588-002
Analysis of the safety data from Study EMR200588-002 identified no new safety signals in subjects who received MSB11022 compared with the labeled safety profile of US-HUMIRA. As summarized below, the overall safety profile was comparable between MSB11022 and EU-HUMIRA during the 16- week, double-blind period (Table 43). In addition, the safety profile was comparable among subjects who transitioned from EU-HUMIRA to MSB11022 during the second 36 weeks of double-blind transition treatment period (Table 44), and between subjects who remained on continuous MSB11022 or continuous EU-HUMIRA during Weeks 1 to 54, Table 45**).** While there were some minor numerical differences in AEs, the small number of events and the inconsistent trends are likely due to chance alone and do not indicate meaningful differences between the two treatment arms. Overall, there were no clinically significant differences in the proportions of deaths, SAEs, TEAEs, AEs leading to discontinuation, and AESIs between the treatment groups.

Relevant Characteristics of the Population Evaluated for Safety

The safety database submitted for assessment of comparative safety between MSB11022, US-HUMIRA and EU-HUMIRA included three clinical studies (two single-dose comparative PK studies, EMR200588-001 and FKS022-022, and one comparative clinical study, EMR200588-002) as summarized above under “Clinical Studies Used to Evaluate Safety.” Due to differences in clinical study design and study population, no pooled analyses by demographic subgroups were performed. Refer to Section 6.2, Table 28, for comparison of the baseline disease characteristics of subjects in study EMR200588-002.

Other Product-Specific Safety Concerns

Deaths

There was one death in Study EMR200588-002 which occurred in the continuous EU-HUMIRA arm. The subject was a 42- year-old male without documented medical history who was found unconscious with possible head injury 173 days after the first dose of EU-HUMIRA (12 days after the most recent dose). The circumstances leading to head injury were unknown. At surgery, the subject had a cerebral hematoma and “brain edema”; subsequently, the subject developed coma and cardiac failure, which lead to

his death. No autopsy was performed. Based on review of the submitted narrative, the death was not likely to be related to the study treatment.

There were no deaths in healthy subjects enrolled in studies EMR200588-001 and FKS022-022.

Treatment Emergent Adverse Events

Serious Adverse Events

Overall, the incidence of serious adverse events (SAEs) was similar across treatment groups for each treatment period. There were no meaningful differences between MSB11022 and EU-HUMIRA. SAEs generally occurred in single subjects by preferred term. There were insufficient numbers of SAEs to allow an analysis by subgroup.

During the Core Treatment Period (Weeks 1 to 16), a total of 14 subjects experienced 14 SAEs: 8 (8/221; 3.6%) subjects treated with MSB11022 reported 8 SAEs and six (6/220; 2.7%) subjects treated with EU-HUMIRA reported 6 SAEs. In the MSB11022 treatment group, two subjects (0.9%) had 2 SAEs (respiratory tract infection viral and erythema multiforme) which were considered related to the study product by investigator. In the EU-HUMIRA treatment group, four subjects (1.8%) had 4 SAEs (intraductal proliferative breast lesion, bacterial arthritis, hepatic enzyme increased, and liver function test increased) which were considered related to the study product by the investigator. Refer to Table 45 below.

During the Extended Treatment Period (Weeks 16 to 54), a total of 19 subjects experienced 27 SAEs, which were generally well balanced across the treatment groups. Refer to Table 46 below.

During the Overall Treatment Period (Weeks 1 to 54), a total of 28 subjects experienced 36 SAEs: 20 (20/221; 9.0%) subjects treated with continuous MSB11022 reported 24 SAEs and eight (8/119; 6.7%) subjects treated with continuous EU-HUMIRA reported 12 SAEs. In the continuous MSB11022 treatment group, three subjects (1.3%) had 3 SAEs (viral respiratory tract infection, erythema multiforme, and accidental overdose) which were considered related to study product by investigator. In the continuous EU-HUMIRA treatment group, five subjects (4.2%) had 6 SAE (cardiac failure and pneumonia, intraductal proliferative breast lesion, bacterial arthritis, hepatic enzyme increased, and liver function test increased) considered related to study product by the investigator. Refer to Table 47 below.

The related SAEs were expected based on the known safety profile of US-HUMIRA.

Table 45. SAEs in the Core Treatment Period by MedDRA Preferred Terms

	MSB11022; N = 221		EU-HUMIRA; N = 220		
	Subjects (%)	Events	Subjects (%)	Events	
Subjects with at least one event and total events	8 (3.60)	8	6 (2.70)	6	
Neutropenia	0 (0.00)	0	1 (0.50)	1	
Atrial fibrillation	1 (0.50)	1	2 (0.91)	0	
Hernia	1 (0.45)	1	0 (0.00)	0	
Cholecystitis chronic	1 (0.50)	1	0 (0.00)	0	
Anaphylactic shock	0 (0.00)	0	1 (0.50)	1	
Arthritis bacterial	0 (0.00)	0	1 (0.50)	1	
Respiratory tract infection viral	1 (0.50)	1	0 (0.00)	0	
Ankle fracture	1 (0.50)	1	0 (0.00)	0	
Hepatic enzyme increased	0 (0.00)	0	1 (0.50)	1	
Liver function test increased	0 (0.00)	0	1 (0.50)	1	
Osteonecrosis	1 (0.50)	1	0 (0.00)	0	
Intraductal proliferative breast lesion	0 (0.00)	0	1 (0.50)	1	
Erythema multiforme	1 (0.50)	1	0 (0.00)	0	
Hypertension	1 (0.50)	1	0 (0.00)	0	

Source: Reviewer's Table adapted from CSR Table 15.3.1.13

Only events that started up to and including the Week 54 analysis cut-off date are included

Table 46. SAEs in the Extended Treatment Period by MedDRA Preferred Terms

	MSB11022; N = 213		EU-HUMIRA; N = 101		EU-HUMIRA/MSB11022; N = 101	
	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)	Events
Subjects with at least one event and total events	12 (5.60)	16	3 (3.00)	7	4 (4.00)	4
Acute myocardial infarction	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Atrial fibrillation	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Cardiac failure	0 (0.00)	0	2 (2.00)	2	0 (0.00)	0
Cardiomyopathy	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Coronary artery stenosis	1 (0.50)	2	0 (0.00)	0	0 (0.00)	0
Hypertensive cardiomyopathy	0 (0.00)	0	1 (1.00)	1	0 (0.00)	0
Mitral valve incompetence	0 (0.00)	0	1 (1.00)	1	0 (0.00)	0
Myocardial infarcation	0 (0.00)	0	0 (0.00)	0	1 (1.00)	1
Conjunctival cyst	0 (0.00)	0	0 (0.00)	0	1 (1.00)	1
Inguinal hernia	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Appendicitis	0 (0.00)	0	0 (0.00)	0	1 (1.00)	1
Peritonsillar abscess	0 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Pneumonia	0 (0.00)	0	1 (1.00)	1	0 (0.00)	0
Sinusitis	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Staphylococcal abscess	0 (0.00)	0	0 (0.00)	0	1 (1.00)	1
Accidental overdose	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Facial bones fracture	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Ligament sprain	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Intervertebral disc protrustion	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Osteoarthritis	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Brain oedema	0 (0.00)	0	1 (1.00)	1	0 (0.00)	0
Cerebral haematoma	0 (0.00)	0	1 (1.00)	1	0 (0.00)	0
Acute kidney injury	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Hypersensitivity vasculitis	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0
Vascular compression	1 (0.50)	1	0 (0.00)	0	0 (0.00)	0

Source: Reviewer's Table adapted from CSR Table 15.3.1.14

Only events that started up to and including the Week 54 analysis cut-off date are included

Table 47. SAEs in the Overall Treatment Period by MedDRA Preferred Terms

	Continuous MSB11022; N = 221		Continuous EU-HUMIRA; N = 119	
	Subjects (%)	Events	Subjects (%)	Events
Subjects with at least one event and total events	20 (9.00)	24	8 (6.70)	12
Neutropenia	0 (0.00)	0	1 (0.80)	1
Acute myocardial infarction	1 (0.50)	1	0 (0.00)	0
Atrial fibrillation	2 (0.90)	2	0 (0.00)	0
Cardiac failure	0 (0.00)	0	2 (1.70)	2
Cardiomyopathy	1 (0.50)	1	0 (0.00)	0
Coronary artery stenosis	1 (0.50)	2	0 (0.00)	0
Hypertensive cardiomyopathy	0 (0.00)	0	1 (0.80)	1
Mitral valve incompetence	0 (0.00)	0	1 (0.80)	1
Inguinal hernia	1 (0.50)	1	0 (0.00)	0
Hernia	1 (0.50)	1	0 (0.00)	0
Cholecystitis chronic	1 (0.50)	1	0 (0.00)	0
Arthritis bacterial	0 (0.00)	0	1 (0.80)	1
Peritonsillar abscess	1 (0.50)	1	0 (0.00)	0
Pneumonia	0 (0.00)	0	1 (0.80)	1
Respiratory tract infection viral	1 (0.50)	1	0 (0.00)	0
Sinusitis	1 (0.50)	1	0 (0.00)	0
Accidental overdose	1 (0.50)	1	0 (0.00)	0
Ankle fracture	1 (0.50)	1	0 (0.00)	0
Facial bones fracture	1 (0.50)	1	0 (0.00)	0
Ligament sprain	1 (0.50)	1	0 (0.00)	0
Hepatic enzyme increased	0 (0.00)	0	1 (0.80)	1
Liver function test increased	0 (0.00)	0	1 (0.80)	1
Intervertebral disc protrustion	1 (0.50)	1	0 (0.00)	0
Osteoarthritis	1 (0.50)	1	0 (0.00)	0
Osteonecrosis	1 (0.50)	1	0 (0.00)	0
Intraductal proliferative breast lesion	0 (0.00)	0	1 (0.80)	1
Brain oedema	0 (0.00)	0	1 (0.80)	1
Cerebral haematoma	0 (0.00)	0	1 (0.80)	1
Acute kidney injury	1 (0.50)	1	0 (0.00)	0
Erythema multiforme	1 (0.50)	1	0 (0.00)	0
Hypersensitivity vasculitis	1 (0.50)	1	0 (0.00)	0
Hypertension	1 (0.50)	1	0 (0.00)	0
Vascular compression	1 (0.50)	1	0 (0.00)	0

Source: Reviewer's Table adapted from CSR Table 15.3.1.15

Only events that started up to and including the Week 54 analysis cut-off date are included

Treatment Emergent Adverse Events and Adverse Reactions:

Overall, TEAEs were comparable between MSB11022 and EU-HUMIRA and before and after transition from EU-HUMIRA to MSB11022. While there were some minor numerical differences in TEAEs, the small number of events and the inconsistent trends are likely due to chance alone and do not indicate meaningful differences between the two treatment arms.

During the Core Treatment Period (Weeks 1 to 16) of Study EMR200588-002, a total of 114 (114/221; 51.6%) subjects who received MSB11022 developed TEAEs (49/221 [22.2%] were considered related), and 117 (117/220; 52.2%) subjects who received EU-HUMIRA developed a TEAE (51/220 [23.2%] were considered related). Selected TEAES reported in ≥ 1% of subjects in the Core Treatment Period are presented below in Table 48, and selected TEAS reported in ≥ 1% of subjects that were considered treatment related by the investigator in the Core Treatment Period are presented below in Table 49.

Table 48. Selected TEAS reported in ≥ 1% of subjects in the Core Treatment Period:

	MSB11022; N = 221	EU-HUMIRA; N = 220
	Subjects (%)	Subjects (%)
Upper respiratory infection*	25 (11.31)	26 (11.82)
Injection site erythema	11 (4.98)	13 (5.91)
Injection site pain	11 (4.98)	11 (5.00)
Injection site bruising	4 (1.81)	5 (2.27)
Injection site pruritus	3 (1.36)	6 (2.73)
Injection site induration	3 (1.36)	4 (1.82)
Hepatic enzyme abnormalities**	10 (4.52)	10 (4.54)
Cholesterol abnormalities***	15 (6.79)	13 (5.91)
Arthralgia†	5 (2.26)	2 (0.91)
Headache	8 (3.62)	7 (3.18)
Hypertension‡	8 (3.62)	2 (0.91)
Hyperuricaemia^	5 (2.26)	3 (1.36)

Source: Reviewer's Table generated using JMP Clinical and ADAE and ADSL datasets

*Upper respiratory infection includes nasopharyngitis, pharyngitis, upper respiratory tract infection, tonsillitis, chronic tonsillitis, acute sinusitis, sinusitis, oropharyngeal pain, rhinorrhoea.

**Hepatic enzyme abnormalities include alanine aminotransferase increased, gamma-glutamyltransferase incerased, hepatic enzyme increased, transaminases increased, aspartate aminotransferase increased, blood bilirubin increased, liver function test increased.

***Cholesterol abnormalities include blood triglycerides increased, hypertriglyceridaemia, hyperlipidaemia, hypercholesterolaemia, dyslipidaemia.

†None of the arthraliga cases in either arm were considered treatment related by the investigator.

‡Hypertension includes blood pressure increased and hypertension. None of the hypertension cases in either arm were considered treatment related by the investigator.

^Hyperuricaemia includes blood uric acid increased and hyperuricaemia. One of the hyperuricaemia cases in the MSB11022 arm was considered treatment related by the investigator.

Table 49. Selected TEAEs reported in ≥ 1% of subjects that were considered treatment related by the investigator in the Core Treatment Period

	MSB11022; N = 221	EU-HUMIRA; N = 220
	Subjects (%)	Subjects (%)
Upper respiratory infection*	8 (3.62)	3 (1.36)
Cholesterol abnormalities**	3 (1.36)	2 (0.91)
Hepatic enzyme abnormalities***	1 (0.45)	4 (1.82)
Injection site erythema	11 (4.98)	13 (5.91)
Injection site pain	10 (4.52)	9 (4.09)
Injection site bruising	3 (1.36)	4 (1.82)
Injection site pruritus	3 (1.36)	5 (2.27)
Injection site induration	3 (1.36)	4 (1.82)

Source: Reviewer's Table generated from JMP Clinical using ADAE and ADSL datasets

*Upper respiratory infection includes nasopharyngitis, pharyngitis, upper respiratory tract infection, tonsillitis, chronic tonsillitis, acute sinusitis, sinusitis, oropharyngeal pain, rhinorrhoea

**Cholesterol abnormalities include blood triglycerides increased, hypertriglyceridaemia, hyperlipidaemia, hypercholesterolaemia, dyslipidaemia

***Hepatic enzyme abnormalities include alanine aminotransferase increased, gamma-glutamyltransferase incerased, hepatic enzyme increased, transaminases increased, aspartate aminotransferase increased, blood bilirubin increased, liver function test increased

The slight imbalance in the incidence of treatment related upper respiratory tract infection in the MSB11022 arm (3.62%) versus the EU-HUMIRA arm (1.36%) during the Core Treatment Period is likely due to chance alone. The limited number of events in a relatively small safety database is insufficient to support a meaningful difference between with two treatment arms.

During the Core Treatment Period, the severity of most TEAEs was Grade 1 (mild) or Grade 2 (moderate). In the MSB11022 arm, 9 subjects (4.1%) had severe TEAEs, all of which were of Grade 3; 2 of these Grade 3 TEAEs (pharyngitis and erythema multiforme) were considered related to the study product. In the EU-HUMIRA arm, 3 subjects (1.4%) had Grade 3 TEAEs and 2 subjects (0.9%) had Grade 4 TEAEs; 2 of the Grade 3 TEAEs (bacterial arthritis and intraductal proliferative breast lesion) and 1 Grade 4 TEAE (increased hepatic enzyme) were considered related to the study product.

During the Extended Treatment Period (Weeks 16 to 52) of Study EMR200588-002, a similar proportion of subjects developed any TEAE in the group that switched from EU-HUMIRA to MSB11022 and the group that remained on EU-HUMIRA. The proportion of subjects who developed a TEAE leading to treatment discontinuation or study termination was greater in among subjects who remained on EU-HUMIRA (5.9% and 5.0%, respectively) than among subjects who switched to MSB11022 (3.0% and 2.0%, respectively).

Selected TEAS reported in ≥ 2% of subjects in the Extended Treatment Period are presented below in Table 50. During this period the frequency of TEAEs by CTCAE grade and distribution of PTs were similar across the treatment groups and consistent with the Core Treatment Period. The most commonly reported TEAEs were nasopharyngitis (14.9% of subjects in the EU-HUMIRA to MSB11022 group and 11.9% in the EU-HUMIRA to EU-HUMIRA group) and injection site erythema (5.9% and 5.0%, respectively). Treatment-related TEAEs were reported for 16 subjects (15.8%) in the EU-HUMIRA to MSB11022 group and 22 subjects (21.8%) in the EU-HUMIRA to EU-HUMIRA group; most of these related TEAEs were injection site reactions (reported for 12 subjects [11.9%] in EU-HUMIRA to MSB11022 group and 11 subjects [10.9%] in the EU-HUMIRA to EU-HUMIRA group).

Table 50. Selected TEAEs reported in ≥ 2% of subjects in the Extended Treatment Period

	MSB11022; N = 213		EU-HUMIRA; N = 101		EU-HUMIRA/ MSB11022; N = 101	
	Subjects (%)		Subjects (%)		Subjects (%)	
Subjects with at least one event	139	(65.30)	64	(63.40)	61	(60.40)
Eosinophilia	1	(0.50)	0	(0.00)	2	(2.00)
Asthenia	0	(0.00)	2	(2.00)	0	(0.00)
Injection site erythema	9	(4.20)	5	(5.00)	6	(5.90)
Injection site induration	4	(1.90)	2	(2.00)	0	(0.00)
Injection site pain	12	(5.60)	4	(4.00)	5	(5.00)
Injection site pruritis	3	(1.40)	3	(3.00)	2	(2.00)
Bronchitis	10	(4.70)	2	(2.00)	2	(2.00)
Latent tuberculosis	5	(2.30)	0	(0.00)	2	(2.00)
Nasopharyngitis	13	(14.60)	12	(11.90)	15	(14.90)
Respiratory tract infection	2	(0.90)	1	(1.00)	2	(2.00)
Rhinitis	2	(0.90)	0	(0.00)	2	(2.00)
Sinusitis	3	(1.40)	2	(2.00)	1	(1.00)
Tooth abscess	1	(0.50)	2	(2.00)	0	(0.00)
Upper respiratory tract infection	11	(5.20)	4	(4.00)	4	(4.00)
Urinary tract infection	2	(0.90)	0	(0.00)	2	(2.00)
Viral upper respiratory tract infection	0	(0.00)	1	(1.00)	2	(2.00)
Blood triglycerides increased	4	(1.90)	2	(2.00)	1	(1.00)
Hypertriglyceridaemia	7	(3.30)	1	(1.00)	1	(1.00)
Hypophosphatemia	3	(1.40)	3	(3.00)	0	(0.00)
Arthralgia	9	(4.20)	3	(3.00)	3	(3.00)
Headache	3	(1.40)	1	(1.00)	5	(5.00)
Cough	2	(0.90)	2	(2.00)	2	(2.00)
Rhinorrhoea	0	(0.00)	2	(2.00)	0	(0.00)
Pruritis	4	(1.90)	3	(3.00)	1	(1.00)
Psoriasis	4	(1.90)	5	(5.00)	0	(0.00)
Seborrhoeic dermatitis	0	(0.00)	0	(0.00)	2	(2.00)
Hypertension	4	(1.90)	3	(3.00)	1	(1.00)

Source: Reviewer's Table adapted from CSR Table 15.3.1.8 and confirmed using JMP Clinical and ADAE and ADSL datasets. Only events that started up to and including the Week 54 analysis cut-off date are included.

The numerical imbalance of latent TB cases in the Extended Treatment Period between treatment groups (2% of subjects in the EU-HUMIRA to MSB11022 group and 0% of subjects in the EU-HUMIRA to EU-HUMIRA group) is discussed under Adverse Events of Special Interest.

During the Overall Treatment Period (Weeks 1 to 54): 173 (173/221; 78.3%) subjects treated with continuous MSB11022 developed a TEAE of which 69 (69/221; 31.2%) were considered related. A total of 91 (91/119; 76.4%) subjects treated with continuous EU-HUMIRA developed a TEAE of which 41 (41/119; 34.5%) were considered related. Selected TEAEs reported in ≥ 1% of subjects in the Overall Treatment Period are presented below in Table 51. Selected TEAEs reported in ≥ 1% of subjects that were considered treatment related by the investigator in the Overall Treatment Period are presented below in Table 52.

Table 51. Selected TEAEs reported in ≥ 1% of subjects in the Overall Treatment Period

	Continuous MSB11022; N = 221	Continuous EU-HUMIRA; N = 119
	Subjects (%)	Subjects (%)
Upper respiratory infection*	72 (32.58)	34 (28.57)
Bronchitis**	10 (4.52)	2 (1.68)
Latent tuberculosis	5 (2.26)	0 (0.00)
Urinary tract infection***	4 (1.81)	1 (0.84)
Viral infection†	5 (2.26)	0 (0.00)
Injection site erythema	17 (7.69)	8 (6.72)
Injection site pain	17 (7.69)	6 (5.04)
Injection site bruising	11 (4.98)	7 (5.88)
Injection site pruritus	5 (2.26)	4 (3.36)
Injection site induration	7 (3.17)	4 (3.36)
Injection site swelling	3 (1.36)	1 (0.84)
Cholesterol abnormalities‡	26 (11.76)	6 (5.04)
Hepatic enzyme abnormalities^	17 (7.69)	9 (7.56)
Arthralgia	12 (5.43)	5 (4.20)
Psoriatic arthropathy	4 (1.81)	0 (0.00)
Hyperuricaemia^^	5 (2.26)	3 (2.52)
Nausea	5 (2.26)	1 (0.84)
Headache	10 (4.52)	1 (0.84)
Hypertension^^^	11 (4.98)	4 (3.36)
Eosinophilia#	3 (1.36)	0 (0.00)

Source: Reviewer's Table generated in JMP Clinical using ADAE and ADSL datasets

*Upper respiratory infection includes nasopharyngitis, pharyngitis, upper respiratory tract infection, tonsillitis, chronic tonsillitis, acute sinusitis, sinusitis, oropharyngeal pain, rhinorrhoea, viral upper respiratory tract infection, throat irritation, nasal congestion.

**Two of the bronchitis cases in the MSB11022 arm (2/221, 0.90%), and one of the bronchitis cases in the EU-HUMIRA arm (1/119, 0.84%) were considered treatment related by the investigator.

***None of the UTI cases were considered treatment related by the investigator.

†None of the viral infection cases were considered treatment related by the investigator.

‡Cholesterol abnormalities include blood triglycerides increased, hypertriglyceridaemia, hyperlipidaemia, hypercholesterolaemia,

^Hepatic enzyme abnormalities include alanine aminotransferase increased, gamma-glutamyltransferase incerased, hepatic enzyme increased, transaminases increased, aspartate aminotransferase increased, blood

^^Hyperuricaemia includes blood uric acid increased and hyperuricaemia.

^^^Hypertension includes blood pressure increased and hypertension.

#One of the eosinophilia cases in the MSB11022 arm (1/221, 0.45%) was considered treatment related by the investigator.

As discussed above for the Core Treatment Period, the small imbalances in the incidence of upper respiratory tract infection and cholesterol abnormalities in the MSB11022 arm versus the EU-HUMIRA arm during the Overall Treatment Period is likely due to chance alone. The higher values observed in the MSB11022 arm are more

consistent with the findings in current labeling for HUMIRA. The numerical imbalance of latent TB cases in the Overall Treatment Period between treatment groups (2% of subjects in the continuous MSB11022 group and 0% of subjects in the continuous EU-HUMIRA group) is discussed under Adverse Events of Special Interest.

Table 52. Selected TEAEs reported in ≥ 1% of subjects that were considered treatment related by the investigator in the Overall Treatment Period

	Continuous MSB11022; N = 221		Continuous EU-Humira; N = 119	
	Subjects (%)		Subjects (%)	
Upper respiratory tract infection*	15	(6.79)	4	(3.36)
Latent tuberculosis	4	(1.81)	0	(0.00)
Injection site erythema	16	(7.24)	8	(6.72)
Injection site pain	15	(6.79)	6	(5.04)
Injection site bruising	8	(3.62)	6	(5.04)
Injection site pruritus	5	(2.26)	4	(3.36)
Injection site induration	7	(3.17)	4	(3.36)
Injection site swelling	3	(1.36)	1	(0.84)
Cholesterol abnormalities**	5	(2.26)	1	(0.84)
Hepatic enzyme abnormalities***	4	(1.81)	5	(4.20)

Source: Reviewer's Table generated from JMP Clinical using ADAE and ADSL datasets

*Upper respiratory infection includes nasopharyngitis, pharyngitis, upper respiratory tract infection, tonsillitis, chronic tonsillitis, acute sinusitis, sinusitis, oropharyngeal pain, rhinorrhoea, viral upper respiratory tract infection, throat irritation, nasal congestion.

**Cholesterol abnormalities include blood triglycerides increased, hypertriglyceridaemia, hyperlipidaemia, hypercholesterolaemia, dyslipidaemia.

***Hepatic enzyme abnormalities include alanine aminotransferase increased, gamma-glutamyltransferase incerased, hepatic enzyme increased, transaminases increased, aspartate aminotransferase increased, blood bilirubin increased. liver function test increased.

During the Overall Treatment Period, the severity of most TEAEs was Grade 1 or Grade 2. In the continuous MSB11022 arm, 21 subjects (9.5%) had Grade 3 TEAEs and no subjects had Grade 4 TEAEs; of these, 4 subjects had Grade 3 TEAEs (1.8%) (laryngitis, pharyngitis, tracheitis, prothrombin time prolonged, and erythema multiforme) that were related to IMP. In the continuous EU-HUMIRA arm, 5 subjects (4.2%) had Grade 3 TEAEs, of which 2 (1.7%) were related to IMP (arthritis bacterial and intraductal proliferative breast lesion), and 1 subject (0.8%) had a Grade 4 TEAE (hepatic enzyme increased) that was related to IMP.

Adverse Events of Special Interest (AESIs)

The Applicant evaluated serious infections, latent TB, active TB, new onset of Lupus-like syndrome, malignancy, and elevations in liver enzymes as AESIs. There were a small number of AESIs and the differences between the treatment arms were not meaningful. There were no reports of new onset of lupus-like syndrome. A 63- year -old female subject with a family history of breast and ovarian cancer had microcalcifications identified in the left breast on routine annual mammogram approximately one month after initiating EU-HUMIRA. Following resection, the subject was diagnosed with ductal carcinoma in situ without lymph node involvement.

During the Core Treatment Period (Weeks 1 to 16), 12 (12/221; 5.4%) subjects who received MSB11022 had at least one AESI [15 total events]. The AESIs that were reported by ≥ 1% of subjects included hepatic enzyme abnormalities in 10 (10/221; 4.52%) subjects. A total of 12 (12/220; 5.5%) subjects who received EU-HUMIRA had at least 1 AESI, [18 total events]. The AESIs reported by ≥ 1% of subjects included hepatic enzyme abnormalities in 10 (10/220; 4.54%) subjects.

During the Overall Treatment Period (Weeks 1 to 54), a total of 27 (27/221; 12.2%) subjects experienced 36 AESI in the continuous MSB11022 arm. The AESIs reported by ≥ 1% of subjects included latent tuberculosis in 5 (5/221; 2.3%) subjects and hepatic enzyme abnormalities in 17 (17/221; 7.69%) subjects. A total of 12 (12/119; 10.1%) subjects experienced 18 AESI in the continuous EU-HUMIRA arm. The AESIs reported by ≥ 1% of subjects included hepatic enzyme abnormalities in 9 (9/221; 7.56%) subjects. Though there was an increased number of AESI in the MSB11022 arm compared to EU-HUMIRA arm, the incidence rate per 100-subjects years was similar for both arms (see Table X53and Table 54 below), and the differences in AESIs between the treatment arms do not appear to be clinically significant.

Initial TB assessments were conducted at Screening and QuantiFERON-TB Gold tests were performed at Weeks 24 and Week 52 during the study. The proportion of subjects with positive TB assessments at Week 24 was similar across the treatment groups (1.1%, 1.2%, and 1.2% for the MSB11022, EU-HUMIRA, and EU-HUMIRA to MSB11022 groups, respectively). At Week 52, the proportion of subjects with positive TB assessments was 1.7% and 1.2% for the MSB11022 and EU-HUMIRA to MSB11022 groups, respectively. Indeterminate TB results were reported in 2.8%, 6.0%, and 2.4% of subjects in the MSB11022, EU-HUMIRA, and EU-HUMIRA to MSB11022 groups, respectively. One (0.5%) subject in the MSB11022 group in the Overall Treatment Period had 1 event of tuberculosis (active disease), resulting in the incidence rate of 0.47 (95% CI: 0.01, 2.64) events per 100 subject years. No event of tuberculosis was reported in EU-HUMIRA group

The numerical imbalance of latent TB cases in the Extended Treatment Period and Overall Treatment Period between treatment groups may be related to a number of factors: regional differences in the prevalence of TB (e.g., higher prevalence in Mexico),

false positive tests (not confirmed on repeated assessment), and relatively small safety database. Representative narrative summaries of latent TB cases are provided below.

- 64-year-old woman (b) (6) from Mexico with chronic plaque psoriasis and no relevant medical history had a positive QuantiFERON-TB gold test on Day 365. The subject received **EU-HUMIRA** until Week 16 and **MSB11022** thereafter. The subject was asymptomatic with normal chest X-ray. Repeat QuantiFERON-TB gold test was negative. The subject received a 6-week course of isoniazid for prophylaxis. The adverse event of "latent" TB was considered related to **MSB11022.** However, the occurrence of a single positive QuantiFERON test that was not confirmed by repeat testing or chest X-ray in this asymptomatic subject suggests that this finding may represent a false positive test. (According to Moses et al. the false positive rate of QuantiFERON-TB Gold testing may be as high as 25%.[5])

- 40-year-old man (b) (6) from Mexico with chronic plaque psoriasis with no relevant medical history had a positive QuantiFERON-TB gold test 357 days after the first administration of **MSB11022**. The subject was asymptomatic with no physical examination findings. Repeat QuantiFERON-TB gold test was negative on two occasions and subsequent chest tomography was negative. The adverse event of "latent" TB was considered related to MSB11022**.**

- 61-year-old woman (b) (6) from Mexico with chronic plaque psoriasis and no relevant medical history and concomitant medications had an indeterminate QuantiFERON-TB gold test 219 days after the first administration of **MSB11022**. Repeat testing showed indeterminate results. The subject had a normal chest X-ray and negative QuantiFERON-TB gold test at screening. The subject was asymptomatic and refused additional assessment or treatment. The administration of MSB11022 was permanently discontinued as a result of the event of latent tuberculosis which was considered related.

- [5] *Moses, M., Zwerling, A., Cattamanchi, A. et al. Serial testing for latent tuberculosis using QuantiFERON-TB Gold In-Tube: A Markov model. Sci Rep 6, 30781 (2016)*

Overview of Treatment-emergent Adverse Events

Table 53. Overview of Treatment-emergent Adverse Events (Core Treatment Period Weeks 1 to 16, safety analysis set)

	MSB11022 N=221				EU-Humira N=220			
Number of Subjects with:	Subjects with events n (%)	Events n	Subject-years	Incidence Rate (95% CI) per 100 subject-years	Subjects with events n (%)	Events n	Subject-years	Incidence Rate (95% CI) per 100 subject-years
Any TEAE	114 (51.6)	291	70.45	413.06 (366.96; 463.35)	117 (53.2)	278	68.79	404.12 (358.01; 454.53)
Any study drug-related TEAE	49 (22.2)	129	70.45	183.11 (152.87; 217.57)	51 (23.2)	111	68.79	161.36 (132.74; 194.32)
Any serious TEAE	8 (3.6)	8	70.45	11.36 (4.90; 22.37)	6 (2.7)	6	68.79	8.72 (3.20; 18.98)
Any study drug-related serious TEAE	2 (0.9)	2	70.45	2.84 (0.34; 10.26)	4 (1.8)	4	68.79	5.81 (1.58; 14.89)
Any Grade 3 TEAE	8 (3.6)	8	70.45	12.77 (5.84; 24.25)	3 (1.4)	3	68.79	4.36 (0.90; 12.74)
Any Grade 4 TEAE	0 (0.0)	0	70.45	0.00 (0.00; 0.00)	2 (0.9)	2	68.79	2.91 (0.35; 10.50)
Any Grade 5 TEAE	0 (0.0)	0	70.45	0.00 (0.00; 0.00)	0 (0.0)	0	68.79	0.00 (0.00; 0.00)
Any study drug-related Grade 3 TEAE	2 (0.9)	2	70.45	2.84 (0.34; 10.26)	2 (0.9)	2	68.79	2.91 (0.35; 10.50)
Any study drug-related Grade 4 TEAE	0 (0.0)	0	70.45	0.00 (0.00; 0.00)	1 (0.5)	1	68.79	1.45 (0.04; 8.10)
Any study drug-related Grade 5 TEAE	0 (0.0)	0	70.45	0.00 (0.00; 0.00)	0 (0.0)	0	68.79	0.00 (0.00; 0.00)
Any AESI	2 (0.9)	2	70.45	2.84 (0.34; 10.26)	3 (1.4)	3	68.79	4.36 (0.90; 12.74)
Any study drug-related AESI	1 (0.5)	1	70.45	1.42 (0.04; 7.91)	1 (0.5)	1	68.79	1.45 (0.04; 8.10)
Any TEAE leading to death	0 (0.0)	0	70.45	0.00 (0.00; 0.00)	0 (0.0)	0	68.79	0.00 (0.00; 0.00)

Source: SDN 1, CSR Applicant Table 44. Events that occurred up to Week 54 cutoff date are included. Incidence Rate (IR) per 100 subject-years was derived using the formula: IR I = [Events (n)/Subject (years)] x 100.

Table 54. Overview of Treatment-emergent Adverse Events (Overall Treatment Period (Weeks 1 to 54, safety analysis set)

	MSB11022 N=221 Subject-years: 211.20			EU-Humira N=119 Subject-years: 100.71			EU-Humira/MSB11022 N=101 Subject-years: 98.76		
Number of Subjects with:	Subjects with events n (%)	Events n	Incidence Rate (95% CI) per 100 subject-years	Subjects with events n (%)	Events n	Incidence Rate (95% CI) per 100 subject-years	Subjects with events n (%)	Events n	Incidence Rate (95% CI) per 100 subject-years
Any TEAE	173 (78.3)	739	349.90 (325.13; 376.07)	91 (76.5)	304	301.85 (268.87; 337.76)	74 (73.3)	339	343.27 (307.69; 381.82)
Any study drug-related TEAE	69 (31.2)	286	135.42 (120.18; 152.05)	41 (34.5)	113	112.20 (92.47; 134.90)	33 (32.7)	130	131.64 (109.98; 156.31)
Any serious TEAE	20 (9.0)	24	11.36 (7.28; 16.91)	8 (6.7)	12	11.92 (6.16; 20.81)	5 (5.0)	5	5.06 (1.64; 11.82)
Any study drug-related serious TEAE	3 (1.4)	3	1.42 (0.29; 4.15)	5 (4.2)	6	5.96 (2.19; 12.97)	0 (0.0)	0	0.00 (0.00; 0.00)
Any Grade 3 TEAE	21 (9.5)	27	12.78 (8.42; 18.60)	5 (4.2)	5	4.96 (1.61; 11.57)	1 (1.0)	1	1.01 (0.03; 5.64)
Any Grade 4 TEAE	0 (0.0)	0	0.00 (0.00; 0.00)	1 (0.8)	1	0.99 (0.03; 5.53)	4 (4.0)	4	4.05 (1.10; 10.36)
Any Grade 5 TEAE	0 (0.0)	0	0.00 (0.00; 0.00)	1 (0.8)	3	2.98 (0.61; 8.70)	0 (0.0)	0	0.00 (0.00; 0.00)
Any study drug-related Grade 3 TEAE	4 (1.8)	6	2.84 (1.04; 6.18)	2 (1.7)	2	1.98 (0.24; 7.17)	0 (0.0)	0	0.00 (0.00; 0.00)
Any study drug-related Grade 4 TEAE	0 (0.0)	0	0.00 (0.00; 0.00)	1 (0.8)	1	0.99 (0.03; 5.53)	1 (1.0)	1	1.01 (0.03; 5.64)
Any study drug-related Grade 5 TEAE	0 (0.0)	0	0.00 (0.00; 0.00)	0 (0.0)	0	0.00 (0.00; 0.00)	0 (0.0)	0	0.00 (0.00; 0.00)
Any AESI	12 (5.4)	12	5.68 (2.94; 9.92)	4 (3.4)	4	3.97 (1.08; 10.16)	4 (4.0)	4	4.05 (1.10; 10.36)
Any study drug-related AESI	8 (3.6)	8	3.79 (1.64; 7.46)	1 (0.8)	1	0.99 (0.03; 5.53)	1 (1.0)	1	1.01 (0.03; 5.64)
Any TEAE leading to death	0 (0.0)	0	0.00 (0.00; 0.00)	1 (0.8)	3	2.98 (0.61; 8.70)	0 (0.0)	0	0.00 (0.00; 0.00)

Source: SDN 1, CSR Applicant Table 45. Only events that started up to and including the Week 54 analysis cutoff date are included. Incidence Rate (IR) per 100 subject-years was derived using the formula: IR = [Events (n)/Subject (years)] x 100.

4 month safety follow-up period: The Sponsor submitted an addendum to the CSR to evaluate the overall AE profile and potential signs of delayed toxicity after treatment withdrawal during the 4-month Safety Evaluation Period following the Week 54 visit (to Week 66). Results were presented cumulatively, over the complete observation period including the 4-month Safety Evaluation Period. In general, incidences of TEAEs during the Overall Treatment Period including the 4-month Safety Follow-up Period were very similar to those reported for the Overall Treatment Period up to Week 54. No safety signals or noteworthy new safety findings were observed.

Dropouts and/or Discontinuations

In Study EMR200588-002, treatment-emergent AEs (TEAEs) were the most common reason for discontinuation of the investigational product (IP) and termination from the study in the Core Treatment Period and Extended Treatment Period. See **Subject Disposition** Table 25 in Section 6.2.1 of this review.

During the Core Treatment Period (Weeks 1 to 16), only 1 (1/221; 0.5%) subject who received MSB11022 had a TEAE that led to study termination (erythema multiforme) and 10 (10/220; 4.5%) subjects who received EU-HUMIRA had at least 1 TEAE leading to study termination (arthropod bite, atrial fibrillation, extrasystoles, increased hepatic

enzyme, increased liver function test, mycobacterium tuberculosis complex test, intraductal proliferative breast lesion, neutropenia, pregnancy [2 subjects], and uterine leiomyoma).

During the Overall Treatment Period (Weeks 1 to 54), 9 (9/221; 4.1%) subjects including those who terminated the study during the Core Treatment Period treated with continuous MSB11022 had at least 1 TEAE leading to study termination (latent tuberculosis [3 subjects], tuberculosis, pregnancy, acute kidney injury, erythema multiforme, hypersensitivity vasculitis, psoriasis) and 13 (13/119; 10.9%) subjects treated with continuous EU-HUMIRA had at least 1 TEAE leading to study termination (neutropenia, atrial fibrillation, bundle branch block left, cardiac failure, extrasystoles, hypersensitive cardiomyopathy, mitral valve incompetence, arthropod bite, hepatic enzyme increased, increased liver function test [2 subjects], mycobacterium tuberculosis complex test, intraductal proliferative breast lesion, brain edema, cerebral hematoma, pregnancy [3 subjects], pustular psoriasis.

Protocol-specified criteria for withdrawal of subjects were reasonable and included:

- Withdrawal of the subject's consent
- Any events that unacceptably endangered the safety of the subject in the opinion of the Investigator, including but not limited to the following:
  - Use of prohibited treatment that in the opinion of the Investigator or Sponsor necessitated the subject being removed
  - Occurrence of an exclusion criterion that was clinically relevant and affected the subject's safety, if discontinuation was considered necessary by the Investigator and/or Sponsor
  - Anaphylactic or other serious allergic reactions
  - Active TB
  - QFT positive at Week 24
  - New or worsening symptoms of congestive heart failure
  - Biopsy confirmation of any malignancy
  - Symptoms suggestive of lupus-like syndrome
  - Pregnancy
  - Subject could not adhere to or complete treatment for LTBI
  - Events that required emergency unblinding
- Noncompliance or protocol violations that in the opinion of the Investigator or Sponsor necessitated the subject being removed. The decision to withdraw the subject was taken in consultation with the Medical Monitor
- PASI response less than PASI 50 at or after Week 16
- Participation in any other study during the duration of this study
- If the whole study was discontinued prematurely
- Lost to follow-up

6.3.3. Additional Safety Evaluations

In addition to TEAEs and SAEs, the safety evaluation for Study EMR200588-002 included an assessment of vital signs, electrocardiograms, laboratory parameters and pregnancy outcomes. There were no meaningful differences between treatment arms or following transition from EU-HUMIRA to MSB11022. Key findings related to these assessments are summarized below.

Vital signs: Examination of shift tables of vital signs demonstrated no clinically meaningful changes from Baseline. In the Core Treatment Period, 8 (3.62%) of the MSB11022 arm and 1 (0.45%) of the EU-HUMIRA arm had a TEAE of hypertension. In the Overall Treatment Period, 11 (4.98%) of subjects in the continuous MSB11022 arm and 3 (2.52%) of subjects in the continuous EU-HUMIRA arm had a TEAE of hypertension. None of these hypertension cases in either the Core or Overall Treatment Periods were considered treatment related by the investigator

ECGs: Only isolated cases of clinically significant abnormal ECG findings were reported: 3 subjects reported ECG category shifts to abnormal in the Extended Treatment Period. One subject in the MSB11022 group had a clinically significant, unrelated Grade 1 TEAE of extrasystoles which did not affect treatment. Another subject in the EU-Humira group discontinued the study after unrelated, clinically significant abnormal ECG assessments due to Grade 2 atrial fibrillation, Grade 2 left bundle branch block, Grade 2 hypertensive cardiomyopathy, and Grade 3 mitral incompetence. The third subject, in the EU-Humira to MSB11022 group, had a clinically significant, unrelated and asymptomatic Grade 2 TEAE of abnormal ECG which did not affect treatment.

Laboratory Evaluations: See discussion in 6.3.2 of cholesterol abnormalities which were slightly higher for the MSB11022 arm but does not appear to be clinically significant.

Pregnancies: Up to Week 54, there were a total of seven pregnancies including two partner pregnancies: three pregnancies (two subjects and one partner of a subject) occurred during the Core Treatment Period (all in the EU-HUMIRA group) and four pregnancies (three subjects and one partner of a subject) occurred during the Extended Treatment Period (two pregnancies in the MSB11022 group and one each in the EU-HUMIRA and EU-HUMIRA to MSB11022 groups). An additional pregnancy occurred after Week 54. In six of the eight pregnancies, the outcome was live birth without congenital anomaly. One subject underwent a therapeutic abortion and one subject had an unknown outcome.

There were no residual uncertainties related to the safety analysis.

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6.4. Clinical Conclusions on Immunogenicity

The immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (from single dose PK studies) and in subjects with plaque psoriasis (multiple doses up to 52 weeks), and an assessment of the impact of ADA on PK, efficacy and safety.

In addition to the evaluation of TEAEs across treatment groups in study EMR200588-002, the safety analyses included an evaluation of the frequencies of hypersensitivity, immune mediated reactions, and injection site reactions for all treatment periods. During the Extended Treatment Period (Weeks 16 to 54), the frequencies of hypersensitivity, immune mediated reactions, and injection site reactions were well-balanced among subjects who remained on EU-HUMIRA compared with subjects who switched from EU-HUMIRA to MSB11022. Overall TEAEs between the two arms were also well balanced. The results regarding TEAEs by ADA and NAb positivity status during the Extended Treatment Period were consistent with those in the Core Treatment Period (Weeks 1-16), showing no notable differences between treatment groups. Frequencies of hypersensitivity and injection site reactions were similar between treatment groups by ADA status, and ADA positivity was not associated with increased reporting of hypersensitivity and injection site reactions.

In the Overall Treatment Period (Weeks 1 to 54), there were no meaningful differences between the frequency of TEAEs in the MSB11022/ MSB11022 group versus the other treatment groups (EU-HUMIRA to MSB11022 and EU-HUMIRA to EU-HUMIRA), regardless of NAb status. It is concluded that MSB11022 was similar to EU-HUMIRA in the production of ADA/NAb and their impact on PK, efficacy and safety. Refer to Section 5.4 Clinical Immunogenicity Studies for results of the immunogenicity assessments.

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6.5. Extrapolation

The Applicant submitted data and information in support of a demonstration that MSB11022 is highly similar to U.S.-Humira notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between MSB11022 and U.S.-Humira in terms of safety, purity and potency in patients with plaque psoriasis (Study EMR200588-002). No extrapolation is needed for the indication of plaque psoriasis.

In addition to the plaque psoriasis indication, the Applicant is seeking licensure of MSB11022 for the following indication(s) for which U.S.-Humira has been previously licensed and for which MSB11022 has not been directly studied:

- Rheumatoid Arthritis (adults)
- Juvenile Idiopathic Arthritis (age 2 and above)
- Psoriatic Arthritis (adults)
- Ankylosing Spondylitis (adults)
- Crohn's Disease (age 6 and above)
- Ulcerative Colitis (adults)

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of MSB11022 as a biosimilar for each such indication for which licensure is sought and for which US-Humira has been previously approved. This Applicant's justification was evaluated and considered adequate. Therefore, the totality of the evidence provided by the Applicant supports licensure of MSB11022 for each of the following indication(s) for which U.S.-Humira has been previously licensed and for which the Applicant is seeking licensure of MSB11022:

- Rheumatoid Arthritis (adults)
- Juvenile Idiopathic Arthritis (age 2 and above)
- Psoriatic Arthritis (adults)
- Ankylosing Spondylitis (adults)
- Crohn's Disease (age 6 and above)
- Ulcerative Colitis (adults)
- Plaque Psoriasis (adults)

6.5.1. Division of Rheumatology and Transplant Medicine

In addition to the plaque psoriasis indication, the Applicant is seeking licensure of for the following indication(s) under the purview of DRTM for which U.S.-Humira has been previously licensed and for which MSB11022 has not been directly studied:

- Rheumatoid Arthritis (RA): reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- Juvenile Idiopathic Arthritis (JIA): reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.
- Psoriatic Arthritis (PsA): reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- Ankylosing Spondylitis (AS): reducing signs and symptoms in adult patients with active AS.

The Applicant provided a justification for extrapolation of data and information submitted in the application to support licensure of MSB11022 as a biosimilar for each of the above indications for which licensure is sought and for which U.S.-Humira has been previously licensed. As discussed above, the Applicant submitted data and information in support of a demonstration that MSB11022 is highly similar to U.S.-Humira notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between MSB11022 and U.S.-Humira in terms of

safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in patients with plaque psoriasis (Study EMR200588-002). Further, the additional points considered in the scientific justification for extrapolation of data and information to support licensure of MSB11022 for treatment of the following rheumatology indications: RA, JIA in patients 2 years of age and older, PsA, and AS include:

- Similar PK was demonstrated between MSB11022 and U.S.-Humira as discussed in the section on Clinical Pharmacology. Importantly, MSB11022 was demonstrated to be highly similar to U.S.-Humira, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between MSB11022 and U.S.-Humira in the rheumatology indications sought for licensure. Thus, a similar PK profile would be expected between MSB11022 and U.S.-Humira in patients across all the rheumatology indications being sought for licensure.
- In general, immunogenicity of U.S.-Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications rather than by patient population. As stated elsewhere in this document, the Agency has concluded that there are sufficient data to support similar immunogenicity between MSB11022 and U.S.-Humira with repeat dosing in patients with plaque psoriasis, and between MSB11022 and U.S.-Humira, after a single dose in healthy subjects. Accordingly, similar immunogenicity would be expected between MSB11022 and U.S.-Humira in patients with RA, JIA, PsA, and AS.
- The Applicant demonstrated that there are no clinically meaningful differences between MSB1102 and U.S.-Humira in patients with plaque psoriasis, and between MSB11022 and U.S.-Humira following single doses in healthy subjects. Additionally, in controlled clinical studies of U.S.-Humira submitted to support its approval, as described in the approved labeling, the types of adverse events and their rates were similar across indications. The foregoing, coupled with the demonstration of analytical and PK similarity between MS11022 and U.S.-Humira, support the conclusion that a similar safety profile would be expected between MSB11022 and U.S.-Humira in patients with RA, JIA, PsA, and AS.
- The Applicant addressed each of the known and potential mechanisms of action of U.S.-Humira and submitted data to support the conclusion that MSB11022 and U.S.-licensed Humira have the same mechanisms for each of the sought indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Conclusions

Based on the above considerations, DRTM has concluded that the Applicant has provided adequate data and information to support licensure of MSB11022 for each of the following rheumatologic indications for which U.S.-Humira has been previously licensed and for which the Applicant is seeking licensure of MSB11022: RA, JIA in

patients 2 years of age and older, PsA, and AS.

6.5.2. Division of Dermatology and Dentistry

Executive Summary:
Consistent with the principles of the FDA Guidance - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015), the Division of Dermatology and Dentistry (DDD) concludes that the Applicant has provided sufficient scientific justification to support extrapolation of data submitted in the application to support licensure of MSB11022 as a biosimilar, under section 351(k) of the PHS Act, for the dermatologic non-studied indication of moderate to severe hidradenitis suppurativa (HS) in adult patients. The scientific justification based on the mechanism of action, pharmacokinetics, immunogenicity and safety supporting this conclusion are summarized in the following paragraphs.

During the late cycle meeting, the FDA discussed the potential implications of the recent decision in Catalyst Pharms. Inc. vs. Becerra for this biosimilar application. To allow the FDA to meet the BsUFA action date, the Applicant proposed to voluntarily remove the adult HS indication from the proposed labeling due to the Catalyst decision. (b) (6)

Mechanism of Action:
The mechanisms of action of adalimumab that are relevant to the indication of plaque psoriasis (PsO; the studied clinical study population) are also relevant to the indication of HS. The Applicant provided data to support that MSB11022 has the same known and potential mechanisms of action as US-HUMIRA, which supports extrapolation to indications not directly studied in the MSB11022 clinical program. Adalimumab belongs to the pharmacologic class of tumor necrosis factor alpha (TNF-α) blockers. Adalimumab neutralizes the biological activity of TNF-α by binding with high affinity to the soluble (s) (sTNF-α) and transmembrane (tm) (tmTNF-α) forms of TNF-α and inhibits binding of TNF-α with its receptors. Similar to the studied indication (PsO), TNF-α plays a central role in the pathogenesis of HS according to the scientific literature. TNF-α inhibition is important in treating the disease, as evidenced by the efficacy of approved TNF-α inhibitors in the treatment of HS. In addition, the efficacy of adalimumab in the treatment of HS is thought to involve reverse signaling via binding to tmTNF-α, and other plausible mechanisms of action involving the Fc region of the antibody. Table 55 below summarizes the known and potential mechanisms of action of US-HUMIRA. Binding to sTNF-α and tmTNF-α involves the fragment antigen-binding (Fab) region of the antibody, while the other plausible mechanisms of action involve the fragment crystallizable (Fc region) region of the antibody.

Table 55. Known and Potential Mechanisms of Action of US-Humira

MOA of US-Humira	RA	AS	PsA	PsO	CD	UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible

ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF

Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors (Celltrion CT-P13 FDA AdComm, 2016; Oikonomopoulos, 2013; Tracey, 2008)

The biological activities of MSB11022 and US-HUMIRA were evaluated by a comprehensive set of comparative functional and binding assays. The product quality reviewers concluded that MSB11022 is highly similar to US-Humira notwithstanding minor differences in clinically inactive components. Data for TNF-α binding and neutralization, the primary function of adalimumab, as well as other mechanisms of action, such as reverse signaling, antibody dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of regulatory macrophages support the determination that MSB11022 and US-HUMIRA are highly similar. These data support the conclusion that MSB11022 and US-HUMIRA utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK): Study EMR200588-001 and study FKS022-002 were comparative PK studies conducted in healthy adult male and female subjects. The clinical pharmacology reviewers concluded that the data from study EMR200588-001 and FKS022-002 support a demonstration of PK similarity of MSB11022 to US-HUMIRA in healthy subjects (refer to Section 5 Clinical Pharmacology Evaluation and Recommendations). Available data on US-HUMIRA do not indicate any major differences in PK based on disease state. Therefore, it is reasonable to conclude that PK for the MSB11022 is expected to be similar between patients with PsO (the studied population) and those with HS. In addition, it should be noted that the PK of adalimumab products is also influenced by immunogenicity. Specifically, the clearance of adalimumab has been shown to be higher in patients who developed anti-drug-antibodies (ADA). Immunogenicity considerations are discussed further below.

Immunogenicity: In the MSB11022 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (PsO, RA, and healthy subjects). Immunogenicity was found to be similar when comparing MSB11022 (C/Acetate), US-HUMIRA, and MSB11022 (A/Citrate) in the PK similarity study FKS022-002 in healthy subjects; between MSB11022 (A/Citrate),

EU-HUMIRA, and US-HUMIRA in the PK similarity study EMR200588-001 in healthy subjects; and between MSB11022 (A/Citrate) and EU-HUMIRA in the comparative clinical study EMR200588-002 conducted in subjects with PsO.

Specifically, the rates of binding and neutralizing anti-drug antibodies were found to be similar between MSB11022, US-HUMIRA, and EU-HUMIRA in these studies. These results support a demonstration of no clinically meaningful differences between MSB11022 and US-HUMIRA. In the comparative clinical study EMR200588-002 in subjects with PsO, subjects who received EU-HUMIRA were re-randomized to either continue on EU-HUMIRA or switch to MSB11022 (A/Citrate), thus providing information on the effect of switching between the two treatments. The single transition was used to specifically assess potential risks with regard to the safety and immunogenicity as a result of switching from EU-HUMIRA to MSB11022 (A/Citrate). There were no meaningful differences in the rates of binding and neutralizing antidrug antibodies in those subjects that underwent a single transition from EU-HUMIRA to MSB11022 (A/Citrate), compared to those that remained on their randomized treatment (EU-HUMIRA or MSB11022 [A/Citrate]). Therefore, it is reasonable to conclude that immunogenicity in patients with HS receiving MSB11022 (A/Citrate) would be similar to that observed in patients with HS receiving US-HUMIRA.

Safety: The safety of MSB11022 compared to EU-HUMIRA was assessed in comparative clinical study (EMR200588-002) conducted in subjects with PsO, and supported by single dose, PK similarity studies (EMR200588-001 and FKS022-002) conducted in healthy subjects.

Safety assessments in the PsO clinical study included adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory testing, and immunogenicity assessments. As described in Section 6.3– Review of Safety Data, the data overall support a similar safety profile between MSB1102 and EU-HUMIRA, and there were no meaningful differences in the frequency of TEAEs, SAEs, and events leading to discontinuation of study drug. In addition, as previously noted, a single transition from EU-HUMIRA to MSB11022 (A/Citrate), was assessed as part of the study EMR200588-002. No meaningful differences in the incidence of adverse events, including hypersensitivity, were observed in patients with PsO that underwent a single transition from EU-HUMIRA to MSB11022 (A/Citrate), compared to those that remained on their randomized treatment (MSB11022 [A/Citrate], or EU-HUMIRA). In controlled clinical studies of US-licensed HUMIRA, as described in the approved labeling, the types of adverse events and their rates were similar across indications. Since the safety profile of MSB11022 (A/Citrate) has been shown to be similar to that of EU-HUMIRA in subjects with PsO, combined with adequate scientific bridging between US-HUMIRA,EU-HUMIRA, and MSB11022, and given the similar product quality attributes, PK, and immunogenicity, we expect that the safety profile in adult patients with HS is unlikely to be different from that observed in adult patients with PsO.

Regulatory Recommendation:
DDD concluded that the Applicant provided adequate scientific justification for extrapolating data and information submitted in the application to support licensure of MSB11022 as a biosimilar for the non-studied dermatologic indication of the treatment of moderate to severe hidradenitis suppurativa in adult patients. However, following a discussion of the potential implications of the recent decision in Catalyst Pharms. Inc. vs. Becerra for this biosimilar application, the Applicant proposed to voluntarily remove the adult HS indication from the proposed labeling (SDN 45 dated October 21, 2022).

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6.5.3. Division of Gastroenterology

Executive Summary:
Consistent with the principles of the FDA Guidance – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)[6], the Division of Gastroenterology (DG) concludes that the Applicant has provided sufficient scientific justification to support extrapolation of data submitted in the application to support licensure of MSB11022 as a biosimilar, under section 351(k) of the PHS Act, for the non-studied indications of moderately to severely active Crohn's disease (CD) in patients 6 years and above, and moderately to severely active ulcerative colitis (UC) in adults. The scientific justification based on the mechanism of action, pharmacokinetics, immunogenicity, and safety supporting this conclusion are summarized in the following paragraphs.

Mechanism of Action:
The mechanisms of action of adalimumab that are relevant to chronic plaque psoriasis (PsO; the studied clinical study population) are also relevant to inflammatory bowel disease (IBD) (i.e., CD and UC). The Applicant provided data to support that MSB11022 has the same known and potential mechanisms of action as US-Humira, which supports extrapolation to indications not directly studied in the MSB11022 clinical program. Adalimumab belongs to the pharmacologic class of tumor necrosis factor alpha (TNF-α) blockers. Adalimumab neutralizes the biological activity of TNF-α by binding with high affinity to the soluble (s) (sTNF-α) and transmembrane (tm) (tmTNF-α) forms of TNF-α and inhibits binding of TNF-α with its receptors. Similar to the studied indication (PsO), TNF-α plays a central role in the pathogenesis of IBD. TNF-α inhibition is important in treating the disease, as evidenced by the efficacy of approved TNF-α blockers for the treatment of IBD. In addition, the efficacy of adalimumab in the treatment of IBD is thought to involve reverse signaling via binding to tmTNF-α, and other plausible

[6] Guidance for Industry- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

mechanisms of action involving the Fc region of the antibody.[7,8] Table 55 summarizes the known and potential mechanisms of action of US-licensed Humira. Binding to sTNF-α and tmTNF-α involves the fragment antigen-binding (Fab) region of the antibody, while the other plausible mechanisms of action involve the fragment crystallizable (Fc region) region of the antibody.

The biological activities of MSB11022 and US-Humira were evaluated by a comprehensive set of comparative functional and binding assays. The product quality reviewers concluded that the comparative analytical assessment was acceptable. Data for TNF-α binding and neutralization, the primary function of adalimumab, as well as other mechanisms of action, such as reverse signaling, antibody dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of regulatory macrophages support the determination that MSB11022 and US-Humira are highly similar. These data support the conclusion that MSB11022 and US-Humira utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK):
PK of MSB11022 was evaluated in 4 studies. Study EMR200588-001 was a randomized, double-blind, parallel-group, single-dose PK similarity study conducted in healthy adults that assessed PK similarity between MSB11022 (A/Citrate), EU-Humira, and US-Humira. Study EMR200688-002 was a randomized, double-blind, parallel-group, multicenter, repeated-dose PK similarity study in subjects with PsO that assessed the PK similarity between MSB11022 (A/Citrate) and EU-Humira. Changes were made to the manufacturing process of the acetate formulation, which resulted in the MSB11022 (C/Acetate) formulation (the proposed to-be-marketed [TBM] product). Study FKS022-002 was a randomized-double-blind, parallel-group, single-dose PK similarity study conducted in healthy adults evaluating the similarity between MSB11022 (C/Acetate), MSB11022 (A/Citrate), and US-Humira. In addition, the Applicant conducted Study FKS022-001, a randomized, open-label, parallel-group, single-dose PK similarity study assessing PK of MSB11022 (C/Acetate) administered via autoinjector (AI) or pre-filled syringe (PFS). The clinical pharmacology reviewers concluded that the data from these studies support a demonstration of PK similarity of MSB11022 (C/Acetate) and US-Humira in healthy subjects, and subjects with PsO (refer to Section 5 Clinical Pharmacology Evaluation and Recommendations). Available data on US-Humira do not indicate any major differences in PK based on disease state. Therefore, it is reasonable to conclude that PK for MSB11022 is expected to be similar between patients with PsO (the studied population) and those with IBD. In addition, it should be noted that the PK of adalimumab products is also influenced by immunogenicity. Specifically, the clearance of adalimumab has been shown to be higher in patients who developed anti-drug antibodies (ADA). Immunogenicity considerations are discussed further below.

[7] Oikonomopolous A, et al., Current Drug Targets 2013; 14: 1421-32

[8] Tracey D, et a., Pharmacology & Therapeutics 2008; 117: 224-79

Immunogenicity:
In the MSB11022 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (healthy subjects and PsO). Immunogenicity was found to be similar when comparing MSB11022 (A/Citrate), US-Humira, EU-Humira in the PK similarity Study EMR200588-001 conducted in healthy subjects.

In Study EMR200688-002 in subjects with PsO, comparing MSB11022 (A/Citrate) and EU-Humira, subjects who received EU-Humira were rerandomized to either continue on EU-Humira or switch to MSB11022 (A/Citrate) at Week 16. This occurred at the transition between 15-Week Core Treatment Period and 37-Week Extended Treatment Period. The single transition was used to specifically assess potential risks with regard to the safety and immunogenicity as a result of switching from EU-Humira to MSB11022 (A/Citrate). There were no meaningful differences in the rates of binding and neutralizing ADAs in subjects that underwent a single transition from EU-Humira to MSB11022 (A/Citrate), compared to those that remained on the randomized treatment assignment of MSB11022 (A/Citrate). Therefore, it is reasonable to conclude that immunogenicity in patients with IBD receiving MSB11022 (A/Citrate) would be similar to that observed in patients with IBD receiving EU-Humira.

Additionally, immunogenicity rates of binding and neutralizing ADAs reported in Study FKS022-002 were found to be similar between the MSB11022 (A/Citrate), MSB11022 (C/Acetate) and US-Humira arms in healthy adults. These results support a demonstration of no clinically meaningful differences between MSB1102 (C/Acetate) and US-Humira.

Safety:
The safety of MSB11022 (A/Citrate) compared to EU-Humira was assessed in comparative clinical Study (EMR200588-002) conducted in patients with PsO. In addition, two single dose, PK similarity studies were conducted in healthy subjects. Study EMR200588-001 assessed similarity between MSB11022, US-Humira, and EU-Humira and Study FKS022-002 assessed similarity between MSB11022 (C/Acetate), MSB11022 (A/Citrate) and US-Humira. Safety assessments in the three clinical studies included adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory testing, and immunogenicity assessments. As described in Section 6.3 – Review of Safety Data, the data overall support a similar safety profile between the MSB11022 and US-Humira, and there were no meaningful differences in the frequency of TEAEs, SAEs, and events leading to discontinuation of study drug. In addition, as previously noted, a single transition from EU-Humira to MSB11022 (A/Citrate) was assessed as part of the study EMR200588-002. No meaningful differences in the incidence of adverse events, including hypersensitivity reactions, were observed in patients with PsO that underwent a single transition from EU-Humira to MSB11022 (A/Citrate), compared to those that remained on their randomized treatment (MSB11022 (A/Citrate) or EU-Humira). In controlled clinical studies of US-licensed Humira, as described in the approved labeling, the types of adverse events and their rates were similar across indications. Since the safety profile of MSB11022 has been

shown to be similar to that of US-Humira in patients with PsO and healthy subjects, and considering their similar product quality attributes, PK, and immunogenicity, the safety profile in the IBD population is unlikely to be different from that observed in patients with PsO.

Extrapolation to pediatric IBD indications:
The following rationale supports extrapolation to the pediatric CD and UC indication.

- The mechanisms by which adalimumab exerts its therapeutic effect are expected to be the same in adults and in pediatric patients with CD and UC. Together with the demonstrated structural and functional similarity between MSB11022 and US-Humira, the mechanisms of action of MSB11022 are not expected to be different from that of US-Humira in pediatric patients with CD and UC, to the extent that the mechanisms are known or can be reasonably determined.
- Adalimumab concentrations are similar in adult and pediatric patients with CD and UC (Humira USPI, 2021). Together with the demonstrated PK similarity (MSB11022 vs. US-Humira) in healthy adult subjects and in subjects with PsO, the PK of MSB11022 is not expected to be different to that of US-Humira in pediatric patients with CD and UC.
- Immunogenicity rates of US-Humira were comparable between adult and pediatric patients with CD and UC (Humira USPI, 2021). Together with the comparable immunogenicity in healthy adult subjects and subjects with PsO, the immunogenicity of MSB11022 is not expected to be different from that of US-Humira in pediatric patients with CD and UC.
- The safety profile of US-Humira was comparable in adult vs. pediatric patients with CD and UC (Humira USPI, 2021). Together with the demonstrated comparable safety profile of MSB11022 vs. US-Humira in adult subjects with PsO and healthy adult subjects, the safety of MSB11022 is not expected to be different from that of US-Humira in pediatric patients with CD and UC.

Note that, while the Applicant has submitted acceptable extrapolation justification for pediatric UC patients 5 years of age to 17 years, FDA has determined that US-Humira is eligible for orphan drug exclusivity for pediatric UC, ages 5 to 17 years. FDA therefore cannot license MSB11022 for this indication prior to the expiration of the orphan drug exclusivity on February 24, 2028.

Regulatory Recommendations:
DG concludes that sufficient scientific justification was provided to support licensure of MSB11022 for the following indications:

- For the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.
- For the treatment of moderately to severely active ulcerative colitis in adult patients.

Authors:

Suruchi Batra, MD	Suna Seo, MD, MSc	Juli Tomaino, MD, MS
Medical Officer	Clinical Team Leader	Deputy Division Director

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, adalimumab-aacf, was found to be conditionally accepted by the Agency (DMAMES memo dated September 15, 2022).

7.2. Proprietary Name

The proposed proprietary name for MSB11022 is conditionally approved as Idacio. This name has been reviewed by DMEPA, who concluded the name was acceptable (DMEPA memo dated March 7, 2022).

7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

(b) (4)

Authors:

Keith Hull, MD
Clinical Reviewer

Anil Rajpal, MD, MPH
Clinical Team Leader

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with

good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.1 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Authors:

Keith Hull, MD
Clinical Reviewer

Anil Rajpal, MD, MPH
Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

Author:

Keith Hull, MD
Clinical Reviewer

Anil Rajpal, MD, MPH
Clinical Team Leader

10. Pediatrics

Fresenius Kabi, LLC submitted iPSP for MSB11022 to IND 124098 and this was reviewed by PeRC on September 28, 2016. A summary of the PeRC from that assessment is as follows: PeRC concurred with the Applicant's plan to request deferral of PREA obligations for the UC indication in ages 5-17 (US-Humira is not approved for this age group) and provide assessments via extrapolation for JIA ages 2-17 and CD ages 6-17 (US-Humira exclusivity for JIA ages 2-<4 and CD ages 6-17 due to expire in September 2021), as well as waiver requests (full waivers for RA, AS, PsA and PsO; partial waivers for JIA ages 0-<2, CD 0-<6 and UC 0-<5) outlined in the iPSP.

Fresenius Kabi, LLC has included assessment via extrapolation for JIA ages 2-17, CD ages 6-17, and UC ages 5-17 in this BLA. See Section 6.5 for review of the assessments.

The adalimumab-aacf 40 mg/0.8 mL single-dose prefilled pen and single-dose prefilled glass syringe are not designed to allow for accurate administration of doses less than 40 mg, which impacts patients who weigh less than 40 kg for CD, and 30 kg for JIA. For accurate weight-based dosing, an age-appropriate formulation (presentation) would be needed. Therefore, a PREA PMR is required to develop a presentation that can be used to accurately administer Idacio (adalimumab-aacf) to patients weighing 10 kg to less than 40 kg (see Section 11.2).

PeRC discussed this application on November 15, 2022 and concurred with the Division's recommendations for PREA waiver, deferral, and PMR's.

Authors:
Anil Rajpal, MD, MPH
Cross-Discipline Team Leader (CDTL)

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

The following PREA PMR description should be included in the Approval letter for the MSB11022 single-dose prefilled pen presentation and the MSB11022 single-dose prefilled glass syringe presentation.

PMR-1. Develop a presentation that can be used to accurately administer Idacio (adalimumab-aacf) to pediatric patients weighing 10 kg to less than 40 kg.

Final Report Submission Date: December 2024

In addition, the following PMC descriptions should be included in the approval letter for the MSB11022 single-dose prefilled pen presentation and the MSB11022 single-dose prefilled glass syringe presentation

PMC-1. To repeat the bacterial retention study (b) (4) .

Final Report Submission: January 2023

PMC-2 To repeat the sterilization validation (b) (4)

Final Report Submission: January 2023

PMC-3 To update the drug substance and drug product release and stability specifications for MSB11022 to include control for purity (monomer) by SE-HPLC and purity (main peak) by non-reduced CE-SDS with appropriately justified acceptance criteria. The updated drug substance and drug product release and stability specifications, method validation data, and other supporting data will be submitted to the BLA per 21 CFR 601.12.

Final Report Submission: June 2023

PMC-4 To update the drug substance and drug product release specifications for MSB11022 to include justified analytical thresholds for new peaks detected by the peptide mapping and icIEF identity tests. The updated release acceptance criteria, method validation data, and other supporting information will be submitted to the BLA per 21 CFR 601.12.

Final Report Submission: June 2023

PMC-5 To update the system suitability testing and criteria for the protein content by O.D. analytical method in the MSB11022 specifications. The updated method procedure, system suitability criteria, and supporting studies will be submitted to the BLA per 21 CFR 601.12.

Final Report Submission: March 2023

PMC-6 To revise the in process control (IPC) acceptance criteria (b) (4) to ensure meeting the label claim. The updated IPC acceptance criteria and supporting studies and data will be submitted to the BLA per 21 CFR 601.12.

Final Report Submission: March 2023

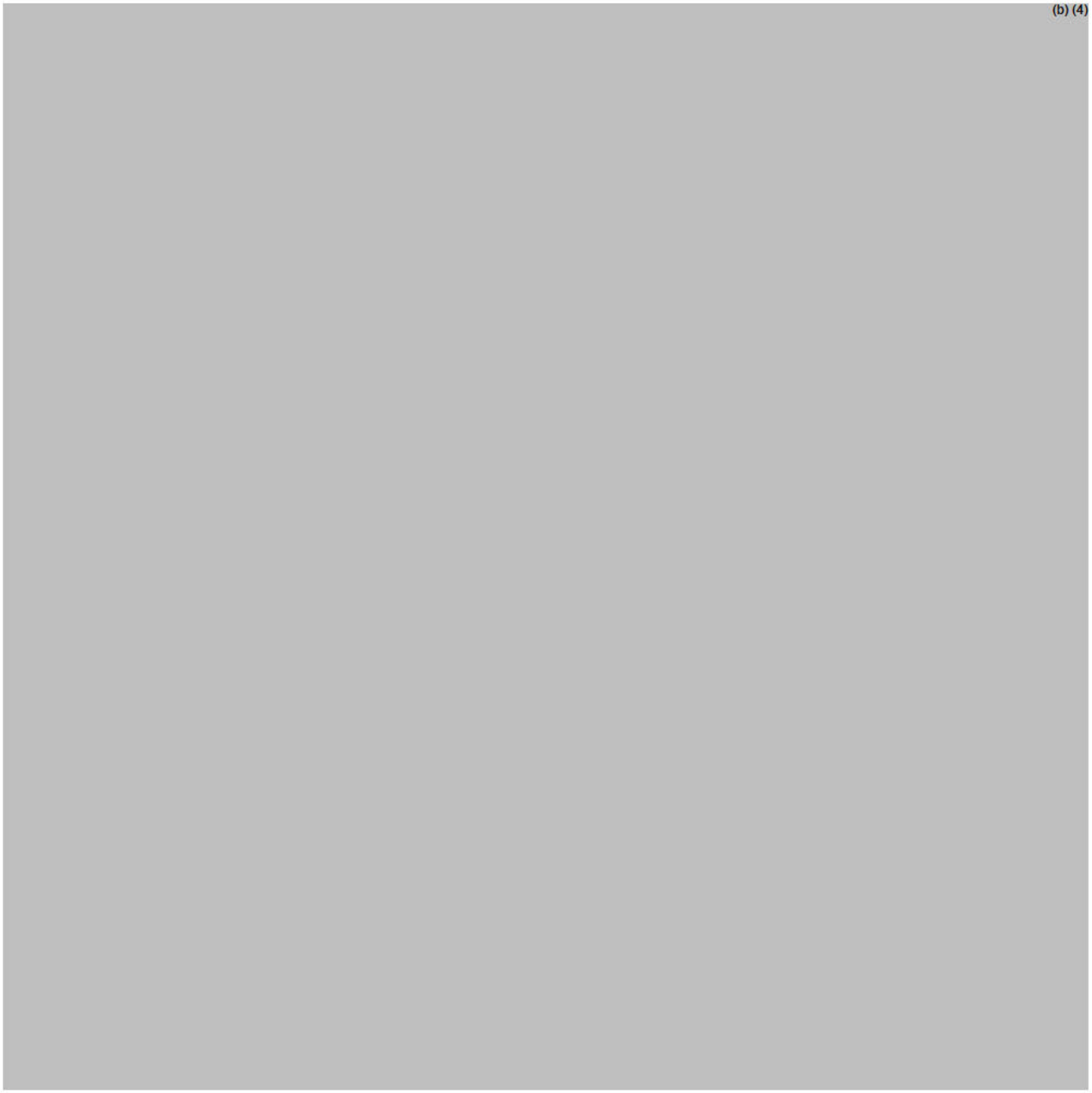
PMC-7 To implement identity test(s) for final MSB11022 drug product assembled in the prefilled syringe with the autoinjector (b) (4) devices after labeling and secondary packaging per 21CFR 610.14. The identity test(s) will distinguish MSB11022 drug product (Process C/Acetate) proposed for the US market from the Process A/Citrate drug product if manufactured at the same facility. The final identity test and supporting information will be submitted to the BLA per 21 CFR 601.12.

Final Report Submission: June 2023

Authors:
Anil Rajpal, MD, MPH
Clinical Team Leader

12. Comments to Applicant

(b) (4)



13. Appendices

13.1. Financial Disclosure

Covered Clinical Study: Studies EMR200588-001; EMR200588-002; EMR200588-003; EMR220588-004; FKS022-001; FSK022-002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 713		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant has adequately disclosed potential financial arrangements with clinical investigators in the provided financial certification and disclosure form attesting that no clinical investigators reported disclosable financial interests or arrangements that would result in a conflict of interest Review of the documents does not raise concerns regarding the integrity of the submitted data to the current application.

13.2. Clinical Pharmacology Appendices

13.2.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity studies FKS022-002, EMR200588-001 and FKS022-001 as well as the comparative clinical study EMR200588-002, serum MSB11022 (C/Acetate), U.S.-Humira, MSB11022 (A/Citrate) and E.U.-Humira concentrations measured using a validated ELISA method (Method ICD 547) were suitable for assessment of PK similarity.

Both the method validation entitled “Validation of an ELISA Method for the Quantification of an Adalimumab Biosimilar in Human Serum” and sample analyses for the individual studies mentioned above were performed at (b) (4)). The Applicant used one method approach using MSB11022 (A/Citrate) as a calibrator to analyze MSB11022 (A/Citrate), MSB11022 (C/Acetate), U.S.-Humira and E.U.-Humira. Calibration curve bioanalytical similarity was assessed using MSB11022 (C/Acetate), MSB11022 (A/Citrate) and U.S.-Humira (Method Validation Report Addendum 9). Accuracy and precision (A&P) were evaluated by analyzing quality control pools by multiple analyses (n=6) prepared at 300, 450, 900, 1800, 3200, 4000, and 7000 ng/mL for MSB11022 (A/Citrate), E.U-Humira and U.S.-Humira (Method Validation Report). Assay validation demonstrated that the assay was precise and accurate for the purpose of quantification of MSB11022 (A/Citrate), MSB11022 (C/Acetate), U.S.-Humira and E.U.-Humira in human serum (Table 3).

A pair-wise comparison of QC bias among MSB11022 (A/Citrate), MSB11022 (C/Acetate) and US-Humira was performed by Applicant per request. Three sets of QCs prepared in blank matrix fortified with MSB11022 (A/Citrate), MSB11022 (C/Acetate) and US-Humira were cross quantitated against the three calibration standards prepared with MSB 11022 (A/Citrate), MSB11022 (C/Acetate) and U.S.-Humira. The three calibration curves overlayed well. The three sets of QCs quantitated against different calibration curves were comparable. The absolute bias difference values calculated between each set of QCs quantitated off each calibration curve were within ± 7.71%.

The long term stability and freeze/thaw stability were initially only assessed with MSB11022 (A/Citrate) (Method Validation Report). The Applicant conducted a long-term stability with MSB1102 (C/Acetate) and freeze/thaw stability studies with MSB1102 (C/Acetate), US-Humira and E.U.-Humira, and reported results in the Response to Information Request on May 16, 2022, that were submitted dated Aug. 26, 2022.

The low- (900 ng/mL) and high- (5300 ng/mL) level QC samples (LQC and HQC) that were prepared with MSB11022 C/Acetate for Study FKS022-002 on Jun 16, 2020 and Jan 7, 2021 and stored until the time of analysis at -80 °C ± 10 °C for at least 530 days were used in the new long-term stability study. The study supported that MSB11022 (C/Acetate) is stable at -80 °C ± 10 °C for 735 days (HQC) and 763 days (LQC). The

bias for one run of LQC stored for 763 days and one run of HQC stored for 530 days were 19.65% and 19.4%, respectively, which were at borderline of the acceptance criteria.

No long-term stability study was performed with U.S.-Humira or E.U.-Humira QCs. The Applicant re-analyzed clinical study samples for U.S.-Humira and E.U.-Humira with concentrations greater than 25% of LLOQ from studies FKS022-002 and EMR205588-002 to generate data for long-term stability. Ninety-four (94) samples from subjects treated with U.S.-Humira (from FKS022- 002 study) stored up to 853 days and seventy-two (72) samples from subjects treated E.U.-Humira (from EMR200588-002 study) stored up to 2162 days were re-analyzed against a calibration curve prepared with MSB11022 C/Acetate. The results showed that the relative percent difference (RPD) between original and re-assayed results within ± 30% for 94.7% U.S.-Humira samples and 94.4% EU-Humira samples, which established the long-term stability for 853 days for US-Humira and 2162 days for E.U.-Humira.

The freeze/thaw stability was evaluated with up to 8 cycles with a set of LQC (900 ng/mL) and HQC (5300 ng/mL) prepared with MSB11022 (C/Acetate) and 8 cycles with LQC and HQC of U.S.-Humira and E.U.-Humira, which met the criteria demonstrating stability.

The benchtop stability was assessed with MSB11022 (A/Citrate), US-Humira and EU-Humira, but not with MSB11022 (C/Acetate). As the bioanalytical method comparability has demonstrated among MSB11022 (C/Acetate), MSB11022 (A/Citrate) and US-Humira with well overlayed calibration curves and comparable QCs, the benchtop stability of MSB11022 (C/Acetate) is expected to be similar to that of MSB11022 (A/Citrate) and US-Humira using this bioanalytical method.

The lipemic and hemolytic effects were only assessed for MSB11022 (A/Citrate) samples. The results showed no impact from either hemolysis or lipemia on the quantification of adalimumab. The impact of hemolysis and lipemia on the quantification of MSB11022 C/Acetate, E.U.- and U.S.-Humira, was not assessed during validation. However, the hemolytic and lipemic status were recorded by the clinical site during samples collection for all studies. The number of hemolytic lipemic samples were in generally low (<1%). The impact of hemolytic and lipemic effects on PK analyses for clinical studies is expected minimal.

The matrix effect on MSB11022 (A/Citrate), U.S.-Humira and E.U.-Humira was assessed in healthy serum, but not on MSB11022 (C/Acetate). The matrix effect on MSB11022 (A/Citrate) was assessed in psoriasis serum but not on E.U.-Humira. No matrix effect was observed with either healthy serum or psoriasis serum on the samples mentioned above. Given that the bioanalytical method comparability has demonstrated among MSB11022 (A/Citrate), MSB11022 (C/Acetate) and U.S.-Humira in biologic matrix based on the results of the pair-wise comparison of QC bias and the calibration curves overlay, the matrix effect on MSB11022(C/Acetate) in healthy serum is expected to be similar to that on MSB11022 (A/Citrate) and US-Humira. As no matrix effect was

observed with MSB11022 (A/Citrate) in psoriasis serum, the matrix effect on EU-Humira in this biologic matrix is also expected to be minimal.

Table 56. Summary of the bioanalytical method validation

Bioanalytical method validation report name, amendments, and hyperlinks	"Validation of an ELISA Method for the Quantification of an Adalimumab Biosimilar in Human Serum (Project RCDN2)"		
Method description	Method ICD 547: An Enzyme-linked Immunosorbent Assay (ELISA) for the Quantitation of "Adalimumab" in Human Serum		
Materials used for calibration curve & concentration	Ten calibration standards, prepared with MSB11022 (A/Citrate), were analyzed over the nominal concentration range of 50 to 7000 ng/mL (50 ng/mL, 100 ng/mL, 300 ng/mL, 450 ng/mL, 900 ng/mL, 1500 ng/mL, 2000 ng/mL, 3200 ng/mL, 4000 ng/mL and 7000 ng/mL)		
Validated assay range	300 ng/mL (LLOQ) to 7000 ng/mL (ULOQ)		
Material used for QCs & concentration	Prepared at 300, 450, 900, 1800, 3200, 4000, and 7000 ng/mL for MSB11022 (A/Citrate), EU-Humira, and US-Humira in human serum		
Minimum required dilutions (MRDs)	1:100 in low cross buffer		
Source & lot of reagents (LBA)	MSB11022 (A/Citrate), (b) (4) U.S.-Humira, (b) (4) E.U.-Humira, (b) (4) Human Serum, (b) (6) Milli-Q water Superblock Blocking Buffer PBS, (b) (6) Low Cross Buffer (b) (6) 1X Dulbecco's Phosphate Buffered Saline (1X DPBS), (b) (6) Tween-20, (b) (6) 35.6 N Sulfuric Acid, (b) (6) TMB, (b) (6) 10X Phosphate Buffered Saline (without Ca/Mg), (b) (6) Recombinant Human TNF-α, (b) (6) Goat Anti-human IgG (Fc specific)-Peroxidase (b) (6)		
Regression model & weighting	A four-parameter logistic, 1/response² weighted regression algorithm was used		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8 (MSB11022 A/Citrate)	Method Validation Report RCDN2 Table 2A
	Cumulative accuracy (%bias) from LLOQ to ULOQ MSB11022 (A/Citrate)	-2.06 to 2.62%	Method Validation Report RCDN2 Table 2A

	Cumulative precision (%CV) from LLOQ to ULOQ MSB11022 (A/Citrate)	≤ 5.35%	Method Validation Report RCDN2 Table 2A
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 7 QCs** QCs: MSB11022 (A/Citrate) E.U.-Humira U.S.-Humira MSB11022 (C/Acetate)	 -2.28 to 2.39% -7.92 to -2.68% -11 to -0.491% -2.73 to 1.82%	Method Validation Report RCDN2 Table 4A, 4B and 4C Response to Information Request on May 16, 2022 (submitted Aug 26, 2022) Table 1
	Inter-batch %CV QCs: MSB11022 (A/Citrate) E.U.-Humira U.S.-Humira MSB11022 (C/Acetate)	 ≤ 17% ≤ 11.1% ≤ 16.3% ≤9.68%	Method Validation Report RCDN2 Table 4A, 4B and 4C Response to Information Request on May 16, 2022 (submitted Aug 26, 2022) Table 1
	Total Error (TE) QCs: MSB11022 (A/Citrate) E.U.-Humira U.S.-Humira MSB11022 (C/Acetate)	 ≤ 9.32% ≤ 16.4% ≤ 21.5% ≤10.4%	Method Validation Report RCDN2 Table 4A, 4B and 4C Response to Information Request on May 16, 2022 (submitted Aug 26, 2022) Table 1

Selectivity & matrix effect	Ten individuals of healthy human serum were tested unspiked and spiked with MSB11022 (A/Citrate), E.U.-Humira, and U.S.-Humira at LLOQ (300 ng/mL). No matrix effect was observed. Eleven individuals of rheumatoid arthritis (RA) patients' serum were tested unspiked and spiked with MSB11022 (C/Acetate) at LLOQ (300 ng/mL) and HCQ (5300 ng/mL). No matrix effect was observed. Ten individuals of psoriasis patients' serum were tested unspiked and spiked with MSB11022 (A/Citrate) at LLOQ (300 ng/mL). No matrix effect was observed.	Method Validation Report RCDN2 Table 10A-1, 10A-2, 10B-1, 10B-2, 10B-3 Method Validation Report Addendum 8 RCDN14 (RA matrix) Method Validation Report Addendum 2 RCDN5 (Crohn's and Psoriasis matrix)
Interference & specificity	Up to 1000 ng/mL anti-adalimumab antibody does not interfere with the quantitation of MSB11022 (A/Citrate) spiked between 3500 and 14,000 ng/mL. At 300 ng/mL MSB11022 (A/Citrate), ADA fortified at levels ≥ 100 ng/mL interferes with quantitation.	Method Validation Report Addendum 5 RCDN10
Hook effect	The prozone or "hook effect" was evaluated for MSB11022 (A/Citrate), E.U.-Humira, and U.S.-Humira by analyzing a 700,000 ng/mL QC sample undiluted and at 4-, 20-, 40-, 200- and 1000-fold dilutions. No apparent "hook effect" was observed at concentrations up to 700,000 ng/mL.	Method Validation Report RCDN2 Table 6A-1, 6A2, 6B-1, 6B-2, 6C-1 and 6C-2
Hemolysis effect	Blanks (0 ng/mL), low- (900 ng/mL) and high-level (3200 ng/mL) QCs, prepared with MSB11022 (A/Citrate) in hemolyzed plasma containing 5% fully lysed whole blood were analyzed. No effect was identified from hemolysis on the quantitation of adalimumab	Method Validation Report RCDN2 Table 11
Lipemic effect	Blanks (0 ng/mL), low- (900 ng/mL), and high-level (3200 ng/mL) QCs prepared with MSB11022 (A/Citrate) in lipemic human serum were analyzed. No effect was identified from lipemia on the quantitation of adalimumab	Method Validation Report RCDN2 Table 12A Table 12B
Dilution linearity	The ability to dilute samples originally above the upper limit of the calibration range was validated by analyzing six replicate QCs, containing 700000 ng/mL MSB11022 (A/Citrate), E.U.-Humira, and U.S.-Humira as 500-fold dilutions. The intra-assay quality control data for the diluted QC pools met the acceptance criteria. MSB11022(A/Citrate): Accuracy: -1.45% bias; Precision: 9.01% CV	Method Validation Report RCDN2 Table 5

	EU-Humira: Accuracy: -5.54% bias; Precision: 2.6% CV US-Humira: Accuracy: -8.86% bias; Precision: 4.81% CV	
Bench-top/process stability	Analyte stability in thawed matrix was evaluated by allowing a set of low- (900 ng/mL) and high- (3200 ng/mL) level quality controls to thaw and remain at room temperature for 24 hours (U.S.-Humira) and 26 hours [MSB11022 (A/Citrate) and E.U.-Humira] prior to analysis. The analyte stability in thawed matrix data met the criteria	Method Validation Report RCDN2 Table 8
Freeze-Thaw stability	Freeze/thaw stability (F/T) was evaluated by analyzing a set of low- (900 ng/mL) and high level (3200 ng/mL) QCs for MSB11022 (A/Citrate) that were subjected to five freeze/thaw cycles. The freeze/thaw stability data met the criteria for demonstrating stability. Freeze/thaw stability (F/T) was evaluated by analyzing a set of low- (900 ng/mL) and high level (3200 ng/mL) QCs for MSB11022 (C/Acetate), U.S.-Humira and E.U.-Humira that were subjected to up to eight freeze/thaw cycles. The freeze/thaw stability data met the criteria for demonstrating stability.	Method Validation Report RCDN2 Table 7 Method Validation Report RCDN2 Table 8 Response to Information Request on May 16, 2022 (submitted Aug. 26, 2022) Table 5, 8, 9
Long-term storage	MSB11022 (A/Citrate) stability samples at low- (900 ng/mL) and high-level (5300 ng/mL) pools in frozen human serum stored for up to 1185 days at -25 °C ± 5 °C and at -80 °C ± 10 °C met the criteria (-0.61% to 14% bias and < 7.09% CV). MSB11022 (C/Acetate) samples at low (900 ng/mL) and high (5300 ng/mL) stored up to 763 days at -80 °C met the criteria (up to 19.65% bias and ≤7.91% CV). US-Humira and EU-Humira clinical study samples with concentrations greater than 25% of LLOQ were re-analyzed after stored in -80°C for up to 853 days (US-Humira) and 2162 days (EU-Humira). Greater than 90% of samples had relative percent difference between original results and re-assay results within ± 30%.	Validation Method Report Addendum 6 RCDN7 Response to Information Request on May 16, 2022 (submitted Aug. 26, 2022) Table 4, 6, 7

Parallelism	Twenty highly quantitating healthy human serum samples from Study EMR200588-003 and psoriasis human serum samples from Study EMR200588-002 were each diluted to three levels (1:2, 1:4 and 1:8 in healthy human serum and 1:5, 1:10 and 1:20 in psoriasis human serum) within the assay range. The relative percent difference between all pairs of results for each sample was within ± 30%. Twenty highly quantitating rheumatoid arthritis human serum samples from Study MS200588-004 were each diluted to three levels (1:3, 1:9 and 1:27) within the assay range. The relative percent difference between all pairs of results for each sample was within ± 30%. Parallelism has been demonstrated for serum collected from rheumatoid arthritis patients, healthy individuals and psoriasis.	Method Validation Report Addendum 4 RCDN8 Table 1, 2A, 2B Method Validation Report Addendum 7 RCDN12 Table 1 and 2
Carry over	Not applicable	---

The serum samples collected during Study FKS022-002, EMR200588-001 and EMR200588-002 and FKS022-001 were analyzed using the validated method with pass rates of 96.06% (488 out of 508 runs), 72.3% (170 out of 235 runs), 91.3% (262 out 287 runs) and 90.08% (227 out of 252 runs) respectively (Table 4 to 7). It was noted the analytical runs passing rate for Study EMR200588-001 was low due to an identified wavelength issue (Table 5). Given that a technical issue has been identified and the incurred sample reanalysis on 9.38 % of study samples showing 96.6 % acceptance rate, the integrity of bioanalytical assay for this study is less likely impacted.

Table 57. In-Study Performance for Study FKS022-002

Method performance in study FKS022-002 "A randomized, double-blind, parallel group, single dose study to compare the pharmacokinetics, safety, tolerability and immunogenicity of MSB11022 (acetate formulation) versus US-licensed reference product Humira® and Idacio® in healthy subjects"		
Assay passing rate	Overall assay pass rate: 96.06% (488 out of 508 runs were accepted)	Bioanalytical Report For Study FKS022-002 RMMW Table 1
Standard curve performance	• Cumulative bias range: -0.331 to 1.92 % • Cumulative precision: ≤ 4.40 % CV	Bioanalytical Report For Study FKS022-002 RMMW Table 6 and 7
QC performance	• Cumulative bias range: -0.23 to 1.66% • Cumulative precision: ≤ 9.88 % CV • TE: ≤ 10.11%	Bioanalytical Report For Study FKS022-002 RMMW Table 8

Method reproducibility	Incurred sample reanalysis was performed in 11 % of study samples and 99.3 % of samples met the pre-specified criteria	Bioanalytical Report For Study FKS022-002 RMMW Table 5
Study sample analysis/ stability	Samples were stored at -80 °C for a maximum of 296 days between sample collection and analysis	

Table 58. In-study method performance in Study EMR200588-001

Method performance in study EMR200588-001 "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"		
Assay passing rate	Overall assay pass rate: 170 out of 235 runs are accepted (72.3%) A wavelength issue (using single wavelength instead of two wavelengths) was identified for 46 sample analysis runs and 5 qualification runs. All runs read at single wavelength were rejected and reanalyzed with two wavelengths.	Bioanalytical Report for Study EMR200588-001 RCGQ Table 2
Standard curve performance	• Cumulative bias range: -5.57 to 4.22 % • Cumulative precision: ≤ 7.97% CV	Bioanalytical Report for Study EMR200588-001 RCGQ Table 5
QC performance	• Cumulative bias range: -4.88 to 3.57% • Cumulative precision: ≤ 28.3% CV (9.62% , 11.3% and 28.3% for QC 900 ng/mL, 1800 ng/mL and 5300 ng/mL, respectively) • TE: ≤ 31.87%	Bioanalytical Report for Study EMR200588-001 RCGQ Table 6
Method reproducibility	Incurred sample reanalysis was performed in 9.38 % of study samples and 96.6 % of samples met the pre-specified criteria	Bioanalytical Report for Study EMR200588-001 RCGQ Appendix F
Study sample analysis/ stability	All samples were stored at -80 °C ± 10°C and analyzed within the 176 days.	

Table 59. In-Study Method Performance for Study EMR200588-002

Method performance in study EMR200588-002 "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"		
Assay passing rate	Overall assay pass rate: 262 out 287 runs are accepted (91.3%)	Bioanalytical Report for Study

		200588-002 RFYN Table 1
Standard curve performance	• Cumulative bias range: -0.215 to 0.595% • Cumulative precision: ≤ 5.44% CV	Bioanalytical Report for Study 200588-002 RFYN Table 5
QC performance	• Cumulative bias range: -0.618 to 2.77% • Cumulative precision: ≤ 9.61% CV • TE: ≤ 11.22%	Bioanalytical Report for Study 200588-002 RFYN Table 6
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of study samples and 94.2 % of samples met the pre-specified criteria	Bioanalytical Report for Study 200588-002 RFYN Table 4
Study sample analysis/ stability	All samples were stored at -80°C ± 10°C and analyzed within the 1185 days.	

Table 60. In-study method performance in Study FKS022-001

Method performance in study FKS022-001 "A phase I, randomized, open-label, parallel-group study to determine the pharmacokinetics, safety, and tolerability of msb11022 (proposed adalimumab biosimilar) following a single subcutaneous injection by an auto-injector or by a pre-filled syringe in healthy subjects"		
Assay passing rate	Overall assay pass rate: 227 out of 252 runs were accepted (90.08%)	Bioanalytical Report For Study FKS022-001 RMHZ Table
Standard curve performance	• Cumulative bias range: -0.541 to 3.7% • Cumulative precision: ≤ 6.61% CV	Bioanalytical Report For Study FKS022-001 RMHZ Table 5
QC performance	• Cumulative bias range: -1.19 to 3.47 % • Cumulative precision: ≤ 8.66 % CV • TE: ≤ 12.13%	Bioanalytical Report For Study FKS022-001 RMHZ Table 6
Method reproducibility	Incurred sample reanalysis was performed in 10.3% of study samples and 95.4% of samples met the pre-specified criteria	Bioanalytical Report For Study FKS022-001 RMHZ Table 4

Study sample analysis/ stability	Samples were stored at -80°C for a maximum of 184 days between sample collection and analysis

13.2.2. Missing PK Data for Study EMR200588-002

During the review of PK data for Study EMR200588-002, it was noted that 9 patients (5 in E.U.-Humira and 4 in MSB11022) who received the study drug did not have any measurable post-dose concentration in Core Treatment Period, while 38 patient who received the study drug did not have any measurable post-dose concentration in Extended Treatment Period (14 in E.U.-Humira, 9 in MSB11022 and 15 in E.U-Humira/MSB11022).

Based on the Applicant's response submitted dated Aug 26, 2022, the 9 patients, who did not have measurable post-dose concentration in Core Treatment Period, were either early withdrawal (n=8) or protocol deviation with no drug administered at Week 2, 12 and 14 (n=1). Among the 38 subjects with no measurable post-dose concentration during the Extended Treatment Period,10 subjects withdrew early or lost to follow up, while 28 subjects completed the treatment but had post-dose concentrations below limit of quantification (< 300 ng/mL). All of these subjects were ADA positive. The proportion of subjects with no measurable post-dose concentration was similar across three treatment groups, which were 6.1% (n=13), 8.9% (n=9) and 5.9% (n=6) for MSB11022 only, E.U.-Humira only and E.U.-Humira/MSB11022, respectively. The reviewer performed a sensitivity analysis by including these patients. The mean trough concentrations were still similar between patients receiving E.U.-Humira and those receiving MSB11022 in Core Treatment Period and between patients who switched from E.U.-Humira to MSB11022 and those who continued with either E.U.-Humira and MSB11022 in Extended Treatment Period.

It was also noted that the Applicant excluded some samples from the descriptive statistics (Table 9 of Section 5.3.3.) due to schedule trough samples collected after dose (15 samples), sample out of window from previous dose (467 samples), unscheduled (19 samples) or protocol deviation (20 samples). A total of 260 patients were affected, 78% of whom had only one or two samples affected. The reviewer includes all excluded samples by the Applicant (Figure 6 and 7 of Section 5.3.3.). In reviewer's analysis, concentrations were still similar between the two treatments during the first 16 weeks (Core Treatment Period) and similar in patients receiving switching from E.U.-Humira to MSB11022 (A/Citrate) and patients who remained in either E.U.-Humira or MSB11022 (A/Citrate) in Extended Treatment Period.

Additionally, the number of data entry in Applicant's PK dataset (4799 samples) was different from the number of total analyzed samples reported in the bioanalytical report of this study (4970 samples). The Applicant addressed this discrepancy in the response submitted dated Aug. 26, 2022, as there were 169 samples collected for a population PK substudy in error and 2 samples for safety follow-up for one pregnant patient who withdrew from the study. The non-reported PK samples in the dataset were mostly for Week 2. The impact on PK analysis is minimal.

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/s/

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12/13/2022 01:16:44 AM

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12/13/2022 08:36:39 AM