BIOSIMILAR MULTI-DISCIPLINARY EVALUATION AND REVIEW

Application Type	351k
Application Number	761154
Submit Date	July 12, 2019
Received Date	July 12, 2019
BsUFA Goal Date	July 12, 2020
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM)/Office of Immunology and Inflammation (OII) in collaboration with the Division of Dermatology and Dentistry (DDD/OII) and Division of Gastroenterology (DG/OII)
Review Completion Date	See electronic stamped date
Product Code Name	FKB327
Proposed Non-Proprietary Name[1]	Adalimumab-fkjp
Proposed Proprietary Name[1]	Hulio
Pharmacologic Class	Tumor Necrosis Factor (TNF) blocker
Applicant	Mylan GmbH
Applicant Proposed Indication(s)	Rheumatoid arthritis, juvenile idiopathic arthritis in patients 4 years of age and older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's Disease, ulcerative colitis, and plaque psoriasis
Recommendation on Regulatory Action	Approval

[1] The proposed proper and proprietary names are conditionally accepted until such time that the application is approved.

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TL=Team Leader
DD=Deputy Director
CDRH=Center for Devices and Radiological Health
CMC=Chemistry, Manufacturing, and Controls
OBP=Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DAV=Division of Anti-Virals
DDD=Division of Dermatolgoy and Dentistry
DG=Division of Gastroenterology
DMEPA=Division of Medication Error and Prevention Analysis
DMPP=Division of Medical Policy Program
DPACC=Division of Pulmonology, Allergy, and Critical Care
DRISK=Division of Risk Management
DRTM=Division of Rheumatology and Transplant Medicine
DPV=Division of Pharmacovigilence
DPMH=Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multi-Disciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CDRH	Center for Devices and Radiological Health
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
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DMC	Data Monitoring Committee
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
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
IR	Information Request
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

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NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
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
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGE	Special Government Employee
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation

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1. Executive Summary

1.1. Product Introduction

Mylan (also referred to as the "Applicant" in this review) has submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for FKB327 as a proposed biosimilar to US-licensed Humira (adalimumab).

FKB327 is a fully human anti-TNFα IgG1 monoclonal antibody produced (b) (4) using recombinant DNA technology. It is proposed as a biosimilar to US-licensed Humira. FKB327 binds to TNF-α, blocks its interaction with the p55 and p75 cell surface TNF receptors and neutralizes its biological function.

Mylan is seeking licensure of FKB327 for the following indications for which US-Humira has been previously approved[2]:

1) 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.
2) Juvenile Idiopathic Arthritis (JIA):
   - Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
3) Psoriatic Arthritis (PsA):
   - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
4) Ankylosing Spondylitis (AS):
   - Reducing signs and symptoms in adult patients with active AS.
5) Adult Crohn's Disease (adult CD):
   - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab products.
6) Ulcerative Colitis (UC):
   - Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine
7) Plaque Psoriasis (PsO):

[2] FDA-approved Humira labeling

• The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

Although the Division of Rheumatology and Transplant Medicine (DRTM) (previously named the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology (DG), and the Division of Dermatology and Dental (DDD) during the course of the review.

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

Not Applicable.

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

FKB327 binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. FKB327 also lyses surface TNF expressing cells *in vitro* in the presence of complement. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques.

FKB327 product is a sterile liquid solution with the following proposed presentations:

- Autoinjector (also referred to as a pre-filled pen (PFP) in this application)
  Injection: 40 mg/0.8 mL in a single-dose prefilled autoinjector

- Prefilled syringe
  Injection: 40 mg/0.8 mL in a single-dose prefilled plastic syringe
  Injection: 20 mg/0.4 mL in a single-dose prefilled plastic syringe

Each strength of FKB327 in prefilled syringes and in the pre-filled pen is the same as that of US-Humira. FKB327 also has the same dosage form and route of administration as that of US-Humira.

1.4. Facilities

FDA's Office of Pharmaceutical Manufacturing Assessment (OPMA) conducted an assessment of

the manufacturing facilities for this BLA.

Kyoma Hakko Kirin Co., Ltd. (FEI 3007588904) is responsible for drug substance (DS) manufacturing. A pre-license inspection (PLI) was conducted from September 25th to October 4th, 2019. A 4-item FDA Form 483 was issued at the conclusion of the inspection, with 3 verbal observations discussed with the firm. Refer to the FDA Form 483 for a list of the observations. The inspection was classified as voluntary response indicated (VAI) and no potential approvability issues were identified.

The drug product (DP) inspection at Terumo Yamaguchi D&D Corp. (FEI 3013611763) was conducted in February 13th-21st, 2020. This was the firm's first FDA inspection. A 10-item Form FDA 483 was issued, with the inspection field recommendation of withhold, pending the firm's adequate response to objectionable conditions. Refer to the FDA Form 483 for a list of the observations. The response was adequate and the final inspection conclusion was VAI.

The OPMA team recommended that BLA 761154 be approved from the standpoint of facilities assessment. CDRH has also recommended approval of this application. I concur with these recommendations.

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

Not applicable.

1.6. Biosimilarity Assessment

Table 1: Summary and Assessment of Biosimilarity

Comparative Analytical Studies: The Office of Pharmaceutical Products, OPQ, CDER has concluded, and I agree, that:	
Summary of Evidence	• FKB327 is highly similar to US-Humira notwithstanding minor difference in clinically inactive components. • FKB327 prefilled syringes (40 mg/0.8 mL and 20 mg/0.4 mL) and autoinjector (40 mg/0.8 mL) each have the same strength as that of US-Humira. • The dosage form and route of administration is also the same as that of US-Humira.
Residual Uncertainties and Outcomes	• There are no residual uncertainties from the product quality assessment.
Animal Studies: The Pharmacology and Toxicology team concluded, and I agree, that:	

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Summary of Evidence	• The information in the pharmacology/toxicology assessment support the demonstration of biosimilarity.
Residual Uncertainties and Outcomes	• There are no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Pharmacology: The Clinical Pharmacology team concluded, and I agree, that:	
Summary of Evidence	• PK similarity has been demonstrated between FKB327 and US-Humira, and supports a demonstration of no clinically meaningful differences between FKB327 and US-Humira. • Comparable incidence of ADA formation between FKB327 and US-Humira in healthy subjects and patients with RA supports a demonstration of no clinically meaningful differences.
Residual Uncertainties and Outcomes	• There are no clinical pharmacology residual uncertainties regarding PK assessments.
Clinical Studies: The Clinical and Statistical teams concluded, and I agree, that:	
Summary of Evidence	• In Study FKB327-002, there were no meaningful differences in terms of efficacy between FKB327 and US-Humira. The frequency of treatment emergent adverse events, serious adverse events, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms.
Residual Uncertainties and Outcomes	• There are no residual uncertainties from the clinical or statistical perspective regarding the demonstration of no clinically meaningful differences between FKB327 and US-Humira.
Extrapolation of Data to Support Licensure as a Biosimilar	

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 toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (RA), to support licensure of FKB327 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 (ulcerative colitis and adult Crohn's disease) o Treatment of moderate to severe plaque psoriasis o Treatment of juvenile idiopathic arthritis in patients 4 years of age and older o Treatment of psoriatic arthritis o Treatment of ankylosing spondylitis
Residual Uncertainties and Outcomes	• There were no residual uncertainties regarding the extrapolation of data and information to support licensure of FKB327 as a biosimilar to US-Humira for the above indications.

1.7. Conclusions on Licensure

In considering the totality of the evidence, the data submitted by the Applicant show that FKB327 is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between FKB327 and US-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 FKB327 for JIA in patients 4 years and older, PsA, AS, PsO, Adult CD, and UC. The information submitted by the Applicant demonstrates that FKB327 is biosimilar to US-Humira for each of the following indications for which US-Humira is currently licensed and the Applicant is seeking licensure of FKB327: RA, JIA in patients 4 years and older, PsA, AS, Adult CD, and UC and should be licensed.[3]

[3] The proposed FKB327 labeling states: "Biosimilarity of HULIO has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information."

Author:
Miya Paterniti, M.D.
Cross-Discipline Team Leader (CDTL)

2. Introduction and Regulatory Background

2.1. Important Safety Issues with Consideration to US-Humira

The US-Humira label (USPI) includes a boxed warning (see below) and several warnings and precautions, in particular serious infections, including tuberculosis and other opportunistic infections, and malignancies including non-melanoma skin cancer and lymphoproliferative disorders, which also apply to other TNF blockers.

US-Humira labeling boxed warning provides:

"SERIOUS INFECTIONS

Patients treated with Humira are at increased risk for developing serious infections that may lead to hospitalization or death [….]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before Humira use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric antifungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients

who tested negative for latent TB infection prior to initiating therapy […].

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA […]. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants […]."

The warning and precautions section (Section 5 of the USPI) lists other known safety issues with Humira and other TNF blockers, including:

- Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystosis have been reported in patients receiving HUMIRA. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicemia. Hospitalization or fatal outcomes associated with infections have been reported. Tuberculosis (including pulmonary and extra-pulmonary tuberculosis) reactivation and new onset cases have been reported in patients receiving HUMIRA. If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, invasive fungal infection is to be considered in the differential diagnosis.
- Malignancies including breast, colon, prostate, lung, and melanoma, nonmelanoma skin cancer, lymphoma and leukemia. Additionally, lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA. Rare cases of hepatosplenic T cell lymphoma have occurred in adolescents and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.
- Hypersensitivity reactions including anaphylaxis
- Hepatitis B reactivation, some cases with fatal outcome, has occurred in patients who are chronic carriers of this virus
- Neurologic reactions (rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome)
- Hematological reactions (rare cases of pancytopenia including aplastic anemia, and

adverse reactions of the hematologic system, including medically significant cytopenia, e.g. thrombocytopenia, leukopenia)
- Concurrent use of anakinra or abatacept (associated with a greater proportion of serious infections and, in case of anakinra, neutropenia). Both anakinra and abatacept were prohibited treatments during study, and patients were only randomized after a 6-month washout period after anakinra or abatacept treatment
- Heart failure, i.e. onset or worsening of congestive heart failure
- Autoimmunity, i.e. formation of autoantibodies and, rarely, development of a lupus-like syndrome
- Immunizations; patients on Humira may receive concurrent vaccinations, except for live vaccines

US-Humira use has been previously described as leading to the development of anti-drug antibody (ADA) formation in clinical studies, and according to the FDA-approved labeling for US-Humira, there was a trend toward higher adalimumab apparent clearance in the presence of anti-adalimumab antibodies, but no apparent correlation between the development of anti-adalimumab antibodies and the occurrence of adverse events (AEs). In the published literature, however, anti-adalimumab antibodies have been described to be associated with increased frequency of clinical adverse effects[1,2], but other authors do not describe such an association[3].

2.2. Summary of Presubmission Regulatory Activity Related to Submission

On February 21, 2013, advice regarding the non-clinical and clinical program for FKB327 was communicated to the applicant in a Type B pre-IND meeting. Additional interactions related to the comparative clinical study were held via a Biosimilar Biologic Product Development (BPD) Type 2 meeting on January 28, 2014. It was during this interaction that it was communicated that ACR20 would be an appropriate primary endpoint for the comparative clinical study of FKB327 in RA patients.

After submitting PK data from Study FKB327-001, the FDA agreed on June 12, 2014, that it appeared PK similarity had been demonstrated between FKB327 and US-licensed Humira. IND 116471 was submitted for the conduct of Study FKB327-002 on July 31, 2014. Non-hold comments provided by DPARP focused on an appropriate similarity margin for the primary endpoint, the need to follow subjects that discontinue trial medication, and CMC comments.

On October 15, 2014, DPARP agreed that the proposed bridging studies for the vial, PFS, and AI would be adequate, given that different presentations of FKB327 would be used throughout the clinical development program. The anti-drug antibody sampling plan was also deemed appropriate on March 20, 2015, and an acceptable similarity margin for the primary endpoints for Study FKB327-002 was agreed upon on October 5, 2015. The most current version of the Initial Pediatric Study Plan (iPSP) is dated July 27, 2016.

Reference ID: 4635331

On April 17, 2015, FDA recommended a similarity margin for the difference in ACR20 response probabilities of ±12%, but also noted that the Agency would consider a proposal for a relaxed upper bound as part of an asymmetric similarity margin. Subsequently, the Sponsor submitted a revised protocol and a proposal for an asymmetric similarity margin of (-12%, +15%), and FDA accepted the asymmetric margin.

On January 13, 2017, a BPD Type 4 meeting was held, followed by the official BLA submission on July 27, 2019.

The BLA filing meeting was held on August 8, 2019. Because it was noted that the Applicant was seeking approval for all indications of US-licensed Humira, an information request (IR) was sent on August 12, 2019 asking the Applicant to clarify which indications were being sought in the BLA and to revise their application to match those indications, as some of the US-Humira indications are protected by orphan drug exclusivity. Further clarification regarding this issue was provided via teleconference on August 19, 2019 and a response to the IR was received from the Applicant on August 22, 2019. The Applicant communicated in this response that they are seeking approval for all indications for which US-licensed Humira is licensed that are not currently covered by orphan drug exclusivity.

2.3. Studies and Publicly Available Information Submitted by the Applicant

Table 2: Submitted Nonclinical Studies

Study Title	Study Number	Duration/Dose	Regimen/Route	Number of Subjects
Nonclinical Studies				
General Toxicology, Repeated Dosing				
Comparative Toxicity Study of FKB327 and Humira in Cynomolgus Monkeys with 4-Week Intermittent Subcutaneous Dosing Followed by an 8-Week Recovery Period	SBL330-00 1	4 weeks with 8-week recovery; 30 mg/kg FKB327 or EU-adalimumab	once weekly for 4 weeks, SC	Main: 3 males/group Recovery: 2 males/group
In vivo Pharmacodynamics or Pharmacokinetics				
Pharmacokinetics of FKB327 and Humira after a single subcutaneous administration in cynomolgus monkeys	r-fkb327-01	29 days 3 mg/kg	Single dose, SC, followed for 29 days	4 males/ group

Clinical

The Applicant has submitted data from one single-dose PK similarity study (FKB327-001), one comparability PK study using the vial, PFS, and AI (FKB327-005) and two comparative clinical studies in patients with RA (Studies FKB327-002 and FKB327-003). The Applicant also

submitted data from two other supportive studies conducted in healthy Japanese participants (Table 2).

Table 3: Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity and Comparability Studies					
FKB327-001	N/A	Comparative assessment of pharmacokinetics, safety, and immunogenicity of FKB327, US-Humira, and EU-Humira	Double-blind, randomized, parallel-group, single-dose, 3-arm	Healthy subjects	FKB327: 60 US-Humira: 60 EU-Humira: 60
FKB327-005	N/A	Assessment of relative bioavailability of a single-dose of FKB327 delivered via vial, PFS or PFP/AI; pharmacokinetics; comparative safety	Randomized, open-label, parallel-group, single-dose	Healthy subjects	FKB327 Vial: 66 PFS: 63 PFP/AI: 66
Comparative Clinical Studies[a]					
FKB327-002	NCT02260791	Comparative clinical study between FKB327 and US-Humira designed to assess efficacy, safety, immunogenicity, and steady-state pharmacokinetics after repeated dosing	Double blind, randomized, parallel-group	Moderate to severe RA on MTX	FKB327 (vial): 367 US-Humira (PFS): 363
FKB327-003	NCT02405780	Comparative clinical study between FKB327 and US-Humira designed to assess efficacy, safety, immunogenicity, and steady-state pharmacokinetics after repeated dosing; assessment of the effect of transitioning between FKB327 and US-licensed Humira	Period I: randomized, OLE Period II: single arm OLE	Moderate to severe RA on MTX that completed Study 002	Period I: FKB327 (PFS): 324 US-Humira (PFS): 321 Period II: FKB327 (PFS or PFP/AI[b]): 572
Other Supportive Studies[c]					
FKB327-	N/A	Comparative assessment	Randomized,	Healthy	FKB327: 66

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
004		of pharmacokinetics, safety, and immunogenicity	single-blind, parallel group	Japanese subjects	US-Humira: 65
FKB327-006	N/A	Comparative assessment of pharmacokinetics, safety, and immunogenicity	Randomized, single-blind, parallel group	Healthy Japanese subjects	FKB327: 66 US-Humira: 65

RA = rheumatoid arthritis, MTX = methotrexate, OLE=open-label extension, PFS=pre-filled syringe, PFP/AI=pre-filled pen, autoinjector

[b]PFS was used in US centers and AI was used in ex-US sites
[c]Trials performed for local product license application
Source: FDA Reviewer

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3. Clinical Studies: Ethics and Good Clinical Practice

3.1. Submission Quality and Integrity

The data quality and integrity of the studies were acceptable. The amount of missing data was minimal and did not impact overall conclusions regarding biosimilarity. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

3.2. Statistical Analysis of Clinical Data

Statistical analysis of the efficacy endpoints were assessed using the comparative clinical study, FKB327-002. The applicant submitted sufficient documentation and reviewers guide to facilitate independent evaluation of efficacy results. In addition, the datasets for all clinical studies were submitted along with the application and were consistent with Clinical Data Interchange Standards Consortium (CDISC) standards. In general, the quality of data submitted for analyses was adequate.

The statistical analysis plan (SAP) was not submitted for FDA review prior to BLA submission; however, all versions of the (SAP) were included in the BLA.. The applicant followed the SAP for efficacy analyses and the statistical reviewer was able to reproduce the relevant key analyses based on the SAP.

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The Applicant informed the Agency that no data monitoring committee (DMC) was used during the comparative clinical study. The Applicant's rationale for not having a DMC are as follows: (i) the indication under investigation is not a disease considered to be within the class of life-threatening diseases, or within a patient population of a specific vulnerability usually requiring a DMC; (ii) the potential risks with FKB327 treatment are expected to follow those associated with US-Humira which are described in detail within the US Prescribing Information (USPI) for US-Humira; and (iii) the processes to be used for the recording and reporting of adverse events are considered adequate to allow the timely identification and management of any unexpected safety event without the additional requirement of DMC oversight. This rationale was thought to be reasonable and appropriate.

3.3. Compliance with Good Clinical Practices

All studies were conducted according to Good Clinical Practice (GCP) as described in the International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters for the studies received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Subjects signed informed consent documents. Written informed consent was obtained prior to subjects entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authority.

3.4. Financial Disclosures

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators. The Applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified. See section 13.2 for additional information.

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4. Summary of Conclusions of Other Review Disciplines

4.1. Chemistry, Manufacturing and Controls (CMC)

The Office of Pharmaceutical Products, OPQ, CDER, recommends approval of BLA 761154 for FKB327 manufactured by Mylan. Refer to the integrated quality assessment (finalized in Panorama on April 22, 2020) and related primary reviews for detailed information. The OPQ team determined that the data submitted in this application are adequate to support the following conclusions:

- The manufacture of FKB327 is well-controlled and leads to a product that is pure, potent, and safe
- FKB327 is highly similar to US-Humira notwithstanding minor differences in clinically inactive components
- Each strength of FKB327 in a prefilled syringe and autoinjector is the same as that of US-Humira. FKB327 also has the same dosage form and route of administration as that of US-Humira.

4.2. Clinical Microbiology

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for approval from a microbial control, sterility assurance and product quality perspective.

4.3. Devices

FKB327 product is a sterile liquid solution with the following proposed strengths and presentations:

- Prefilled syringe
  Injection: 40 mg/0.8 mL in a single-dose prefilled plastic syringe
  Injection: 20 mg/0.4 mL in a single-dose prefilled plastic syringe

- Autoinjector (also referred to as a pre-filled pen (PFP) in this application)
  Injection: 40 mg/0.8 mL in a single-dose prefilled autoinjector

Container closure:

- HULIO PFS: The container closure system (CCS) is a single-use PLAJEX plastic syringe with safety device, comprised of syringe barrel (1 mL long), stainless steel needle, needle shield, rigid needle shield, and (b) (4) coated stopper.

- HULIO AI: The CCS consists of a PLAJEX plastic syringe assembled into an auto-injector.

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4.3.1. Center for Devices and Radiological Health (CDRH)

CDRH recommends approval based on assessment of device constituent parts of the combination product.

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

FKB327 is a proposed combination product, with PFS and AI presentations. To support the proposed presentations, the Applicant has submitted product quality, clinical pharmacology, and device data, reviewed elsewhere in this document. In addition, the Applicant provided a Use-Related Risk Analysis (URRA) to support the use of these devices in the intended patient populations, which were reviewed by DMEPA. The Applicant submitted human factor (HF) data for use of both the PFS and the AI.

With regards to the FKB327 PFS presentation, DMEPA notes that a pediatric user group was not included in the submitted HF studies despite the indication of juvenile idiopathic arthritis. DMEPA deferred to DRTM on addressing this data gap and determining the appropriate labeling for this user group.

DRTM acknowledges the DMEPA assessment and recommendations. However, in reviewing the DMEPA recommendations, DRTM also considered that irrespective of whether the patient is an adult with RA or a JIA patient, it is expected that the patient will only self-administer FKB327 when willing to do so, having received appropriate training, and having demonstrated the ability to self-inject. This is explicitly stated in the product labeling, Section 2.7, General Considerations for Administration:

> *HULIO is intended for use under the guidance and supervision of a physician. A patient may self-inject HULIO or a caregiver may inject HULIO using either the HULIO Pen or prefilled syringe if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.*

Additional instructions are included in Section 17. Patient Counseling Information.

Considering the above contextual information, DRTM concludes that no additional HF studies are needed in JIA for this application and current labeling is appropriate and sufficient to ensure the safe and effective use of both the PFS and AI presentations.

DMEPA also provided recommendations for labeling changes based on the available data within the submitted HF study results reports, as well as heuristic and expert review of the user interface. For this particular review, DMEPA determined the changes can be implemented without additional validation testing. These changes were incorporated in the product labeling.

4.4. Office of Study Integrity and Surveillance (OSIS)

A clinical and bioanalytical site inspection for Study FKB327-001 was performed at Kyowa Hakko Kirin California, Inc. in La Jolla, California. Objectional conditions were observed and a Form FDA 483 was issued. Based on the firm's response, OSIS determined that the data from the audited study are reliable to support a regulatory decision. The final inspection classification was Voluntary Action Indicated (VAI). Refer to the review memo by Dr. Amanda Lewin dated April 14, 2020 for additional information.

4.5. Office of Scientific Investigations (OSI)

The following clinical study sites were selected from the comparative clinical study FKB327-002 for inspection by CDER Office of Scientific Investigations (OSI).

- Site 0104 (Dr. Maria Greenwald, California, USA): enrolled n=33
- Site 0702 (Dr. Elias Chalouhi El Khouri, Lima, Peru); enrolled n=36

These sites were selected for inspection based on high enrollment and high rates of discontinuation as identified by the Clinical Site Selection Tool. In addition, Site 0104 previously had a history of a for-cause inspection. 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 March 10th, 2020 for detailed information regarding the clinical site inspections.

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5. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

5.1. Nonclinical Executive Summary and Recommendation

FKB327 has been developed as a biosimilar product to US-Humira. One repeat-dose 4-week toxicity and toxicokinetic study in cynomolgus monkey (study number SBL330-001) was reviewed for the pharmacology/toxicology assessment of FKB327. The results from the FKB327 and vehicle groups of study SBL330-001 support the demonstration of biosimilarity. FKB327 contains monosodium glutamate (MSG) as an excipient, while US-Humira does not. Study number SBL330-001 supported the safety of MSG for subcutaneous injection. While study SBL330-001 included the use of a non-US-licensed comparator product, EU-Humira, the data generated using EU-Humira was not used to support the demonstration of biosimilarity. A review of this study is included in the Nonclinical Appendix, Section 13.3.4.

Pharmacology
FKB327 is a human monoclonal immunoglobulin G (IgG1 κ subtype). It was demonstrated that FKB327 binds to human TNFα with high affinity and produced a dose-dependent inhibition of TNFα in in vitro assays. Refer to the OBP review finalized in Panorama on March 12, 2020, for a detailed comparative physiochemical and functional evaluation of epitopes of the Fab and Fc regions of FKB327.

Toxicology
In the 4-week monkey toxicity study (Report SBL330-001, refer to the Nonclinical Appendix of this document), male cynomolgus monkeys were administered 30 mg/kg FKB327 or EU-Humira, subcutaneously, once weekly for 4 weeks. A control group was administered the vehicle for FKB327, which was the same as the clinical vehicle. Recovery animals were followed for an additional 8 weeks without treatment. Although the study included an EU-Humira arm, only the information from the vehicle and FKB327-treated groups was used to support the demonstration of biosimilarity.

There were no mortalities during the treatment period. There was no effect of FKB327 or EU-Humira on clinical observations, body temperature, blood pressure, body weight, feed consumption, ophthalmoscopy, ECG parameters, hematology, bone marrow nucleated cell count, clinical chemistry, C-reactive protein, serum cytokines, urinalysis, macroscopic findings, or organ weights. There was a very slight perivascular mononuclear cell infiltration in the subcutis at the injection site in all 3 main study animals of the FKB327 treatment group (necropsy 1-week after the last dose), but not in the other treatment groups. This finding was also not present in the FKB327 recovery animals, 8 weeks later. In both the FKB327 and EU-Humira treatment groups, there were decreases (compared to control staining) in the staining with anti-CD21 in the follicle of the spleen, mesenteric lymph node, and submandibular lymph node at the end of the dosing period, and in the follicle of the spleen, mesenteric lymph node,

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and submandibular lymph node at the end of the recovery period. This occurred in 1 to 3 animals for each tissue and treatment group. .

The dose selected for this toxicological study was low, yet still produced an expected TK and treatment effect.. Anti-drug antibodies were detected in 1 FKB327 animal but did not appear to affect plasma FKB327 values when compared to other FKB327-treated animals. Overall, there were no safety concerns identified in this study, other than slight injection site reactions in monkeys treated with FKB327. In terms of safety, this is considered a clinically monitorable finding.

The nonclinical program described above supported the safety of FKB327 for clinical use. Additionally, the information from the FKB327 and vehicle arms of study SBL330-001 support the safety of Monosodium Glutamate by the SC route of administration.

5.1.1. Nonclinical Residual Uncertainties Assessment

There were no residual uncertainties identified based on review of the nonclinical studies.

5.2. Product Information

Table 4: Composition of FKB327 Drug Product (from Applicant's Module 2.3), 20 mg drug product in prefilled syringe

Component	Function	Quality Standard	Concentration	Quantity per DP Prefilled Syringe
FKB327	API	In-house[a]	50 mg/mL	20 mg
Monosodium Glutamate	(b) (4)	NF, JPC	10 mmol/L	0.75 mg
Sorbitol		NF/Ph. Eur./JP	262 mmol/L	19.1 mg
Methionine		USP/Ph. Eur./JP	5 mmol/L	0.30 mg
Polysorbate 80		NF/Ph. Eur./JP	1.0 mg/mL	0.40 mg
Diluted Hydrochloric Acid		NF/Ph. Eur./JP	Adjust to pH 5.2	As required
Water for Injection (distilled)		USP/Ph. Eur./JP	q.s. to 0.4 mL	q.s. to 0.4 mL

a: Meets the Drug Substance (DS) specification (see Section 3.2.S.4.1)
Abbreviations: API: Active Pharmaceutical Ingredient; JP: Japanese Pharmacopoeia; JPC: Japanese Pharmacopoeia Codex; NF: National Formulary; Ph. Eur. European Pharmacopoeia; q.s.: quantum sufficit; USP: United States Pharmacopeia.

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Table 5: Composition of FKB327 Drug Product (from Applicant's Module 2.3), 40 mg drug product in prefilled pen

Component	Function	Quality Standard	Concentration	Quantity per DP Prefilled Syringe
FKB327	API	In-house[a]	50 mg/mL	40 mg
Monosodium Glutamate	(b) (4)	NF, JPC	10 mmol/L	1.50 mg
Sorbitol		NF/Ph. Eur./JP	262 mmol/L	38.2 mg
Methionine		USP/Ph. Eur./JP	5 mmol/L	0.60 mg
Polysorbate 80		NF/Ph. Eur./JP	1.0 mg/mL	0.80 mg
Diluted Hydrochloric Acid		NF/Ph. Eur./JP	Adjust to pH 5.2	As required
Water for Injection (distilled)		USP/Ph. Eur./JP	q.s. to 0.8 mL	q.s. to 0.8 mL

a: Meets the Drug Substance (DS) specification (see Section 3.2.S.4.1)

Abbreviations: API: Active Pharmaceutical Ingredient; JP: Japanese Pharmacopoeia; JPC: Japanese Pharmaceutical Codex; NF: National Formulary; Ph. Eur. European Pharmacopoeia; q.s.: quantum sufficit; USP: United States Pharmacopeia.

Comments on Novel Excipients

The excipients differ from those of US-Humira except for polysorbate 80. All excipients, except for monosodium glutamate (MSG), are within the levels of previously approved products for subcutaneous administration (and are within the ranges that are found in the inactive ingredient database). Although MSG has been an excipient in approved drug products, it is considered a novel excipient because it will be used at a higher dose, for longer duration, and administered by a different route of administration than previously approved products.

The use of MSG was discussed at the January 13, 2017, meeting with the Applicant. They indicated that a toxicological assessment would be provided in the BLA submission. The assessment submitted to the BLA was a summary of FDA-approved products that contained MSG and their amounts. The assessment did not address the proposed route of administration, dosage, dose frequency, and duration of use of MSG. An information request was sent to the Applicant on March 20, 2020, asking for a toxicological assessment to address these specific topics. On March 27, 2020 (SD-43), the Applicant submitted this information, which summarized the available literature, concluding that there are no safety concerns for MSG at the proposed dose, dosing frequency, duration of use, and route of administration. Based on the toxicological assessment, including the results from the FKB327 and vehicle arms of Study SBL330-001, and also considering the clinical safety results (refer to Section 7.4), all three review divisions that have indications for this adalimumab biosimilar (DRTM, DDD, and DG) agreed with this conclusion.

The Nonclinical Appendix includes a high level summary of the data submitted by the Applicant.

Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern. These are within appropriate specifications as reviewed by OBP.

With regards to the nonclinical assessment, only one lot (Lot TVK120117) was used for the nonclinical studies of in vivo pharmacodynamic efficacy and comparative toxicity and PK/TK to EU-Humira. The sponsor indicated that one non-GMP lot used for the toxicology study (Lot TVK120117), and two cGMP lots (Lots VK001 and VK002), for engineering and clinical purposes, were manufactured at the (b) (4) commercial scale. The non-GMP toxicology lot was manufactured using the identical process and at the same facility used for the cGMP production. The lot is not GMP compliant due to the lack of a quality assurance (QA) review of records for this lot. For safety assessment, this lot was judged to be appropriate although the QA records were not available.

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6. Clinical Pharmacology Evaluation and Recommendations

6.1. Clinical Pharmacology Executive Summary and Recommendation

Table 6. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics Similarity	• PK similarity between FKB327 and US-Humira was established, and supports a demonstration of no clinically meaningful differences between FKB327 and US-Humira.
Pharmacodynamics Similarity	• Not applicable
Immunogenicity	• Comparable incidence of ADA formation between FKB327 and US-Humira in healthy subjects and patients with RA supports a demonstration of no clinically meaningful differences between FKB327and US- Humira. •
Other - PK comparability assessment	• PK of FKB327 administered using vial, PFS, and AI was comparable.

The clinical development for FKB327 included 4 clinical studies:

(1) Study FKB327-001, a PK similarity study to compare the PK, safety, tolerability, and immunogenicity of FKB327 (vial), US-Humira (PFS), and EU-Humira (PFS) in healthy subjects (n=60/treatment arm);
(2) Study FKB327-005, a comparability study of FKB327 in healthy subjects administered using FKB327 vial (n=66), PFS (n=63), and AI (n=66);
(3) Study FKB327-002, a comparative clinical study in patients with active RA using FKB327 vial (n=366) and US-Humira PFS (n=362);
(4) Study FKB327-003, an open-label extension study using FKB327 PFS (n=324) and US-Humira PFS (n=321) in Period I and using FKB327 PFS or AI (n=572) in Period II.

The results of the PK similarity study (Study FKB327-001) demonstrated PK similarity between FKB327 and US- Humira. For this submission, there was no need to establish an adequate scientific bridge to non-US-Humira. Therefore, while the clinical pharmacology study FKB327-001 included the use of a non-US-licensed comparator product, EU-Humira, the data generated using EU-Humira was not used to support the demonstration of biosimilarity.

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In the PK similarity study (Study FKB327-001), the 90% CI for the least square (LS) geometric means ratios (LS GMRs) for area under the serum drug concentration-time curve (AUC) from time 0 to infinity (AUC0-inf), AUC from time 0 to the last quantifiable concentration (AUClast), and maximum observed drug concentration (Cmax) were contained within the prespecified criteria of 80 to 125% (Table 7).

Table 7. PK similarity assessment-summary of statistical analyses (Study FKB327-001)

Primary	LS Geometric Mean (% geoCV)		LS GMR * (90% CI)
	FKB327 (n=60)	US-Humira (n=60)	FKB327 vs US-Humira
$AUC_{0\text{-inf}}$ (h*ng/mL)	2346336 (35.8)	2390725 (46.2)	98.14 (87.15, 110.52)
AUC_{last} (h*ng/mL)	2147368 (32.9)	2149549 (40.7)	99.90 (89.77, 111.16)
C_{max} (ng/mL)	3309 (34.5)	3102 (34.2)	106.69 (96.67, 117.75)

*Presented as percent.
Source: FDA analysis

The immunogenicity of FKB327 was comparable to that of US-Humira after a single dose in healthy subjects, after multiple doses in RA patients and after single transition from US-Humira to FKB327.

The overall incidence of anti-drug antibody (ADA) formation over the course of the study in healthy subjects was 69.5% and 70.0% for FKB327 and US-Humira treatment groups, respectively (Study FKB327-001). After multiple 40 mg SC doses, the incidence was also similar (57.9% and 55.5%, respectively) between FKB327 and US-Humira in patients with RA (Study FKB327-002). The overall incidence of neutralizing antibodies (nAb) formation over the course of the study in healthy subjects was 59.3% and 56.7% for FKB327 and US-Humira, respectively, (Study FKB327-001). After multiple SC doses of FKB327 or US-Humira, the incidence of nAb formation was also similar (57.1% and 55.2%, respectively) between FKB327 and US-Humira in patients with RA (Study FKB327-002). The ADA and nAb formation was not increased after single transition from US-Humira to FKB327, with the incidence of ADA and NAb are 45.2% and 45.2%, respectively (Study FKB327-003).

6.1.1. Clinical Pharmacology Residual Uncertainties Assessment

PK similarity was demonstrated between FKB327 and US-Humira in the PK similarity study (Study FKB327-001). Comparable incidence of immunogenicity for FKB327 and US-Humira was observed in Studies FKB327-001, FKB327-002 and FKB327-003. There were no clinical pharmacology residual uncertainties regarding the PK or immunogenicity assessment to support a demonstration of biosimilarity.

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

Not applicable. Data generated from studies using a non-US-licensed comparator product, EU-Humira, were not used to support the demonstration of biosimilarity.

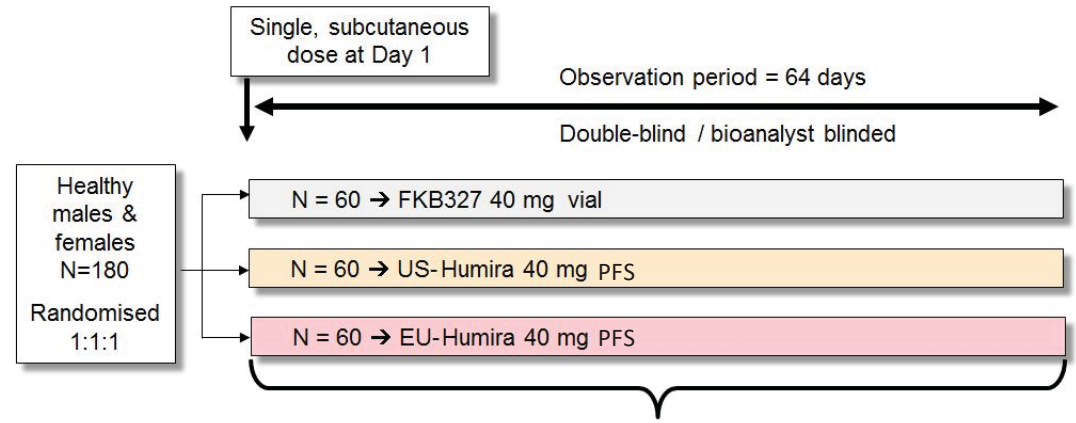
6.3. Human Pharmacokinetics and Pharmacodynamics

6.3.1. Clinical Pharmacology Study Design Features

The PK similarity study comparing FKB327 vial, EU-Humira PFS and US-Humira PFS was conducted in healthy subjects (Study FKB327-001, Figure 1). The study was conducted at Hammersmith Medicines Research in United Kingdom. Approximately 180 healthy subjects were planned for dosing as described in the schematic below.

In addition, PK comparison between FKB327 PFS/AI and US-Humira PFS was also assessed in adult patients with RA (Studies FKB327-002 and FKB327-003, see Section 6.4 for study design). To compare the PK profiles of FKB327 using vial, PFS, and AI, a comparability study was conducted in healthy subjects (Study FKB327-005, Figure 2). Refer to Table 2 for a summary of the studies listed above.

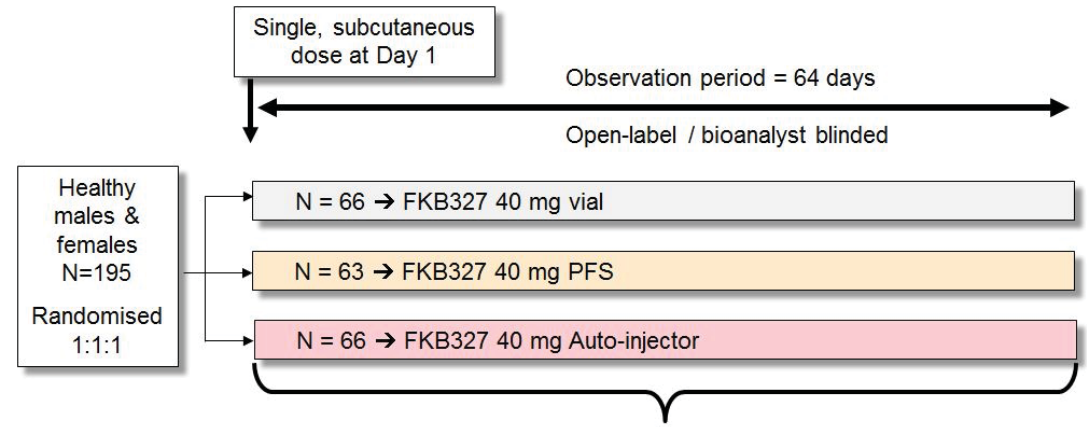
Figure 1. Study design of the PK similarity study (Study FKB327-001)



	Study Day																
Parameter	Pre-dose	1	2	3	4	5	6	7	8	9	16	23	30	37	44	51	65
Drug concentration (PK)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-Drug Antibody (ADA)	X										X		X				X
Neutralizing Antibody (nAb)	X										X		X				X

Source: Figure 22 of Integrated Summary of Immunogenicity

Figure 2. Study design of Study FKB327-005



	Study Day																
Parameter	Pre-dose	1	2	3	4	5	6	7	8	9	16	23	30	37	44	51	65
Drug concentration (PK)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-Drug Antibody (ADA)	X										X		X				X
Neutralizing Antibody (nAb)	X										X		X				X

Source: Figure 42 of Integrated Summary of Immunogenicity

6.3.2. Clinical Pharmacology Study Endpoints

In Study FKB327-001, the primary endpoints were Cmax, AUClast, and AUC0-inf to evaluate and compare the PK profiles of FKB327, EU-Humira and US-Humira in healthy subjects. Safety, tolerability and immunogenicity were the secondary endpoints.

Study FKB327-002 was the comparative clinical study in RA patients and Study FKB327-003 was the open-label extension study with RA patients who completed Study FKB327-002. The primary efficacy endpoint was the proportion of patients achieving clinical response (according to the ACR20 criteria) at Week 24, whereas PK (Ctrough), safety, immunogenicity and other efficacy endpoints (Disease Activity Score 28 (DAS28), ACR20, ACR50, and ACR70, DAS28-CRP, tender and swollen joint counts, CRP, and others) were secondary endpoints. For the choice of efficacy and safety endpoints in Studies FKB327-002 and FKB327-003, see details in Section 7.

The PK primary endpoints in Study FKB327-005 were Cmax, AUClast, and AUC0-inf to compare the PK profiles of FKB327 administered using vial, PFS, and AI in healthy subjects. Safety and tolerability were the secondary endpoints.

6.3.3 Bioanalytical PK Method and Performance

The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated.

The serum concentrations of FKB327 and US-Humira were appropriately quantified using a validated electrochemiluminescence assay (ECL) in Study FKB327-001 (validation reports 327-PK12-001, 327-PK13-009, 327-PK12-002), and Studies FKB327-002, FKB327-003, and FKB327-005 (validation report 8380.083014.1). During the method validation, FKB327 was used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ)) was evaluated using FKB327 and US-Humira as QC samples. See detailed information about the assay validation in Appendix 13.4.1.

6.3.4 PK Similarity Assessment

PK similarity has been demonstrated between FKB327 and US-Humira in the PK similarity Study FKB327-001. In the PK similarity comparison between FKB327 and US-Humira, the mean serum concentration-time profiles were similar between FKB327 and US-Humira treatment groups. The 90% CIs for the LS GMRs of Cmax, AUC0-t and AUC0-inf were all within the pre-defined criteria of 80% –125% (Figure 3,Table 7).

Note that the biopharmaceutical inspections were requested for both clinical site and

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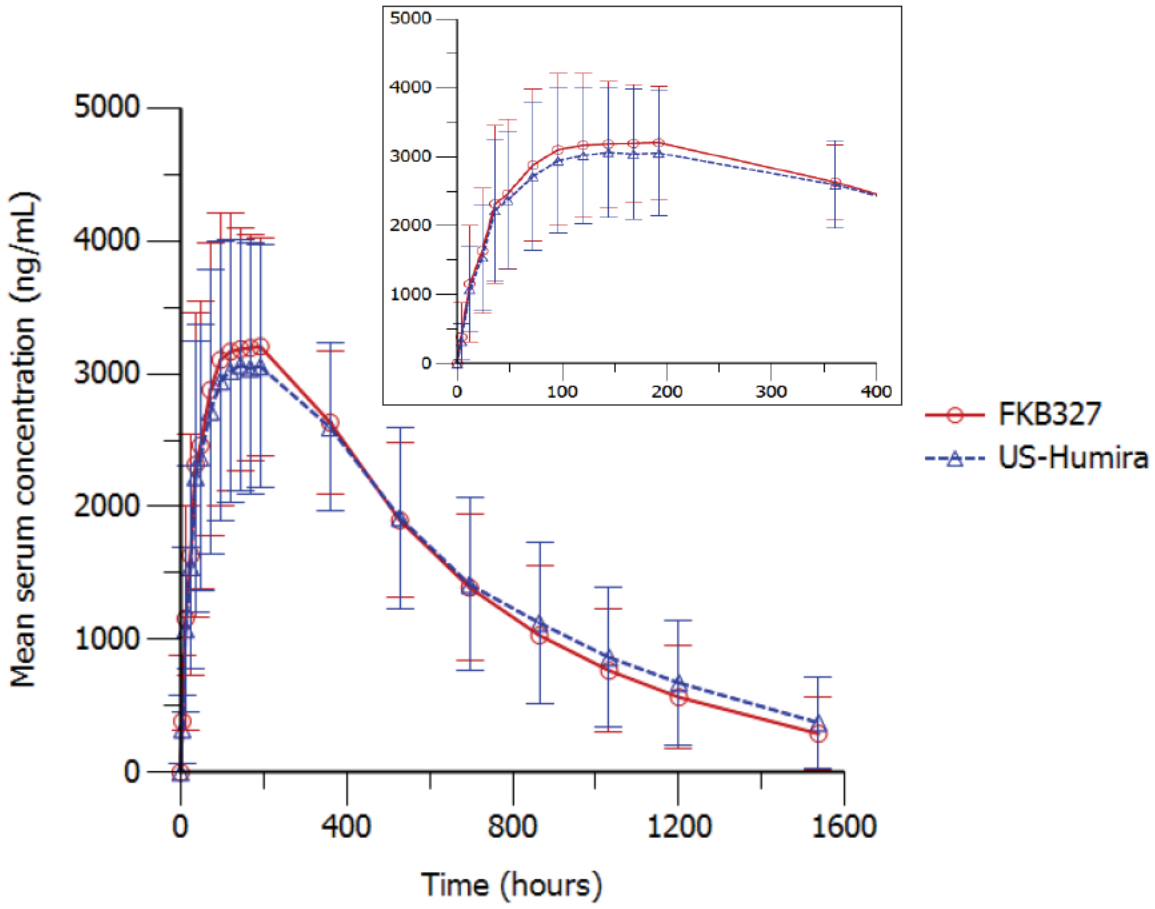
bioanalytical site of Study FKB327-001. Refer to section 4.4 regarding the OSIS recommendation.

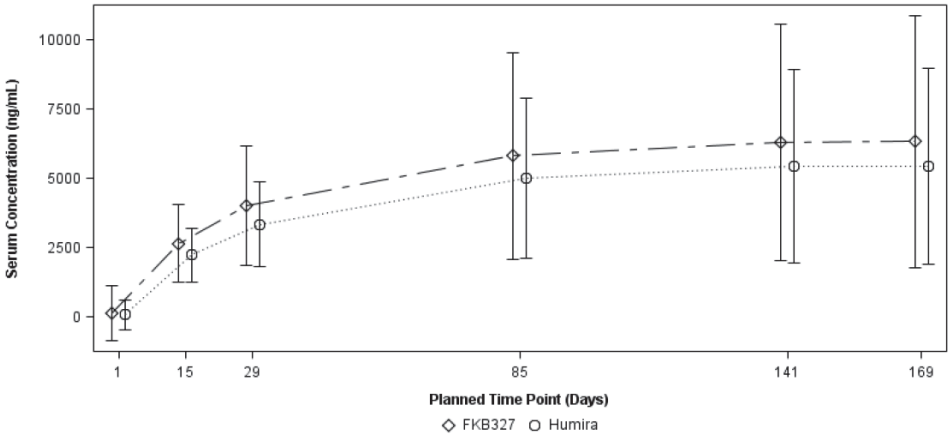
Figure 3. PK profiles following a single SC dose of FKB327 using vial or US-Humira using PFS in healthy subjects (n=60/treatment group) (Study FKB327-001)



Source: FDA analysis

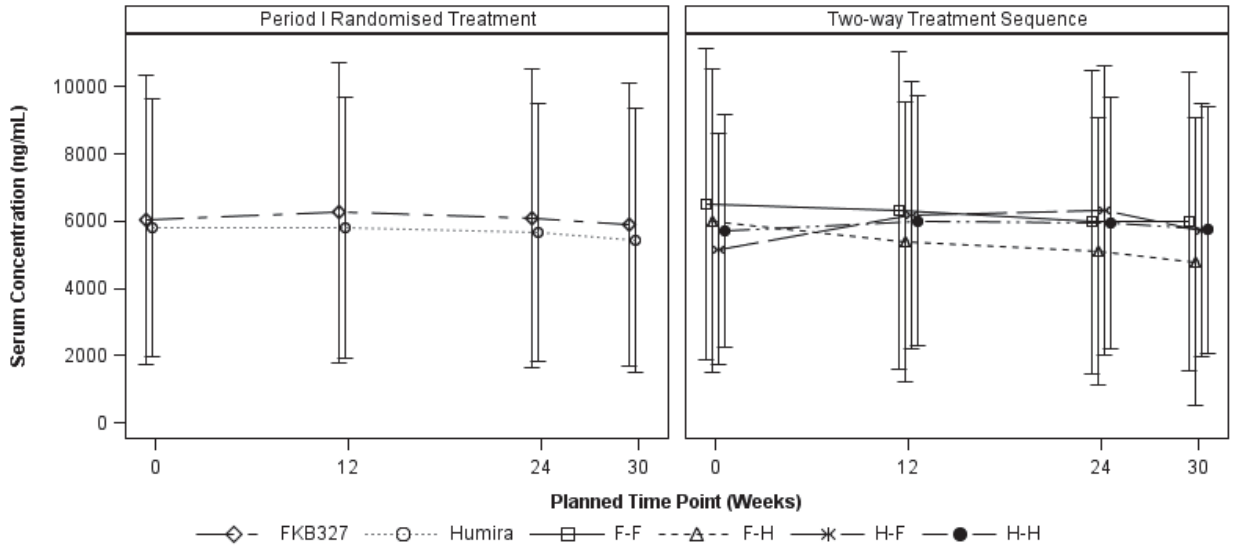
In the comparative clinical Study FKB327-002 and the open-label extension Study FKB327-003 in adult patients with RA, following multiple SC doses of either FKB327 or US-Humira, the serum trough concentrations (Ctrough) over time, including transition periods, were generally in the same range in RA patients among treatment arms (Figure 4 and Figure 5).

Figure 4. Adalimumab serum trough concentration (mean ± SD) comparison following multiple SC dose of FKB327 using vial or US-Humira using PFS in patients with RA (Study FKB327-002)



Source: Figure 2 of Summary of Clinical Pharmacology Studies

Figure 5. Adalimumab serum trough concentration (mean ± SD) comparisons in the open-label extension study in adult patients with RA (Study FKB327-003)



F: FKB327; H: US-Humira

Source: Figure 3 of Summary of Clinical Pharmacology Studies

6.3.5 PD Similarity Assessment

Not applicable.

6.3.6 Other Assessments - PK comparability study for FKB327 when administered using vial, PFS, or AI

The Applicant conducted a PK comparability study (Study FKB327-005) to support the proposed presentations of FKB327, PFS and AI.

The PK profiles of FKB327 using vial, PFS or AI were compared in Study SB5-G12-NHV. A total of 195 healthy subjects were randomized to receive a single dose of 40 mg FKB327 through SC injection using vial, PFS, or AI. The mean serum concentration-time profiles were similar across vial, PFS, and AI presentations (Figure 6). Statistical analysis showed that the PFS was comparable to the vial in terms of all primary PK parameters (AUC0-t, AUC0-inf and Cmax), as the 90% CIs of the LS GMRs were fully contained within the predefined criteria of 80% to 125%. For the AI/vial and AI/PFS comparisons, the 90% CIs of the LS GMRs for AUC0-inf and Cmax were fully contained within the predefined criteria of 80% to 125%. The upper limit of the 90% CIs of the LS GMRs for AUC0-t was slightly outside the predefined criteria (Table 8), which does not preclude the conclusion of comparable exposure between presentations and hence are not expected to produce any meaningful differences in clinical efficacy and safety.

FKB327 PK remains comparable using vial, PFS, and AI by body weight (50 to 75 kg and >75 to 100 mg) as well as by injection site (abdomen and thigh) (Table 9 andTable 10).

Reference ID: 4635331

Figure 6. PK profiles following a single SC dose of FKB327 using vial, PFS, or AI in healthy subjects (n=195) (Study FKB327-005)

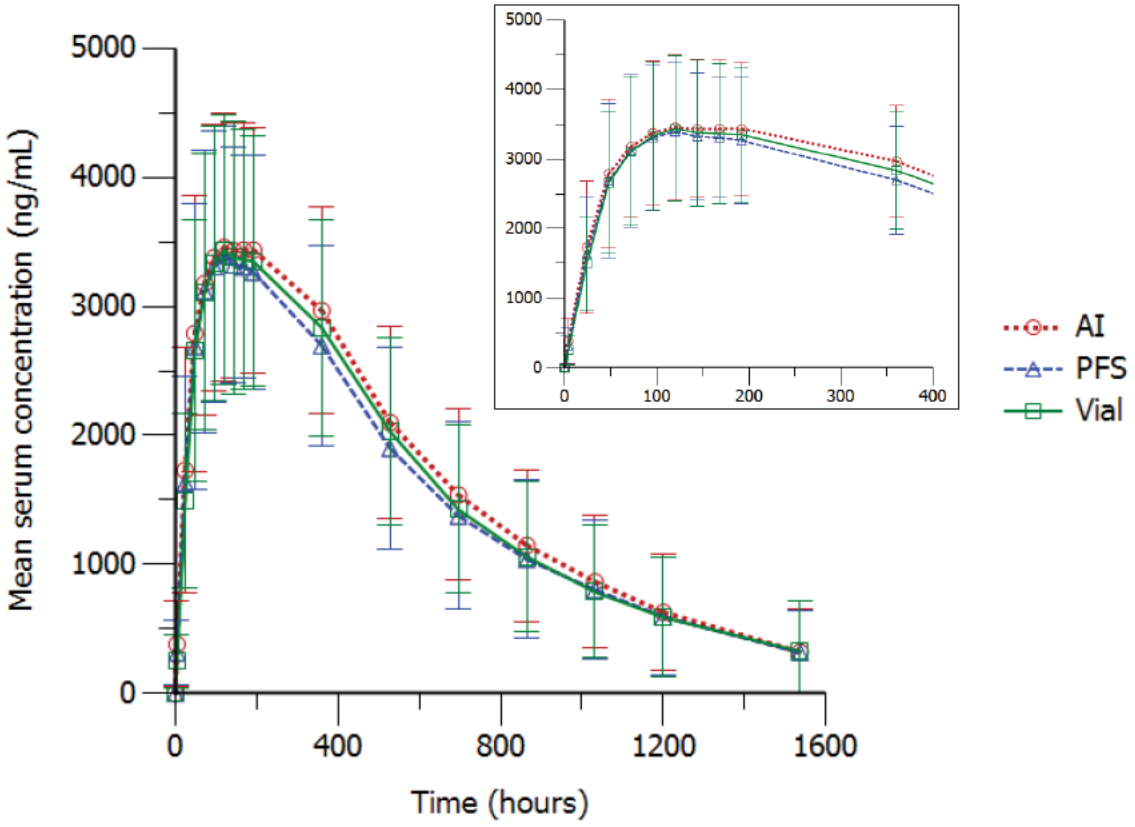


Table 8. PK comparability assessment - statistical analysis for FKB327 PK parameters using vial, PFS, and AI (Study FKB327-005)

Parameter	Comparison (T vs R)	LS geometric mean (%geoCV) (T)	LS geometric mean (%geoCV) (R)	LS GMR (90% CI)
AUC0-inf	PFS vs Vial	2353608 (46.7)	2474812 (39.4)	95.10 (84.39, 107.17)
	AI vs Vial	2600159 (41.1)	2474812 (39.4)	105.06 (93.27, 118.35)
	AI vs PFS	2600159 (41.1)	2353608 (46.7)	110.48 (98.03, 124.50)
AUC0-t	PFS vs Vial	2160538 (42.8)	2177302 (35.4)	99.23 (87.53, 112.50)
	AI vs Vial	2406775 (36.4)	2177302 (35.4)	110.54 (97.55, 125.26)
	AI vs PFS	2406775 (36.4)	2160538 (42.8)	111.40 (98.13, 126.45)
Cmax	PFS vs Vial	3447 (30.1)	3449 (31.3)	99.95 (91.78, 108.86)
	AI vs Vial	3606 (27.9)	3449 (31.3)	104.57 (96.05, 113.84)

	AI vs PFS	3606 (27.9)	3447 (30.1)	104.62 (96.04, 113.96)

The units of Cmax and AUC are ng/mL and h*ng/mL, respectively.
T: test; R: reference
N=65 (vial), 63 (PFS), AI (64)
*Presented as percent.
Source: FDA analysis

Table 9. Summary of the PK parameters for FKB327 using vial, PFS, and AI by body weight (Study FKB327-005)

Body weight	**PK**	**FKB327 vial (N=31)**	**FKB327 PFS (N=31)**	**FKB327 AI (N=32)**
50 to 75 kg	AUC0-inf	2840000 (34.5)	2520000 (38.9)	2880000 (25.5)
	AUC0-t	2370000 (73.0)	2470000 (33.9)	2790000 (24.2)
	Cmax	3770 (32.9)	4010 (24.2)	4110 (21.4)
>75 to 100 kg		**FKB327 vial (N=34)**	**FKB327 PFS (N=32)**	**FKB327 AI (N=33)**
	AUC0-inf	2010000 (35.0)	2110000 (38.5)	2150000 (43.0)
	AUC0-t	1960000 (32.7)	1860000 (46.4)	2040000 (39.7)
	Cmax	3180 (27.9)	2980 (27.5)	3150 (27.0)

The units of Cmax and AUC are ng/mL and h*ng/mL, respectively.
Geometric mean (CV%) data are presented.
Data source: Table 11-3 of Study FKB327-005 CSR

Table 10. Summary of the PK parameters for FKB327 using vial, PFS, and AI by injection site (Study FKB327-005)

Injection site	**PK**	**FKB327 vial (N=33)**	**FKB327 PFS (N=32)**	**FKB327 AI (N=32)**
Abdomen	AUC0-inf	2150000 (40.0)	2050000 (38.2)	2500000 (43.6)
	AUC0-t	1890000 (70.0)	2020000 (35.4)	2350000 (41.3)
	Cmax	3100 (36.0)	3150 (32.1)	3450 (34.1)
Thigh		**FKB327 vial (N=32)**	**FKB327 PFS (N=31)**	**FKB327 AI (N=33)**
	AUC0-inf	2620000 (36.0)	2560000 (38.0)	2420000 (33.5)
	AUC0-t	2450000 (31.4)	2270000 (49.8)	2410000 (32.1)
	Cmax	3860 (20.9)	3790 (24.7)	3730 (20.2)

The units of Cmax and AUC are ng/mL and h*ng/mL, respectively.
LS geometric mean (CV%) data are presented.
Data source: Table 11-4 of Study FKB327-005 CSR

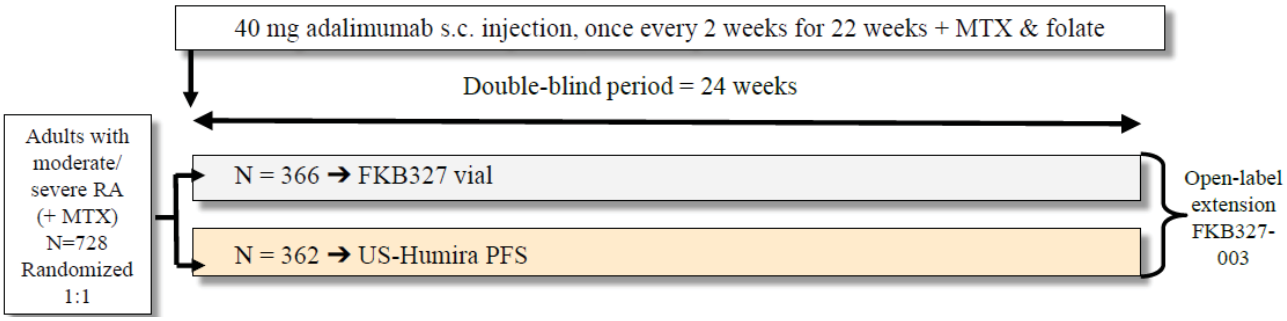
6.4. Clinical Immunogenicity Studies

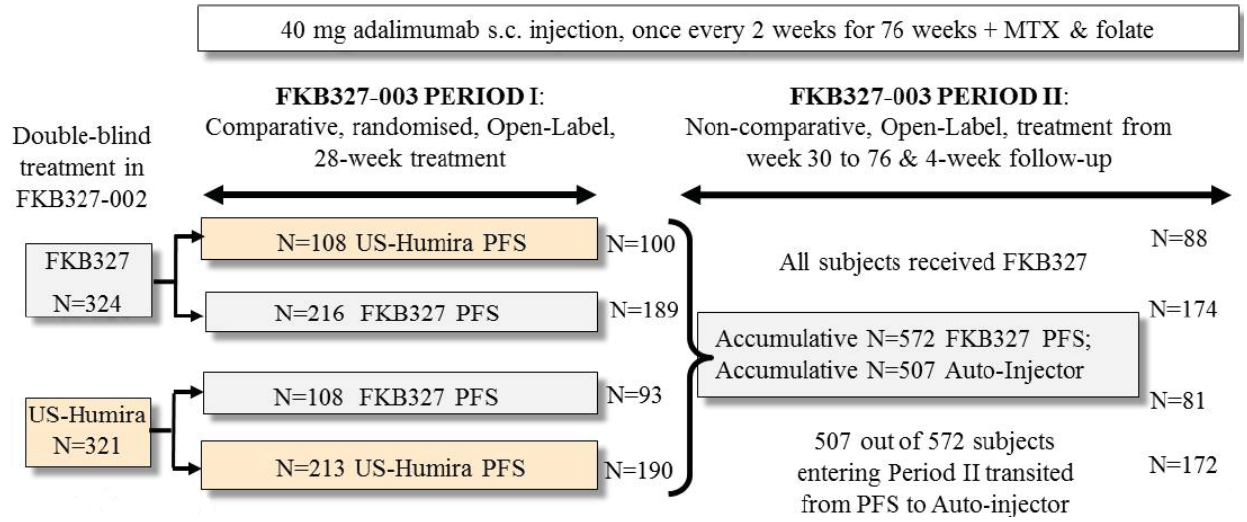
Design features of the clinical immunogenicity assessment

Immunogenicity upon single dosing has been evaluated in healthy subjects in Study FKB327-001. See Table 3 and Figure 1 for more details regarding the study design.

Immunogenicity upon repeated dosing has been evaluated in Studies FKB327-002 and FKB327-003. Studies FKB327-002 was a randomized, double-blind, parallel group, multicenter clinical study in patients with moderate to severe, active RA who were already taking MTX for at least 3 months at a stable dose (10 to 25 mg/week) for a minimum of 8 weeks prior to Screening but who required additional therapy to control their disease. Eligible patients were randomized in a 1:1 ratio to receive either FKB327 40 mg using vial (n=366) or US-Humira 40 mg using PFS (n=362) every other week from Week 0 to Week 22 via SC injection. At Week 24, patients who completed Study FKB327-002 were eligible to enter the open-label extension study (Study FKB327-003), otherwise they were to attend the Week 26 Follow-up visit. The open-label extension study FKB327-003 was conducted in 2 parts: In Period I, patients were randomized in a 2:1 ratio to continue the same treatment, or to switch to the alternate treatment to that received in Study FKB327-002. In Period II, all patients received SC FKB327 40 mg (PFS or AI) every other week from Week 30 to Week 76, followed by a 4-week follow-up period.

Figure 7. Study design of Studies FKB327-002 (upper panel) and FKB327-003 (lower panel)





Note that 645 patients completed Study FKB327-002 and were randomized into Study FKB327-003.
Source: Adapted from Figures 28 and 34 of Integrated Summary of Immunogenicity

Immunogenicity endpoints

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

Immunogenicity assay's capability of detecting the antidrug antibodies (ADA) in the presence of proposed product, reference product, and any other comparator product (as applicable) in the study samples

Mylan developed binding and neutralizing antibody assays for detecting ADA and nAb in the presence of concentrations of FKB327 and US-Humira expected following administration. Refer to OBP review for more details.

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

The sampling plan is adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation.

- Study FKB327-001: serum samples were collected at baseline, Days 16, 30, and the end-of study visit (Day 65) for assessment of the ADA formation of FKB327 and US-Humira.
- Study FKB327-002: serum samples were collected at baseline, Weeks 2, 4, 12, and 24 for assessment of the ADA formation of FKB327 and US-Humira.
- Study FKB327-003: serum samples were collected at Weeks 0, 12, 24, 30, 54, 76, and 80 for assessment of the ADA formation of FKB327 and US-Humira.

- Study FKB327-005: serum samples were collected at baseline, Days 16, 30, and the end-of study visit (Day 65) for assessment of the ADA formation of FKB327 vial, PFS, and AI.

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

In Study FKB327-001, following a single 40 mg SC dose of study drug, 69.5% and 70.0% subjects in the FKB327 and US-Humira treatment groups, respectively, developed treatment-emergent ADA by Day 65 (Table 11). Overall, the ADA incidence is similar between FKB327 and US-Humira treatment arms in healthy subjects.

In Study FKB327-002, following multiple 40 mg SC doses of study drug, by Week 24, 212/339 (57.9%) and 201/337 (55.5%) subjects developed ADA in FKB327 and US-Humira treatment groups, respectively (Table 12). In the OLE Study FKB-003 Period I, at Week 30, 97/187 (51.9%), 61/100 (61.0%), 98/190 (51.6%), and 42/93 (45.2%) subjects developed ADA in FKB327/FKB327, FKB327/US-Humira, US-Humira/US-Humira, and US-Humira/FKB327 treatment groups, respectively. In Study FKB-003 Period II, at Week 80, 91/173 (52.6%), 48/87 (55.2%), 72/170 (42.4%), and 37/80 (46.3%) subjects developed ADA in FKB327/FKB327/FKB327, FKB327/US-Humira/FKB327, US-Humira/US-Humira/FKB327, and US-Humira/FKB327/FKB327 treatment groups, respectively(Table 13). Overall, the incidence of ADA is comparable between FKB327 and US-Humira throughout the study, including the transition-extension period.

In Study FKB327-005, following a single 40 mg SC dose of FKB327 using vial, PFS, and AI, 100% , 100%, and 98.5% subjects developed treatment-emergent ADA by Day 65 in the FKB327 vial, PFS, and AI treatment groups, respectively (Table 14). Overall, the ADA incidence is similar across the three treatment arms using different FKB327 presentations in healthy subjects.

Table 11. Immunogenicity results for binding ADA and nAb in Study FKB327-001

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

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

Source: Table 50 of Integrated Summary of Immunogenicity

Table 12. Immunogenicity results for binding ADA and nAb in Study FKB327-002

Category	Treatment week				
	Pre-dose	2	4	12	24
FKB327 (N=366)					
No. of subjects	365	362	357	345	339
No. ADA positive	16	42	141	202	212
% ADA positive[a]	4.4	11.5	38.5	55.2	57.9
Median titer	0.0625	0.0625	0.0625	400	800
Mean titer	40	2676	3423	3466	8642
No. nAb positive	10	35	132	199	209
% nAb positive[a]	2.7	9.6	36.1	54.4	57.1
US-licensed Humira (N=362)					
No. of subjects	361	353	347	333	337
No. ADA positive	20	46	129	183	201
% ADA positive[a]	5.5	12.7	35.6	50.6	55.5
Median titer	0.0625	0.0625	0.0625	200	640
Mean titer	298	3140	4082	3371	7335
No. nAb positive	16	36	118	180	200
% nAb positive[a]	4.4	9.9	32.6	49.7	55.2

If data at last sampling time point (Day 169) is missing, result carried forward from previous time point.
Negative titer results presented as 0.0625, titer results <1 (including <LLOQ) presented as 0.25.
[a] A Denominator is number of patients of Safety Analysis Set in each treatment group.

Source: Table 55 of Integrated Summary of Immunogenicity

Table 13. Immunogenicity results for binding ADA and nAb in Study FKB327-003

Category	Treatment week						Follow-up
	0	12	24	30	54	76	80
Study-002 = **FKB327**	Study -003 PERIOD I = **FKB327**				Study -003 PERIOD II = **FKB327**		
No. of subjects	216	202	197	187	181	176	173
No. ADA positive	133	107	99	97	103	90	91
% ADA positive[b]	**61.6**	**53.0**	**50.3**	**51.9**	**56.9**	**51.1**	**52.6**
Median titer	800	440	140	500	640	200	240
Mean titer	10761	85761	29633	46346	28460	28626	7593
No. nAb positive	132	106	99	97	100	90	91
% nAb positive[b]	**61.1**	**52.5**	**50.3**	**51.9**	**55.2**	**51.1**	**52.6**
Study-002 = **FKB327**	Study -003 PERIOD I = **US-Humira**				Study -003 PERIOD II = **FKB327**		
No. of subjects	108	103	100	100	93	90	87
No. ADA positive	69	60	58	61	49	49	48
% ADA positive[b]	**63.9**	**58.3**	**58.0**	**61.0**	**52.7**	**54.4**	**55.2**
Median titer	1040	800	760	1600	800	280	300
Mean titer	6180	13981	46375	144074	22948	7042	7246
No. nAb positive	67	60	57	60	49	49	48
% nAb positive[b]	**62.0**	**58.3**	**57.0**	**60.0**	**52.7**	**54.4**	**55.2**
Study-002 = **US-Humira**	Study -003 PERIOD I = **US-Humira**				Study -003 PERIOD II = **FKB327**		
No. of subjects	212	202	199	190	181	174	170
No. ADA positive	123	101	100	98	77	74	72
% ADA positive[b]	**58.0**	**50.0**	**50.3**	**51.6**	**42.5**	**42.5**	**42.4**
Median titer	400	160	115	150	0.0625	0.0625	0.0625
Mean titer	6343	16881	25422	53557	58823	6454	2782
No. nAb positive	122	101	98	96	75	73	71
% nAb positive[b]	**57.5**	**50.0**	**49.2**	**50.5**	**41.4**	**42.0**	**41.8**
Study-002 = **US-Humira**	Study -003 PERIOD I = **FKB327**				Study -003 PERIOD II = **FKB327**		
No. of subjects	108	103	96	93	89	81	80
No. ADA positive	67	54	47	42	41	39	37
% ADA positive[b]	**62.0**	**52.4**	**49.0**	**45.2**	**46.1**	**48.1**	**46.3**
Median titer	1080	480	30	0.0625	0.0625	0.0625	0.0625
Mean titer	8704	9499	30180	26374	15745	11880	14594
No. nAb positive	67	53	47	42	41	38	37
% nAb positive[b]	**62.0**	**51.5**	**49.0**	**45.2**	**46.1**	**46.9**	**46.3**

Source: Tables 14.2.2.1.1, 14.2.2.2.1 & 14.2.2.4.1, Clinical Study Report for FKB327-003, Module 5.3.5.1

[a] A couple of patients at any time point/s did not have the ADA titer values, therefore, data of such patients was not included in the calculation of summary statistics (Details see source Table 14.2.2.2.1).
[b] A Denominator is number of patients of Safety Analysis Set in each treatment sequence.

Source: Table 65 of Integrated Summary of Immunogenicity

Table 14. Immunogenicity results for binding ADA and nAb in Study FKB327-005

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

Source: Table 73 of Integrated Summary of Immunogenicity

Neutralizing antibodies (nAb)

In Study FKB327-001, following a single 40 mg SC dose of study drug, 35/59 (59.3%) and 34/60 (56.7%) subjects in the FKB327 and US-Humira treatment groups, respectively, developed nAb by Day 65 (Table 11).

In Study FKB327-002, following multiple 40 mg SC doses of study drug, by Week 24, 209/339 (57.1%) and 200/337 (55.2%) subjects developed nAb in FKB327 and US-Humira treatment groups, respectively (Table 12).

In the OLE Study FKB-003 Period I, at Week 30, 97/187 (51.9%), 60/100 (60.0%), 96/190 (50.5%), and 42/93 (45.2%) subjects developed nAb in FKB327/FKB327, FKB327/US-Humira, US-Humira/US-Humira, and US-Humira/FKB327 treatment groups, respectively. In Study FKB-003

Period II, at Week 80, 91/173 (52.6%), 48/87 (55.2%), 71/170 (41.8%), and 37/80 (46.3%) subjects developed nAb in FKB327/FKB327/FKB327, FKB327/US-Humira/FKB327, US-Humira/US-Humira/FKB327, and US-Humira/FKB327/FKB327 treatment groups, respectively (Table 13).

In Study FKB327-005, following a single 40 mg SC dose of FKB327 using vial, PFS, and AI, 59/66 (89.4%) , 57/63 (90.5%), and 63/65 (95.5%) subjects developed nAb by Day 65 in the FKB327 vial, PFS, and AI treatment groups, respectively (Table 14).

Impact of ADA on the PK, PD, safety, and clinical outcomes of the proposed biosimilar product

Impact of ADA and nAb on PK

In Study FKB327-001, the systemic exposure was lower in ADA-positive subjects than those in ADA-negative subjects after single dose for both FKB327 and US-Humira. Subgroup analysis showed that the exposure of FKB327 was slightly different from that of US-Humira likely due to the small sample size in each subgroup (Table 15). Similarly, the systemic exposure was lower in nAb-positive subjects than those in nAb-negative subjects after single dose for both FKB327 and US-Humira. Subgroup analysis showed that the exposure of FKB327 was slightly different from that of US-Humira potentially due to the small sample size in each subgroup (Table 15).

In Study FKB327-002 in patients with RA, Ctroughs of FKB327 and US-Humira in patients who were ADA-positive were generally highly variable and lower as compared to patients who were ADA-negative. In each of the ADA subgroups, the mean serum drug Ctroughs were slightly higher for FKB327 as compared to US-Humira (Table 16). Similar trend was also observed in the subgroup comparison by Nab. However, this was likely due to high variability; further, this was a descriptive assessment with no prespecified endpoint evaluation. Additionally, despite the slightly higher concentrations observed for FKB327 compared to the US-Humira, there is no clinically significant difference in efficacy or safety between the two arms (See Section 7). Accordingly, these minor differences in drug concentrations observed in patients with RA do not preclude a finding of PK similarity.

Table 15. Summary of serum PK Parameters by ADA and nAb status (Study FKB327-001)

PK Parameter	Statistic	ADA Status				nAb Status			
		Negative		Positive		Negative		Positive	
		FKB327 N=18	US-Humira N=18	FKB327 N=41	US-Humira N=42	FKB327 N=20	US-Humira N=22	FKB327 N=35	US-Humira N=34
Cmax (ng/mL)	Geometric Mean	3120	3620	3380	2900	3070	3560	3350	2790
	Geometric CV(%)	(43.5)	(26.7)	(30.7)	(34.9)	(43.8)	(31.2)	(29.1)	(33.2)
	n	18	18	41	42	20	22	35	34
AUC0-t (h*ng/mL)	Geometric Mean	2450000	2890000	2000000	1870000	2370000	2840000	1910000	1690000
	Geometric CV(%)	(32.9)	(20.0)	(31.5)	(40.4)	(33.3)	(23.4)	(27.7)	(34.7)
	n	18	18	41	42	20	22	35	34
AUC0-inf (h*ng/mL)	Geometric Mean	2840000	3540000	2140000	2040000	2820000	3430000	2000000	1810000
	Geometric CV(%)	(34.6)	(22.7)	(32.9)	(41.6)	(33.9)	(25.6)	(27.9)	(34.3)
	n	18	18	39	41	19	22	34	33

Source: Table Q1-1 of Clinical Response to Information Request dated October 31, 2019

Table 16. Summary of serum concentration by ADA and nAb status (Study FKB327-002)

	ADA Status				nAb Status			
	Negative		Positive		Negative		Positive	
	FKB327 N=138	US-Humira N=144	FKB327 N=226	US-Humira N=214	FKB327 N=142	US-Humira N=145	FKB327 N=222	US-Humira N=213
Week 0 (Day 1)								
Mean (CV%)	127 (679.3)	123 (542.0)	137 (784.0)	52.3 (832.9)	124 (689.3)	151 (493.3)	139 (776.9)	32.6 (1003.9)
n	137	143	226	214	141	144	222	213
Week 2 (Day 15)								
Mean (CV%)	2800 (48.6)	2430 (45.3)	2570 (54.4)	2100 (41.4)	2790 (48.3)	2450 (45.4)	2570 (54.7)	2090 (40.9)
n	138	141	223	212	142	142	219	211
Week 4 (Day 29)								
Mean (CV%)	4650 (39.2)	3910 (37.7)	3640 (61.2)	2970 (49.7)	4640 (39.1)	3920 (37.6)	3630 (61.6)	2960 (49.7)
n	134	140	223	209	138	141	219	208
Week 12 (Day 85)								
Mean (CV%)	8100 (39.7)	6730 (35.9)	4420 (74.7)	3840 (68.1)	8110 (39.6)	6740 (35.7)	4340 (74.9)	3810 (68.2)
N	131	137	216	200	135	138	212	199
Week 24 (Day 169)								
Mean (CV%)	9390 (42.5)	7750 (37.4)	4470 (85.3)	3890 (78.6)	9360 (42.3)	7740 (37.4)	4420 (86.2)	3880 (79.0)
N	128	136	212	202	131	137	209	201

Source: Table Q1-2 of Clinical Response to Information Request dated October 31, 2019

Impact of ADA and nAb on efficacy

In Studies FKB327-002 and FKB327-003, the ACR20 response rates in patients who were ADA-negative or who were ADA-positive remain comparable between FKB327 and US-Humira over 24 Weeks and after transitions (Table 17 andTable 18) . Similarly, in the efficacy comparison by nAb status, the ACR20 response rates in patients who were nAb-negative or who were nAb-positive remain comparable between FKB327 and US-Humira over 24 Weeks and after transitions (Table 17 andTable 18). Overall, no evidence of impact of immunogenicity on efficacy was observed.

Table 17. Summary of the ACR20 response rate, by time by ADA and nAb status (Study FKB327-002)

	ADA Status				nAb			
	Negative		Positive		Negative		Positive	
	FKB327 N=138	US-Humira N=144	FKB327 N=225	US-Humira N=214	FKB327 N=142	US-Humira N=145	FKB327 N=221	US-Humira N=213
Week 2								
n	138	139	224	213	142	140	220	212
Responders (%)	49 (35.5%)	39 (28.1%)	86 (38.4%)	70 (32.9%)	50 (35.2%)	40 (28.6%)	85 (38.6%)	69 (32.5%)
95% CI	(27.6, 44.1)	(20.8, 36.3)	(32.0, 45.1)	(26.6, 39.6)	(27.4, 43.7)	(21.3, 36.8)	(32.2, 45.4)	(26.3, 39.3)
Week 4								
n	135	140	224	209	139	141	220	208
Responders (%)	67 (49.6%)	69 (49.3%)	116 (51.8%)	114 (54.5%)	68 (48.9%)	70 (49.6%)	115 (52.3%)	113 (54.3%)
95% CI	(40.9, 58.4)	(40.7, 57.9)	(45.0, 58.5)	(47.5, 61.4)	(40.4, 57.5)	(41.1, 58.2)	(45.5, 59.0)	(47.3, 61.2)
Week 8								
n	133	136	220	211	137	137	216	210
Responders (%)	93 (69.9%)	96 (70.6%)	135 (61.4%)	139 (65.9%)	96 (70.1%)	97 (70.8%)	132 (61.1%)	138 (65.7%)
95% CI	(61.4, 77.6)	(62.2, 78.1)	(54.6, 67.8)	(59.1, 72.2)	(61.7, 77.6)	(62.4, 78.3)	(54.3, 67.7)	(58.9, 72.1)
Week 12								
n	133	140	218	201	137	141	214	200
Responders (%)	97 (72.9%)	104 (74.3%)	146 (67.0%)	142 (70.6%)	101 (73.7%)	105 (74.5%)	142 (66.4%)	141 (70.5%)
95% CI	(64.5, 80.3)	(66.2, 81.3)	(60.3, 73.2)	(63.8, 76.8)	(65.5, 80.9)	(66.4, 81.4)	(59.6, 72.7)	(63.7, 76.7)
Week 24								
n	128	135	213	203	131	136	210	202
Responders (%)	108 (84.4%)	114 (84.4%)	155 (72.8%)	154 (75.9%)	110 (84.0%)	115 (84.6%)	153 (72.9%)	153 (75.7%)
95% CI	(76.9, 90.2)	(77.2, 90.1)	(66.3, 78.6)	(69.4, 81.6)	(76.5, 89.8)	(77.4, 90.2)	(66.3, 78.7)	(69.2, 81.5)

Source: Table Q2-2 of Clinical Response to Information Request dated October 31, 2019

Table 18. Summary of the ACR20 response rate, by time by ADA and nAb status (Study FKB327-003)

	ADA Status								nAb Status							
	Negative				Positive				Negative				Positive			
	F-F-F N=101	H-H-F N=114	F-H-F N=45	H-F-F N=59	F-F-F N=115	H-H-F N=99	F-H-F N=63	H-F-F N=49	F-F-F N=99	H-H-F N=112	F-H-F N=45	H-F-F N=59	F-F-F N=117	H-H-F N=101	F-H-F N=63	H-F-F N=49
Period I																
Week 0																
n	101	113	45	59	115	99	63	49	99	111	45	59	117	101	63	49
Responders (%)	82 (81.2)	97 (85.8)	39 (86.7)	48 (81.4)	81 (70.4)	78 (78.8)	48 (76.2)	34 (69.4)	81 (81.8)	95 (85.6)	39 (86.7)	48 (81.4)	82 (70.1)	80 (79.2)	48 (76.2)	34 (69.4)
95% CI	72.2, 88.3	78.0, 91.7	73.2, 94.9	69.1, 90.3	61.2, 78.6	69.4, 86.4	63.8, 86.0	54.6, 81.7	72.8, 88.9	77.6, 91.5	73.2, 94.9	69.1, 90.3	60.9, 78.2	70.0, 86.6	63.8, 86.0	54.6, 81.7
Week 12																
n	94	112	44	58	109	91	58	45	92	110	44	58	111	93	58	45
Responders (%)	75 (79.8)	97 (86.6)	38 (86.4)	50 (86.2)	85 (78.0)	74 (81.3)	51 (87.9)	32 (71.1)	75 (81.5)	96 (87.3)	38 (86.4)	50 (86.2)	85 (76.6)	75 (80.6)	51 (87.9)	32 (71.1)
95% CI	70.2, 87.4	78.9, 92.3	72.6, 94.8	74.6, 93.9	69.0, 85.4	71.8, 88.7	76.7, 95.0	55.7, 83.6	72.1, 88.9	79.6, 92.9	72.6, 94.8	74.6, 93.9	67.6, 84.1	71.1, 88.1	76.7, 95.0	55.7, 83.6
Period II																
Week 30																
n	85	104	43	51	100	85	55	41	85	105	43	51	100	84	55	41
Responders (%)	72 (84.7)	89 (85.6)	38 (88.4)	45 (88.2)	82 (82.0)	69 (81.2)	44 (80.0)	34 (82.9)	72 (84.7)	90 (85.7)	38 (88.4)	45 (88.2)	82 (82.0)	68 (81.0)	44 (80.0)	34 (82.9)
95% CI	75.3, 91.6	77.3, 91.7	74.9, 96.1	76.1, 95.6	73.1, 89.0	71.2, 88.8	67.0, 89.6	67.9, 92.8	75.3, 91.6	77.5, 91.8	74.9, 96.1	76.1, 95.6	73.1, 89.0	70.9, 88.7	67.0, 89.6	67.9, 92.8
Week 54																
n	83	100	41	49	97	80	52	41	83	101	41	49	97	79	52	41
Responders (%)	72 (86.7)	89 (89.0)	34 (82.9)	43 (87.8)	77 (79.4)	63 (78.8)	44 (84.6)	34 (82.9)	72 (86.7)	90 (89.1)	34 (82.9)	43 (87.8)	77 (79.4)	62 (78.5)	44 (84.6)	34 (82.9)
95% CI	77.5, 93.2	81.2, 94.4	67.9, 92.8	75.2, 95.4	70.0, 86.9	68.2, 87.1	71.9, 93.1	67.9, 92.8	77.5, 93.2	81.3, 94.4	67.9, 92.8	75.2, 95.4	70.0, 86.9	67.8, 86.9	71.9, 93.1	67.9, 92.8
Week 76																
n	82	97	41	43	93	75	49	38	82	98	41	43	93	74	49	38
Responders (%)	64 (78.0)	84 (86.6)	37 (90.2)	40 (93.0)	76 (81.7)	63 (84.0)	40 (81.6)	31 (81.6)	64 (78.0)	85 (86.7)	37 (90.2)	40 (93.0)	76 (81.7)	62 (83.8)	40 (81.6)	31 (81.6)
95% CI	67.5, 86.4	78.2, 92.7	76.9, 97.3	80.9, 98.5	72.4, 89.0	73.7, 91.4	68.0, 91.2	65.7, 92.3	67.5, 86.4	78.4, 92.7	76.9, 97.3	80.9, 98.5	72.4, 89.0	73.4, 91.3	68.0, 91.2	65.7, 92.3
Week 80/EOS																
n	81	97	39	43	92	73	49	38	81	98	39	43	92	72	49	38
Responders (%)	67 (82.7)	88 (90.7)	35 (89.7)	35 (81.4)	66 (71.7)	52 (71.2)	37 (75.5)	27 (71.1)	67 (82.7)	88 (89.8)	35 (89.7)	35 (81.4)	66 (71.7)	52 (72.2)	37 (75.5)	27 (71.1)
95% CI	72.7, 90.2	83.1, 95.7	75.8, 97.1	66..6, 91.6	61.4, 80.6	59.4, 81.2	61.1, 86.7	54.1, 84.6	72.7, 90.2	82.0, 95.0	75.8, 97.1	66.6, 91.6	61.4, 80.6	60.4, 82.1	61.1, 86.7	54.1, 84.6

F: FKB327; H: US-Humira
Source: Table Q2-3 of Clinical Response to Information Request dated October 31, 2019

Impact of ADA or nAb on safety

The incidence of any treatment-emergent adverse events (TEAEs) was comparable between FKB327 and US-Humira treatment groups in both ADA-positive and ADA-negative subgroups. Similarly, the incidence of TEAEs was also comparable between FKB327 and US-Humira treatment groups in both nAb-positive and nAb-negative subgroups. The incidence of injections site reaction was generally low in each of the treatment groups (Table 19, Table 20,Table 21). Overall, no evidence of impact of immunogenicity on safety was observed in Studies FKB327-002 and FKB327-003.

Table 19. Comparison of the incidence of TEAE and injection site reaction at week 24 by ADA and nAb status (Study FKB327-002)

Safety	ADA-		ADA+		nAb-		nAb+	
	FKB327	US-Humira	FKB327	US-Humira	FKB327	US-Humira	FKB327	US-Humira
TEAE	34/140 (24.3%)	33/148 (22.3%)	40/226 (17.7%)	51/214 (23.8%)	35/144 (24.3%)	33/149 (22.1%)	39/222 (17.6%)	51/213 (23.9%)
Injection site reaction	6/140 (4.3%)	4/148 (2.7%)	9/226 (4.0%)	11/214 (5.1%)	6/144 (4.2%)	4/149 (2.7%)	9/222 (4.1%)	11/213 (5.2%)

Date source: Tables Q3-3 and Q3-5 of Clinical Response to Information Request dated October 31, 2019

Table 20. Comparison of the incidence of TEAE and injection site reaction by ADA Status (Study FKB327-003)

Safety		ADA-				ADA+			
		F-F-F	H-H-F	F-H-F	H-F-F	F-F-F	H-H-F	F-H-F	H-F-F
TEAE		82/101 (81.2%)	92/114 (80.7%)	33/45 (73.3%)	44/59 (74.6%)	81/115 (70.4%)	74/99 (74.7%)	48/63 (76.2%)	29/49 (59.2%)
Injection site reaction	Period I	3/105 (2.9%) (F-F)	3/102 (2.9%) (H-H)	0 (F-H)	1/57 (1.8%) (H-F)	0 (F-F)	0 (H-H)	2/67 (3.0%) (F-H)	0 (H-F)
	Period II	2/83 (2.4%)	0	1/41 (2.4%)	1/49 (2.0%)	1/97 (1.0%)	0	1/52 (1.9%)	0

F: FKB327; H: US-Humira

Date source: Tables Q3-6 and Q3-7 of Clinical Response to Information Request dated October 31, 2019

Table 21. Comparison of the incidence of TEAE and injection site reaction by nAb Status (Study FKB327-003)

Safety		nAb-				nAb+			
		F-F-F	H-H-F	F-H-F	H-F-F	F-F-F	H-H-F	F-H-F	H-F-F
TEAE		80/99 (80.8%)	90/112 (80.4%)	33/45 (73.3%)	44/59 (74.6%)	83/117 (70.9%)	76/101 (75.2%)	48/63 (76.2%)	29/49 (59.2%)
Injection site reaction	Period I	3/98 (3.1%) (F-F)	2/97 (2.1%) (H-H)	0 (F-H)	1/55 (1.8%) (H-F)	0 (F-F)	1/116 (0.9%) (H-H)	2/67 (3.0%) (F-H)	0 (H-F)
	Period II	2/83 (2.4%)	0	1/41 (2.4%)	1/49 (2.0%)	1/97 (1.0%)	0	1/52 (1.9%)	0

F: FKB327; H: US-Humira

Date source: Tables Q3-6 and Q3-7 of Clinical Response to Information Request dated October 31, 2019

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7. Statistical and Clinical Evaluation and RecommendationsStatistical and Clinical Executive Summary and Recommendation

Comparative Efficacy:
FKB327-002 was a multicenter, randomized, double-blind, parallel group, active-controlled, comparative studyin patients with moderate to severe, active RA who were already taking methotrexate (MTX) for at least three months at a stable dose (10 to 25 mg/week) for a minimum of eight weeks prior to screening but required additional therapy to control their disease.

The primary objective of the Study FKB327-002 was to assess the efficacy of FKB327 compared with US-Humira, when each was administered in combination with MTX. Efficacy variables included in the study were ACR20, ACR50, and ACR70 response rates, change from baseline in DAS28-CRP score, change from baseline in DAS28-ESR score and change from baseline in individual ACR Core Set variables (TJC, SJC, CRP, ESR, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of pain, and HAQ-DI). In the analysis of the primary endpoint based on all randomized subjects, ACR20 response rate at Week 24, the FKB327 treatment group had a 72% response rate and the US-Humira treatment group had a 73% response rate. The adjusted treatment difference in ACR20 response rate between the FKB327 and US-Humira treatment groups in the randomized population was -1.6% with a 90% CI of (-7.0%, 3.8%), which was contained within the similarity margin of [−12%, +15%] recommended by FDA. Furthermore, ACR20, ACR50, and ACR70 responses over time, mean changes from baseline in the components of the ACR composite endpoint and the disease activity score (DAS28), and other secondary efficacy endpoint results, showed no obvious differences between FKB327 and US-Humira.

Up to Week 24, there were 69 (10%) patients who withdrew from the study: 34 (9%) patients from the FKB327 arm and 35 (10%) patients from US-Humira arm. We conducted tipping point analyses to explore the sensitivity of results to violations in assumptions about the missing data. Confidence intervals for the differences between FKB327 and US-Humira failed to rule out concerning losses in efficacy only under the assumption that patients who dropped out on FKB327 had much worse outcomes than dropouts on US-Humira. Given the similar proportions of patients and distributions of reasons for early withdrawal on the two treatment arms, in addition to the similar baseline characteristics between dropouts on the two arms, an assumption of such large differences between the outcomes in dropouts on the two treatments seems implausible. That is, the finding of similar efficacy is highly credible notwithstanding the number of dropouts.

Comparative Safety and Immunogenicity: The comparative safety evaluation plan of FKB327 reflected the known safety profile of US-Humira as described in the USPI and other published data. The submitted safety and immunogenicity data from Studies FKB327-002 and FKB327-003, supported by the data from the single-dose PK study, FKB327-001, are adequate to

support the demonstration of no clinically meaningful differences in safety and immunogenicity between FKB327 and US-Humira. Study FKB327-005 provides support of bioequivalence between the vial presentation, used in Study FKB327-002, and the PFS and AI presentations, used in Study FKB327-003. Additionally, supportive safety information was obtained through two studies, FKB327-004 and FKB327-006, though these studies will only be briefly reviewed as they are single dose, PK studies conducted exclusively in Japanese adults.

The safety database submitted for FKB327 includes a total of 751 participants who received at least one dose of FKB327 (385 healthy individuals and 366 patients with RA) 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 FKB327 and US-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 FKB327. In addition, a single transition of non-treatment naïve patients to the proposed biosimilar, i.e., patients previously treated with US-Humira to FKB327, did not result in an increase immunogenicity or clinically significant adverse reactions.

To reliably evaluate whether there are clinically meaningful differences between two products, a comparative clinical study must have assay sensitivity, or the ability to detect meaningful differences between the products, if such differences exist. Historical evidence of sensitivity to drug effects and appropriate study conduct may be used to support the presence of assay sensitivity and a conclusion that the treatments are similarly effective rather than similarly ineffective. Based on an evaluation of historical, randomized, placebo-controlled clinical studies of Humira, we concluded that (1) the design of the historical studies were largely similar to that of comparative clinical study FKB327-002; and (2) there were relatively large and consistent treatment effects across the five historical studies. We did not identify any issues with the quality of study conduct, with the exception of the high rate of study withdrawal. The totality of available information largely supports the assay sensitivity of study FKB327-002.

Overall, the collective evidence from the comparative clinical development program supports a demonstration of no clinically meaningful differences between FKB327 and US-Humira.

7.1.1. Statistical and Clinical Residual Uncertainties Assessment

During this statistical review, a few important statistical issues arose. These issues were adequately addressed by the applicant and/or the reviewer.

The first significant issue occurred during the development phase of the study and was to determine similarity margin for primary efficacy analysis. The determination of similarity margins was a critical design aspect of this comparative clinical study as it determines the differences in efficacy that need to be ruled out at an acceptable significance level. Initially, the applicant proposed a biosimilarity margin of (b) (4)% for the ACR20 response rate based on the

Reference ID: 4635331

fixed effects meta-analysis of these studies. However, in the written response given on April 17, 2015, FDA recommended that the similarity margin should not be greater in magnitude than ±12%. For the upper margin, FDA suggested that a relaxed upper bound as part of an asymmetric similarity margin (e.g., -12%, +15%) could be considered as long as it was adequately justified. The applicant decided to propose the asymmetric margin with adequate justification and FDA found the proposed similarity margin of (-12%, +15%) in study FKB327-002 acceptable.

The second major issue was on defining analysis populations. Applicant's primary analyses for all endpoints were conducted using the FAS, defined as the set of patients who received at least one dose of the randomized treatment and who had at least one evaluable primary efficacy measurement after their first dose of randomized treatment. In particular, 9 patients (1%) were excluded from the FAS, either because they did not receive study drug or because they did not have a primary efficacy measurement after the first study drug dose. Therefore, the efficacy analysis of ACR20 endpoint at Week 24 was also performed on all randomized patients (RAN). As discussed below, the conclusions were similar and this issue did not preclude a conclusion of no clinically meaningful differences between FKB327 and US-Humira.

7.2. Review Strategy

The evaluation of supportive evidence of no clinically meaningful difference in efficacy between FKB327 and US-Humira was primarily based on Study FKB327-002. While the vial presentation of FKB327 was used during the conduct of this study, data from the bridging Study FKB327-005 provides evidence of comparable bioavailability of this presentation to the to-be-marketed PFS and AI. The statistical reviewer analyzed the Applicant's primary endpoint and key secondary endpoints and included additional analyses to evaluate the robustness of the results for Study FKB327-002. The key findings are presented and described in tables and figures in the subsequent sections.

In addition to Study FKB327-002, the review of no clinically meaningful differences in safety included FKB327-003. Though supplemental safety data from the other studies were also summarized by the Applicant, these studies involved only a single-dose of study medication in healthy volunteers (FKB327-001, FKB327-004, FKB327-005, and FKB327-006), and therefore were not the primary focus of the safety review. A discussion of the safety evaluation is presented in Section 7.4.

7.3. Review of Clinical Studies with Statistical Endpoints

7.3.1. PK Similarity Study FKB327-001

Trial FKB327-001 was a randomized, double-blind, single-dose trial to compare pharmacokinetic characteristics and safety of FKB327 with those of US-Humira in healthy subjects.

Reference ID: 4635331

Study Design and Endpoints

Trial FKB327-001 enrolled 180 healthy male and females individuals, ages 18-65 years old; the females were of non-childbearing potential. Individuals with acute or chronic illnesses were excluded, as were those who had previous treatment with adalimumab. Volunteers were also excluded if they had a history of severe adverse reaction or history of anti-drug antibodies to any medication.

Because FKB327 had not previously been administered to humans, a small group of sentinel subjects were exposed to trial medications first, prior to dosing a larger cohort. The first 12 subjects were male and were split into 3 subgroups: 1a, 1b, and 1c (Table 5).

Table 22: Dosing subgroups, Trial FKB327-001

Group	FKB327	US-Humira	EU-Humira	Total
1a	1	1	1	3
1b	1	1	1	3
1c	2	2	2	6

Source: Table 1, FKB327-001 Report Body, Page 14

Drug was not administered to Group 1b until at least 7 days had elapsed from the dosing of participants in Group 1a. Group 1c was not dosed until at least 47 hours after Group 1b had received trial medications. A minimum of 23 hours was required before the remaining 168 participants could be dosed in groups of 6-14 men and 4-5 women. No more than 24 subjects received trial medication within any 7-day period. Groups were only dosed after safety and tolerability in the previous group was confirmed.

Participants were randomized 1:1:1 to receive 40 mg of FKB327, US-Humira, or EU-Humira subcutaneously. Patients were randomized base on weight strata (60-75 kg and 75-90 kg). Subjects were screened within 4 weeks of Day 1, the day of trial drug administration. Participants were domiciled and monitored until Day 9, and then returned for follow-up visits on Days 16, 23, 30, 37, 44, 51, and 65.

The prespecified primary PK endpoints were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The secondary PK endpoints were $AUC_{0\text{-}360h}$, t_{max}, and $t_{1/2}$. Although defined as a secondary endpoint, t_{max} was not subjected to a formal statistical analysis; t_{max} summary statistics were compared between treatments.

Trial location: This trial was conducted at a single site in London, England.

Trial subjects: Participants were healthy males or females of non-childbearing potential.

- Participants were deemed healthy on the basis of medical history, physical examination, ECG, vital signs, and laboratory testing.

- Female volunteers were post-menopausal (last menstrual period at least 12 months ago, with FSH level at screening consistent with post-menopausal level) or had undergone hysterectomy, a bilateral oophorectomy or a bilateral salpingectomy.
- Male volunteers were required to use contraception for 4 months after dosing.
- Participants were 18 to 65 years old, weighed 60 to 90 kg, and had BMI of 18 – 30 kg/m^2.
- Participants were required to have systolic blood pressure of 90 to 140 mm Hg, diastolic blood pressure of 40 to 90 mm Hg, and heart rate of 40 to 110 beats per minute.

Trial treatment: Subjects received a single dose of 40 mg FKB327, US-Humira, or EU-Humira in a volume of 0.8 mL by subcutaneous injection. FKB327 was provided in vials, but was placed in a syringe identical to that of Humira PFS in order to maintain blind.

Concomitant medications: Medications were given to participants if it was deemed necessary. Immunizations with live vaccines were prohibited in the three months leading up to trial drug administration, through end of trial which is consistent with the Humira USPI.

Statistical Methodologies

Given that Trial FKB327-001 was a phase 1 trial, there were no pre-specified efficacy endpoints. For a discussion of the statistical analysis of the primary PK endpoints, see Section 6.3.

Subject Disposition

A total of 180 participants were randomized, with 60 participants in each group (FKB327, US-Humira and EU-Humira). One subject in the FKB327 group voluntarily withdrew from the trial, while all others completed participation.

Demographics and Baseline Characteristics

Participants in Trial FKB327-001 were on average 33 years old, and were mostly male (94%) and white (65%). The average BMI at Screening was 24 (Table 23).

Table 23: Demographic Characteristics, Trial FKB327-001 (Safety Analysis Set)

Demographic	FKB327 N=60	US-Humira N=60	EU-Humira N=60	Totals n=728
Age (years)				
mean (SD)	31 (11)	32.3 (12.4)	35.2 (14.1)	32.8 (12.6)
range	19, 64	19, 62	18, 64	18, 64
Sex – n (%)				
Male	58 (97%)	57 (85%)	55 (92%)	170 (94%)
Female	2 (3%)	3 (5%)	5 (8%)	10 (6%)
Race – n (%)				
White	34 (57%)	38 (63%)	45 (75%)	117 (65%)

Black or African American	14 (23%)	8 (13%)	9 (15%)	31 (17%)
Asian	6 (10%)	12 (20%)	5 (8%)	23 (13%)
Other	6 (10%)	2 (3%)	1 (2%)	9 (5%)
Ethnicity – n (%)				
Not Hispanic or Latino	57 (95%)	57 (95%)	58 (97%)	172 (96%)
Hispanic or Latino	3 (5%)	3 (5%)	2 (3%)	8 (4%)
BMI at Screening (kg/m^2)				
mean (SD)	24 (2.3)	24.2 (2.8)	23.8 (2.3)	24 (2.4)
range	19.8, 28.6	18.7, 29.3	19.4, 29.4	18.7, 29.4
Weight at Screening (kg)				
mean (SD)	74.6 (7.9)	73.7 (8.4)	74.9 (7.5)	74.4 (7.9)
range	61.2, 89.3	60.1, 88.9	61.8, 89.4	60.1, 89.4

Source: Adapted from Table 5, FKB327-001 Report Body, Page 40

7.3.2. Comparative Clinical Study FKB327-002

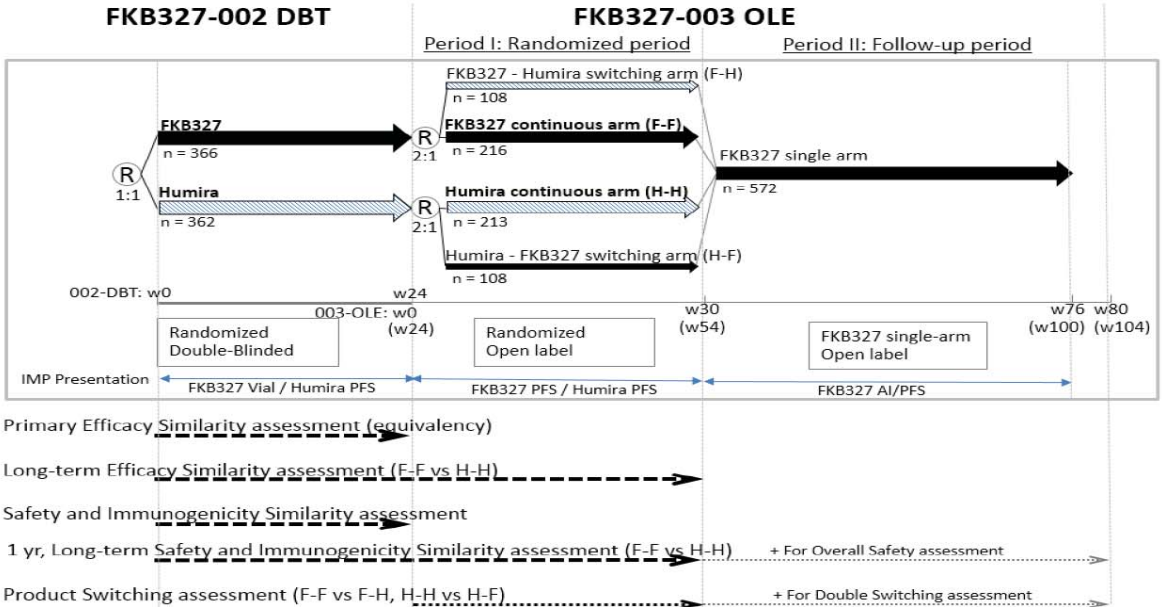
FKB327-002 was a randomized, double-blind, parallel arm, active-comparator study, designed to assess relative efficacy, safety, immunogenicity, and multi-dose PK of FKB327 compared to US-Humira in patients with RA.

Study Design and Endpoints

Study FKB327-002 randomized 730 adult patients with active RA for at least three months who were currently receiving a stable dose of MTX. In order to be eligible to enroll in this study, patients were required to have at least 6 tender and at least 6 swollen joint counts (TJC & SJC, respectively) out of 68 (TJC68) and 66 (SJC66) joints, respectively, at Screening and at Baseline and CRP ≥10 mg/L at Screening. Patients were randomized in a 1:1 ratio, stratified by prior biological treatment for RA (yes or no) and screening disease activity (DAS28-CRP ≤5.1/>5.1), to receive FKB327 or US-Humira. Patients were excluded if they had prior treatment with adalimumab, or treatment with more than one biologic or one protein kinase inhibitor DMARD for RA. Patients who had used other TNF inhibitors and experienced lack of efficacy were excluded. The study was conducted at 109 sites in 12 countries in North America (with 78 (11%) patients from US sites), Europe, and Rest of World (Chile, Peru, Russia and the Ukraine).

Patients received subcutaneous treatment with 40 mg every other week of FKB327 or US-Humira from Week 0 to Week 22 (Figure 8). Clinical visits were scheduled every two weeks until Week 24. At Week 24, patients who had received a minimum of 9 doses of study drug and had shown clinical response to treatment were eligible to enroll into the OLE study (Study FKB327-003). Patients that did not agree to participate attended a Week 26 follow-up visit.

Figure 8: Schematic of Comparative Clinical Studies



R=randomization; DBT=double-blind trial, OLE=open-label extension; F=FKB327, H=US-Humira, n= number of patients who received at least one dose of study drug
Source: Figure 1, Clinical Overview, page 12

The prespecified primary endpoint in this study was the proportion of patients achieving an ACR20 response at Week 24. ACR20 is a responder-type, multi-component endpoint defined by achieving at least 20% improvement from baseline in TJC68 and SJC66, with at least 20% or more improvement from baseline in three of the five additional measures of disease signs or symptoms: CRP, patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of pain on a visual analog scale, and HAQ-DI.

Secondary efficacy endpoints included DAS28-CRP and DAS28-ESR. The DAS28 score is a combined index that has been developed to measure disease activity in patients with RA which involves evaluating the number of tender and swollen joints (out of 28 specified joints), serum CRP or ESR, and patient global assessment of disease activity using a visual analogue scale (VAS). The following formula are used to calculate the DAS28-CRP and DAS28-ESR, respectively:

$$DAS28\text{-}CRP = 0.56*\sqrt{TJC} + 0.28*\sqrt{SJC} + 0.36*\ln(CRP+1) + 0.014*VAS + 0.96$$
$$DAS28\text{-}ESR = 0.56*\sqrt{TJC} + 0.28*\sqrt{SJC} + 0.7*\ln(ESR) + 0.014*VAS$$

Other secondary efficacy endpoints included in this study were ACR20, ACR50, and ACR70 response rates, TJC, SJC, CRP, VAS score, and HAQ-DI.

Study location: This was a multi-national study. A total of 730 patients with RA were recruited from 109 sites across 12 countries. Overall, 38% were recruited from Europe (Bulgaria, Czech

Republic, Germany, Poland, Romania, and Spain), 12% from North America, and 50% from the Rest of World (Chile, Peru, Russia, and Ukraine). There were 78 (11%) subjects studied in the US. The proportion of patients studied in each region was evenly distributed across FKB327 and Humira treatment groups (Table 26).

Study subjects: Participants with active RA who required additional therapy to control their disease despite MTX treatment, were defined by the following criteria:

- Diagnosis of RA based on the 2010 ACR criteria for at least 3 months prior to Screening
- ≥6 tender and ≥6 swollen joint counts out of 68 and 66 joints, respectively, at Screening and Baseline
- CRP ≥10 mg/L at Screening
- Have received oral or parenteral MTX for at least 3 months prior to Screening and a stable dose between 10 and 25 mg/week for at least 8 weeks
- ACR functional Class I-III
- No prior treatment with adalimumab, cyclophosphamide or with more than 1 biologic or 1 protein kinase inhibitor DMARD for RA
- No intra-articular or parenteral steroids within 28 days prior to Screening
- No treatment with any DMARD, other than MTX, within a period prior to Screening appropriate to the pharmacodynamic profile of the drug concerned
- No treatment with an investigational agent within 12 weeks or 5 half-lives of the drug prior to Screening

Study treatment: FKB327 or US-Humira 40 mg was administered to participants every other week for the duration of the study. Blinded kits containing a single dose of either FKB327 or US-Humira were supplied to each clinical study site. FKB327 was provided in vials and US-Humira was provided as a PFS. If the kit contained FKB327, study staff would withdraw 0.8mL (40 mg) of FKB327 from the vial using a provided syringe prior to administration. The syringe was then placed in a masking unit and was taken to the location of the patient, which allowed for a dose to be administered without revealing the appearance of the syringe. Humira kits had a PFS already placed in the masking unit. The masking units for both FKB327 and Humira were identical in order to maintain the blind for participants. An unblinded nurse who was not involved in the study assessments administered the injection into the thigh or anterior abdominal wall of patients.

Concomitant medications: The following mediations at stable doses were allowed during the conduct of the study:

- MTX: oral or parenteral stable dose of 10-25 mg/week for the 8 weeks prior to screening. The dose was could be reduced for toxicity only.
- Folic/folinic acid: oral folate or folinic acid (≥5 mg/week)
- Corticosteroid: ≤10 mg/day prednisone or equivalent was permitted if patients were on a stable dose at least 4 weeks prior to Screening and the same dose was continued. An increase in oral steroid dose was permitted to treat a concomitant condition, but the

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dose was to be tapered back down to a stable dose as soon as medically viable and within 2 weeks.

- NSAIDs: Oral NSAID up to the maximum approved dose were permitted if the patient was on a stable regimen for at least 4 weeks prior to Screening and the same dose was continued. An increase in dose was permitted to treat an RA flare, but the dose was to be tapered back down to stable dose as medically viable and within 2 weeks. Patients who were not receiving NSAIDs could be treated with an NSAID for up to 2 weeks or an additional NSAID could be added to an existing regimen for up to 2 weeks to treat an RA flare. Analgesics up to the maximum approved dose were permitted during the study but were not to be taken 24 hours prior to efficacy evaluations.
- Anti-mycobacterial treatment: Patient with evidence or suspicion of latent TB at Screening could commence prophylactic anti-mycobacterial treatment if it was at least 3 weeks prior to randomization and committed to completing the course of treatment.
- Medications for chronic conditions: Patients who met inclusion criteria were able to continue medications for chronic conditions.

Statistical Methodologies

Analysis Populations

The following datasets were used in different analyses:

The Randomized Set (RAN) consisted of all enrolled patients who were randomized, i.e., received a randomization number at the randomization visit.

The Safety Analysis Set (SAS) was defined as the set of all patients who received at least one dose of randomized treatment. This analysis set was used for all safety analyses. Patient safety data were analyzed according to treatment actually received (i.e., the last treatment received prior to recording the safety data).

The Full Analysis Set (FAS) was defined as the set of all patients who received at least one dose of the randomized treatment and who had at least one evaluable primary efficacy measurement after their first dose of randomized treatment. Patients were analyzed according to their randomized treatment in the primary analysis. The sponsor used the FAS was the primary efficacy analysis and other efficacy endpoints and analyses. Because this analysis set conditions on a post-randomization variable (at least one evaluable primary efficacy measurement after their first dose of randomized treatment), the reviewer also performed analyses using the RAN (discussed further in Additional Analyses).

Per-protocol Analysis Set (PPAS) was defined as the set of patients in the FAS that did not have major protocol deviations expected to impact on the primary efficacy endpoint. This criteria leading to exclusion from the PPAS were fully defined prior to unblinding the study data.

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Determination of Sample Size

The applicant reported that the sample size calculations were performed using nQuery Advisor 7 with the option of two-sided CIs for the difference in proportions (simulation-based) selected. A total of 680 patients were planned to be randomized to FKB327 and US-Humira treatment in a 1:1 ratio. This sample size was calculated to have 80% power to observe differences in the ACR20 response rate at Week 24 of FKB327 and US-Humira to be within a margin of (b) (4). This calculation assumed an estimated ACR20 response rate at Week 24 of 57% to 63% and a maximum of 15% of patients ineligible for the PPAS. With this sample size, the applicant computed that there would be approximately 88% power to show no clinically meaningful differences between FKB327 and US-Humira using a 90% CI for comparison to the asymmetric similarity margin of -12% to +15% . The applicant's approach to compute the planned sample size based on PPAS was reasonable, although the primary analyses were ultimately specified to be performed on the FAS.

Analysis of the Primary Endpoint

ACR20 response rate at Week 24 was the primary efficacy endpoint of the study. In the primary analysis of this endpoint, the applicant planned to compare efficacy response rate between treatment groups using the FAS and the PPAS. The 90% confidence interval (CI) for the differences in treatments (FKB327 – US-Humira) would be calculated using a normal approximation with no continuity correction. Patients without an ACR response evaluable at Week 24 (regardless of the reason) and those who had permanently discontinued treatment prior to Week 24, were to be imputed as non-responders. A conclusion of no clinically meaningful differences between FKB327 and US-Humira would be made if the 90% CI of the treatment difference fell entirely within the pre-specified margin, discussed further below.

Analysis of Secondary Endpoints

The secondary endpoint, DAS28-CRP score at Week 24, was analyzed using mixed models for repeated measures (MMRM) with patient included as a random effect and prior biological treatment for RA, site, baseline DAS28-CRP, week, treatment group, week × treatment group were included as fixed effect parameters in the model. The least square mean (LSM) for week × treatment group from the marginal model for repeated measures were estimated with 95% CIs and the difference in LSMs of FKB327-Humira at Week 24 was estimated with 95% CI. The 90% CI was also computed by the reviewer. In this analysis, the missing values were not imputed in this analysis and thus effectively were assumed to follow a missing at random (MAR) mechanism.

The percentage of patients achieving ACR20, ACR50 and ACR70 response were summarized as the ACR response rate (%) using counts and percentages along with 95% CIs for these rates. Other secondary endpoints such as tender and swollen joint counts, CRP, HAQ-DI, DAS28-ESR

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were summarized by treatment group, using the FAS, at Weeks 0, 2, 4, 8, 12, 16, 20 and 24 and presented graphically over time.

Additional Analyses

The primary analyses by the Applicant for all endpoints were conducted using the FAS, defined as the set of patients who received at least one dose of the randomized treatment and who had at least one evaluable primary efficacy measurement after their first dose of randomized treatment. In particular, 9 patients (1%) were excluded from the FAS, either because they did not receive study drug or because they did not have a primary efficacy measurement after the first study drug dose. Therefore, the efficacy analysis of ACR20 endpoint at Week 24 was also performed on all randomized patients (RAN).

Subgroup analyses were performed for the ACR20 response rate, as done in the primary analysis for the following subgroups: demographic subgroups, geographical region, body mass index (BMI) and the results were presented as a forest plot.

To assess the impact of missing data, various additional analyses were performed by the sponsor and the reviewer, including tipping point analyses. The analyses presented here, performed by the statistical reviewer, considered a range of possible response rates in subjects with missing data in the primary analysis (e.g., systematically changing assumed responses rates for these subjects in a stepwise manner). This analysis included all observed data for all randomized subjects. This analysis is two-dimensional, varying response rates in these subjects on both arms independently, and included scenarios where dropouts on FKB327 have worse outcomes than dropouts on US-Humira. The results from this analysis are presented in a tabular form to identify the "tipping point" where a conclusion of similarity is lost based on a comparison of the 90% confidence interval to the pre-specified margin. The details for this analysis are provided in the Appendix (13.5.1). In addition, the applicant performed their own multiple imputation tipping point analyses with similar results.

Potential Effects of Missing Data

The 2010 National Research Council (NRC) report *The Prevention and Treatment of Missing Data in Clinical Trials* recommends that "examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting." As given in Table 25, up to Week 24, there were 69 (10%) patients who withdrew from the study: 34 (9%) patients from the FKB327 arm and 35 (10%) patients from US-Humira arm. In the primary analysis of ACR20 using the FAS, patients who dropped out or who discontinued treatment were considered non-responders, such that the primary endpoint was a composite measure of treatment success defined by adherence to the treatment through Week 24 and achieving an ACR20 response at Week 24. Comparing treatments with respect to this composite measure of treatment success may confound differences between treatments in efficacy with differences in tolerability or ability to adhere to the protocol. For example, the composite measure could fail

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to identify clinically meaningful differences in efficacy if the proposed biosimilar was better tolerated than the reference product but had lower efficacy in the subset of patients who adhered. Therefore, it is important to evaluate differences in each of these components of the composite primary endpoint. This includes an evaluation of ACR20 at Week 24 in all randomized patients regardless of adherence (an evaluation of the de facto or intention-to-treat estimand), in addition to de facto evaluations of the components of ACR20. However, such evaluations are subject to some residual missing data (because patients who discontinued treatment were not followed up for assessment) and rely on strong and unverifiable assumptions. Therefore, we requested that the applicant include tipping point analyses to explore the sensitivity of results to violations in assumptions about the missing data.

Similarity Margin

The determination of similarity margins was a critical design aspect of this comparative clinical study because it determined the differences in efficacy that the study would need to rule out at an acceptable significance level.

To determine the margin, the applicant conducted literature review of three placebo-controlled studies in adalimumab and proposed a biosimilarity margin of (b) (4)% for the ACR20 response rate based on the fixed effects meta-analysis of these studies. In the written response given on April 17, 2015, FDA recommended that the similarity margin should not be greater in magnitude than ±12%. The recommended margin of ±12% was based on considerations aimed at weighing the clinical importance of various differences in effect against the feasibility of different study sizes. Furthermore, FDA advised that observed differences larger than approximately 6% would result in failure to establish similarity in the comparative clinical study designed with 90% power to reject absolute differences greater than 12% in magnitude. The lower bound of the proposed similarity margin (-12%) corresponds to the retention of approximately 50–60% of conservative estimates of treatment effect sizes relative to placebo for adalimumab. These estimated effect sizes were calculated from the lower bounds of 95% CIs based on meta-analyses of historical clinical studies in patients with active RA despite treatment with methotrexate (Table 24). For the upper margin, FDA suggested that a relaxed upper bound as part of an asymmetric similarity margin (e.g., -12%, +15%) could be considered as long as it was adequately justified.

In response, the applicant reported results from a fixed effects analysis of three historical studies in RA and estimated that the difference in the ACR20 response rate to be 37.0% with a 95% CI, (29.9%, 44.0%). Further, the applicant claimed that with a lower 95% CI bound of around 30%, and taking half of this value, a larger upper equivalence margin bound of 15% is considered reasonable to rule out clinically meaningful superiority. FDA found the proposed similarity margin of (-12%, +15%) in study FKB327-002 acceptable and informed the sponsor of this decision on October 5, 2015.

Table 24: Historical Effect of Adalimumab on ACR20 Response[1] in Randomized Clinical Trials of Patients with Active RA Despite Treatment with Methotrexate (MTX)

Study	Week	MTX + Placebo		MTX + Adalimumab		Difference in % Response
		N	% Response	N	% Response	
Keystone et al.[2]	12	200	25%	207	57%	33%
Weinblatt et al.[3]	12	62	23%	67	66%	43%
Kim et al.[4]	12	63	25%	65	57%	32%
Chen et al.[5]	12	12	33%	35	54%	21%
Meta-Analysis (fixed effects[6]): Difference (95% CI)						34.0% (27.1%, 40.8%)
Meta-Analysis (random effects[7]): Difference (95% CI)						34.1% (27.3%, 41.0%)
Heterogeneity p-value						0.54

[1] ACR20 response probabilities at Week 12 estimated based on graphical displays in Keystone et al., Weinblatt et al, and Kim et al. publications
[2] Keystone, E. C., Kavanaugh, A. F., Sharp, J. T., Tannenbaum, H., Hua, Y., Teoh, L. S., ... & Chartash, E. K. (2004). Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial. Arthritis & Rheumatism, 50(5), 1400-1411.
[3] Weinblatt, M. E., Keystone, E. C., Furst, D. E., Moreland, L. W., Weisman, M. H., Birbara, C. A., ... & Chartash, E. K. (2003). Adalimumab, a fully human anti–tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis & Rheumatism, 48(1), 35-45.
[4] KIM, H. Y., LEE, S. K., SONG, Y. W., YOO, D. H., KOH, E. M., Yoo, B., & Luo, A. (2007). A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology, 10(1), 9-16.
[5] Chen, D. Y., Chou, S. J., Hsieh, T. Y., Chen, Y. H., Chen, H. H., Hsieh, C. W., & Lan, J. L. (2009). Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. Journal of the Formosan Medical Association, 108(4), 310-319.
[6] Based on Mantel-Haenszel weights
[7] Based on DerSimonian-Laird approach

Subject Disposition

Overall, 661 patients (91%) completed the study through Week 24. Comparable rates of completion as well as enrollment in the OLE were seen in both the FKB327 and US-Humira treatment groups (Table 25). Premature study discontinuation rates were also similar between treatment groups (9% in FKB327 group and 10% in US-Humira), though patients in the FKB327 group more commonly discontinued treatment due to an AE than those in the US-Humira treatment group. Ten randomized patients (1%; 4 patients and 6 patients in the FKB327 and US-Humira treatment groups, respectively), discontinued study treatment but continued participation in study procedures as per the protocol.

Table 25: Disposition of Patients, Study FKB327-002

	FKB327 n (%)	US-Humira n (%)	Total n (%)
Number of patients randomized to treatment	367 (100%)	363 (100%)	730 (100%)
Number of patients with study drug administered	366 (100%)	362 (100%)	728 (100%)
Number of patients who completed the study	333 (91%)	328 (90%)	661 (91%)
Number of patients who continued treatment in Study FKB327-003 (OLE)	324 (88%)	321 (88%)	645 (88%)
Number of patients who prematurely discontinued from the study	34 (9%)	35 (10%)	69 (10%)
Primary reason for premature study discontinuation[a]			
Adverse event	14 (41%)	9 (26%)	23 (33%)
Screen failure	0	1 (3%)	1 (1%)
Withdrawal of consent	10 (29%)	16 (46%)	26 (38%)
Lack of efficacy	2 (6%)	1 (3%)	3 (4%)
Other[b]	8 (24%)	8 (23%)	16 (23%)

Source: FDA reviewer; Table 10-2, FKB327-002 Report Body, page 74
[a]Percentages for reasons based on the number of patients who discontinued from the study
[b]Reasons included lack of efficacy, missing visit(s), lost to follow-up, missing QuantiFERON test samples, sponsor decision, and protocol noncompliance.

Out of 730 patients in the RAN, one patient (0.3%) in each of the FKB327 and US-Humira treatment groups was excluded in the SAS because they did not receive a dose of study drug (Table 26: Summary of Analysis Sets). Nine patients (1.2%) were excluded in the FAS, either because they did not receive study drug or because they did not have a primary efficacy measurement after the first study drug dose. Furthermore, 91 patients (12.5%) were excluded from the PPAS, with the main reasons for exclusion being missed visit, missed/invalid efficacy procedure and violation of efficacy inclusion/exclusion criterion.

Table 26: Summary of Analysis Sets

	FKB327 n (%)	US-Humira n (%)	Total n (%)
Number of patients randomized to treatment	367 (100%)	363 (100%)	730 (100%)
Safety Analysis Set	366 (99.7)	362 (99.7)	728 (99.7)
Full Analysis Set	363 (98.9)	358 (98.6)	721 (98.8)
PP Analysis Set	314 (85.6)	325 (89.5)	639 (87.5)

Source: Statistical Reviewer

Demographics and Baseline Characteristics

Patient demographics and baseline characteristics were similar across the two treatment groups (Table 27). The average age in the study was 53 years old, and most patients were female (78%), white (85%), and from outside of North America and Europe (50%). Weight and height were similar in the FKB327 and US-Humira treatment groups.

Table 27: Demographics Characteristics, Study FBK327-002 (Safety Analysis Set)

Demographic	FKB327 N=366	US-Humira N=362	Totals N=728
Age (years)			
mean (SD)	53 (12)	53.6 (12.3)	53.3 (12.2)
range	18, 85	21, 93	18, 93
Sex – n (%)			
Female	281 (77%)	284 (78%)	565 (78%)
Male	85 (23%)	78 (22%)	163 (22%)
Race – n (%)			
White	311 (85%)	308 (85%)	619 (85%)
Other	51 (14%)	48 (13%)	99 (14%)
Black or African American	2 (1%)	4 (1%)	6 (1%)
American Indian or Alaska Native	1 (0%)	1 (0%)	2 (0%)
Asian	1 (0%)	1 (0%)	2 (0%)
Region – n (%)			
Rest of World	184 (50%)	180 (50%)	364 (50%)
Europe	140 (38%)	139 (38%)	279 (38%)
North America	42 (11%)	43 (12%)	85 (12%)
Height at Baseline (cm)			
mean (SD)	163.6 (9.7)	163 (8.9)	163.3 (9.3)
range	141, 193	144, 192	141, 193
Weight at Baseline (kg)			
mean (SD)	73.3 (16)	73.6 (15.6)	73.5 (15.8)
range	39.9, 118.6	40.5, 116.2	39.9, 118.6

Source: Generated by FDA reviewer
SD=standard deviation, N= Number of patients in Safety Analysis Set, n= Number patients in subgroup

Baseline RA disease characteristics were consistent with active RA disease (Table 28). Patients had 26 tender joints, 16 swollen joints and had a Health Assessment Questionnaire score of 1.8 on average. Baseline DAS28-CRP and DAS28-ESR values were on average 6.1 and 6.5, respectively. Seventy-six percent of patients were rheumatoid factor positive. Overall, these characteristics were similar across the two treatment groups.

Table 28: Rheumatoid Arthritis Disease Characteristics, Study FBK327-002 (Safety Analysis Set)

Patient Characteristic	FKB327 N=366	US-Humira N=362	Totals N=728
Rheumatoid factor status, n (%)			
Positive	277 (75.7%)	277 (76.5%)	554 (76.1%)
Negative	88 (24.0%)	83 (22.9%)	171 (23.5%)
Missing	1 (0.3%)	2 (0.6%)	3 (0.4%)
Serum MMP-3 concentration (ng/mL)			
n	361	358	719
Mean (SD)	73.4 (78.5)	80.5 (95.4)	76.9 (87.3)
Range	4.5, 687	4.1, 752.5	4.1, 752.5
Anti-CCP antibody concentration			
n	287	287	574
Mean (SD)	1907.9 (3375.5)	1651.2 (2032.8)	1779.6 (2786.7)
Range	18, 41728	22, 13888	18, 41728
CRP level (mg/L)			
n	365	362	727
Mean (SD)	25 (26.7)	26.6 (28.4)	25.8 (27.6)
Range	0.9, 193	0.9, 230	0.9, 230
ESR (mm/hr)			
n	364	359	723
Mean (SD)	38.8 (19.2)	41.2 (20.7)	40 (20)
Range	2, 98	4, 110	2, 110
Tender joint count (68 joint count)			
n	365	362	727
Mean (SD)	26.2 (14.5)	25.9 (14.5)	26.1 (14.5)
Range	0, 68	6, 68	0, 68
Swollen joint count (66 joint count)			
n	365	362	727
Mean (SD)	16.3 (9.1)	16 (9)	16.1 (9)
Range	0, 66	0, 58	0, 66
Patient's assessment of disease activity			
n	365	362	727
Mean (SD)	68 (18)	68.2 (18.2)	68.1 (18)
Range	7, 100	0, 100	0,100
Physician's assessment of disease activity			
n	364	361	725
Mean (SD)	68.4 (14.6)	66.4 (15)	67.4 (14.8)
Range	30, 99	7, 99	7, 99
Patient's assessment of pain			
n	365	362	727
Mean (SD)	66.7 (18.7)	67.9 (18.6)	67.3 (18.6)
Range	8, 100	1, 100	1, 100
Health Assessment Questionnaire			
n	365	362	727
Mean (SD)	1.77 (0.5)	1.8 (0.5)	1.8 (0.5)
Range	0, 3	0.1, 3	0, 3
DAS28-CRP			
n	364	362	726
Mean (SD)	6.1 (0.9)	6.1 (0.9)	6.1 (0.9)
Range	2.9, 8.5	3.7, 8	2.9, 8.5
DAS28-ESR			
n	363	359	722
Mean (SD)	6.5 (0.9)	6.6 (0.9)	6.5 (0.9)
Range	3.5, 8.6	4.1, 8.7	3.5, 8.7

Source: Table 10-6, FKB327-002 Report Body, page 80

ESR=erythrocyte sedimentation rate, CCP=cyclic citrullinated peptide; CRP=C-reactive protein, DAS=disease activity score, MMP-3=matrix metalloproteinase-3, SD=standard deviation, N=Number of patients in Safety Analysis Set, n=Number patients in the subgroup
The rheumatoid factor values are categorized as "negative" if <12 kU/l and "positive if >12 kU/l.

Analysis of Primary Clinical Endpoint

The primary efficacy analysis of the primary endpoint, ACR20 response rate, showed that US-US-Humira treatment group had slightly higher response rate compared to FKB327 treatment group (74.3% vs 72.5%) (Table 29). However, the 90% CI of the difference between FKB327 and US-Humira ACR20 response rates was (-7.3%, 3.6%), and contained within the FDA recommended margin of (-12% to +15%).

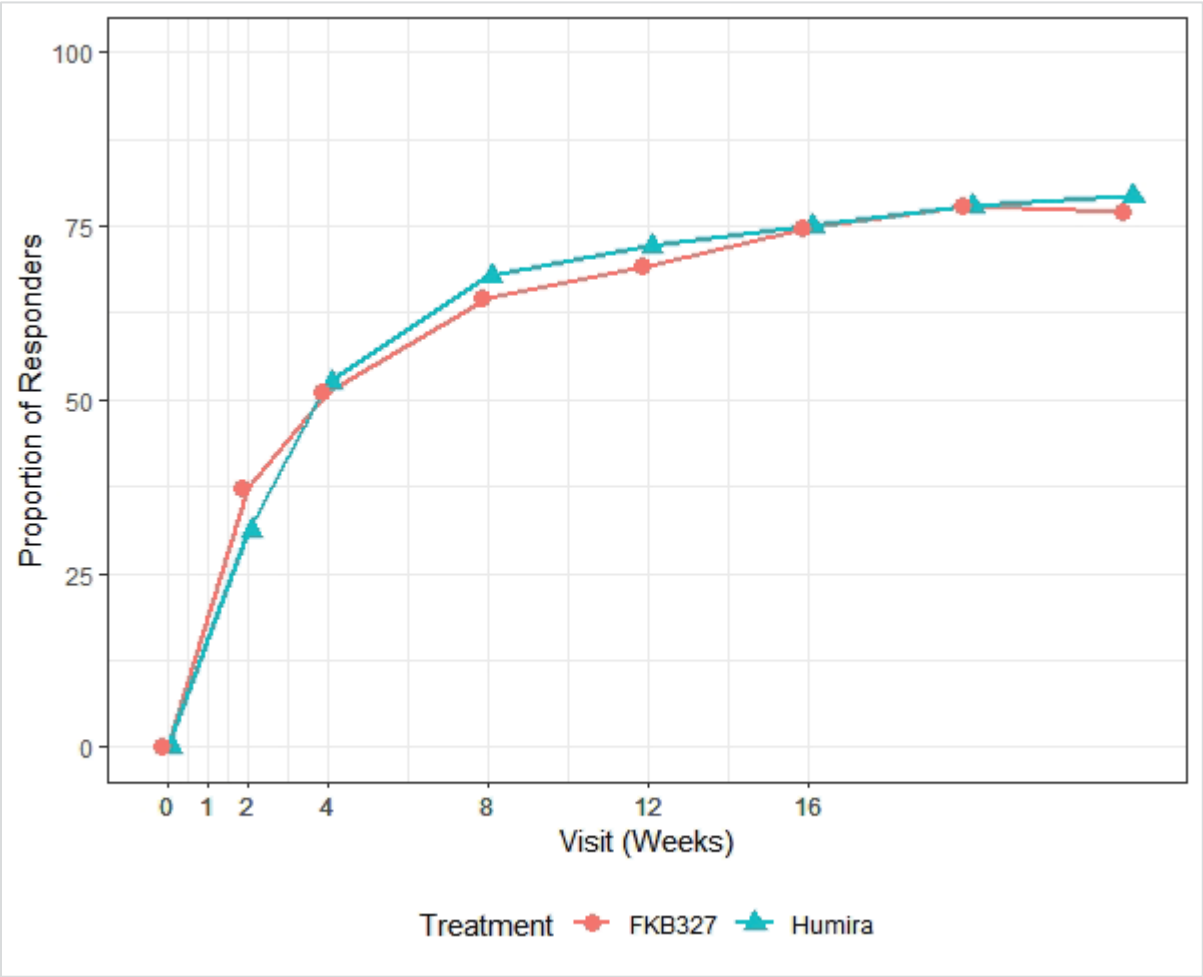
Table 29: Analysis of the ACR20 Response Rate at Week 24 in Study FKB327-002 – Full Analysis Set

Treatment	n/N	%	Adjusted Difference Rate (%)	90% CI
FKB327	263/363	72.5	**-1.8**	(-7.3, 3.6)
US-Humira	266/358	74.3		
Total	529/721	73.4		

ACR=American College of Rheumatology; CI=confidence interval; N= Total number of patients in the full analysis set; n=total number of responders;
Missing Week 24 responses for the ACR and responses for patients who discontinued the treatment prior to Week 24 were imputed using non-responder imputation.
CIs calculated using a normal approximation with no continuity correction.
Source: Statistical Reviewer

The ACR20 response rates over 24 weeks in two treatment groups of the study are shown in Figure 9. From Week 4 onwards, the response rate was slightly higher for the US-Humira group compared to the FKB327 group and the overall trend is largely similar between the groups.

Figure 9: ACR20 Response Rate over Time (Full Analysis Set)



Source: Statistical Reviewer

The efficacy analysis of ACR20 endpoint at Week 24 was also performed using the RAN and the PPAS (Table 30). These results were consistent with the Applicant's primary analysis using FAS. Using the RAN, the 90% CI of the difference between FKB327 and US-Humira ACR20 response rates was (-7.0%, 3.8%), which was contained within the FDA recommended margin. In the PPAS, the results were also consistent with the primary analysis. Of the 249 patients (79.3%) in the FKB327 treatment group achieved an ACR20 response at Week 24, compared to 259 patients (79.7%) in the US-Humira treatment group. The estimated difference was -0.4 with 90% CI: (-5.6, 4.9) which was also contained within the FDA recommended margin.

Table 30: Analysis of the ACR20 Response Rate at Week 24 in Study FKB327-002- All Randomized patients

Analysis Population	Treatment	n/N	%	Adjusted Difference Rate (%)	90% CI
All Randomized	**FKB327**	263/367	71.7	**-1.6**	(-7.0, 3.8)
	US-Humira	266/363	73.2		
PPAS	**FKB327**	249/314	79.3	**-0.4**	(-5.6, 4.9)
	US-Humira	259/325	79.7		

ACR=American College of Rheumatology; CI=confidence interval, N= Total number of patients in the analysis population; n=total number of responders, PPAS: Per-protocol Analysis Set
Source: Statistical Reviewer

The statistical reviewer performed a tipping point analysis to assess the potential impact of assuming non-response for subjects with missing data (see Appendix for methodology). This analysis included all observed data for all randomized subjects. Table 31 shows the results from this analysis for the comparison of FKB327 to US-Humira, i.e., the estimated resulting differences between FKB327 and US-Humira in the ACR20 response at Week 24, with varying assumptions about the differences on each treatment arm between outcomes in patients who withdrew from the study early and outcomes in patients who completed the study. In order for the 90% CI to fail to rule out a 12% absolute loss in the probability of ACR20 response, the response among FKB327 dropouts would need to be more than 80 percentage points lower than the response in FKB327 completers, while the response among US-Humira dropouts would need to be higher than the response among US-Humira completers. Given the similar proportions of patients and distributions of reasons for early withdrawal on the two treatment arms, in addition to the similar baseline characteristics between dropouts on the two arms, an assumption of such large differences between the outcomes in dropouts on the two arms seems implausible. Therefore, these tipping point sensitivity analyses largely support the findings of the key efficacy analyses.

Table 31: Tipping Point Analysis of the ACR20 Response Rate at Week 24

		Shift for US-Humira[1]					
Shift for FKB327[2]		-0.8	-0.6	-0.4	-0.2	0	0.2
	-0.8	-0.02 (-0.06, 0.03)	-0.03 (-0.07, 0.01)	-0.04 (-0.09, 0)	-0.06 (-0.1, -0.01)	-0.07 (-0.11, -0.03)	-0.08 (-0.12, -0.04)
	-0.6	-0.01 (-0.05, 0.04)	-0.02 (-0.06, 0.02)	-0.03 (-0.07, 0.01)	-0.04 (-0.09, 0)	-0.06 (-0.1, -0.01)	-0.07 (-0.11, -0.03)
	-0.4	0 (-0.04, 0.05)	-0.01 (-0.05, 0.03)	-0.02 (-0.06, 0.02)	-0.03 (-0.08, 0.01)	-0.05 (-0.09, 0)	-0.06 (-0.1, -0.02)
	-0.2	0.02 (-0.03, 0.06)	0 (-0.04, 0.05)	-0.01 (-0.05, 0.03)	-0.02 (-0.06, 0.02)	-0.04 (-0.08, 0.01)	-0.05 (-0.09, -0.01)
	0	0.03 (-0.02, 0.07)	0.01 (-0.03, 0.06)	0 (-0.04, 0.04)	-0.01 (-0.05, 0.03)	-0.02 (-0.07, 0.02)	-0.04 (-0.08, 0)
	0.2	0.04 (-0.01, 0.08)	0.02 (-0.02, 0.07)	0.01 (-0.03, 0.05)	0 (-0.04, 0.04)	-0.01 (-0.05, 0.03)	-0.03 (-0.07, 0.02)

Cell contents are estimated difference (90% confidence interval). Grey cells indicate where the resulting confidence interval did not rule out the pre-specified margin.
[1] Assumed difference of ACR20 response at Week 24 between completers and dropouts on US-Humira. Response in US-Humira completers was 0.78.
[2] Assumed difference of ACR20 response at Week 24 between completers and dropouts on FKB327. Response in FKB327 completers was 0.76.
Source: Statistical Reviewer

The tipping point analysis performed by the sponsor showed similar results and indicated that missing data did not impact the conclusion that FKB327 has similar efficacy to US-Humira.

Analysis of Secondary Clinical Endpoints

Analyses of the secondary endpoints also showed similar efficacy between FKB327 and US-Humira. An important secondary endpoint in the study defined by the Applicant was DAS28-CRP at Week 24. Other secondary endpoints considered include ACR20 response over time, ACR50 and ACR70 response rate at Week 24, DAS28-ESR at Week 24, TJC, SJC, CRP, VAS and HAQ-DI scores.

DAS28-CRP scores at Week 24 were similar in the FKB327 and US-Humira treatment (3.43 and 3.42 respectively) with a treatment difference of 0.01 with 95% CI for the difference of (-0.16, 0.18), as shown in Table 32. These analyses, based on MMRM, were repeated using an ANCOVA approach with consistent results.

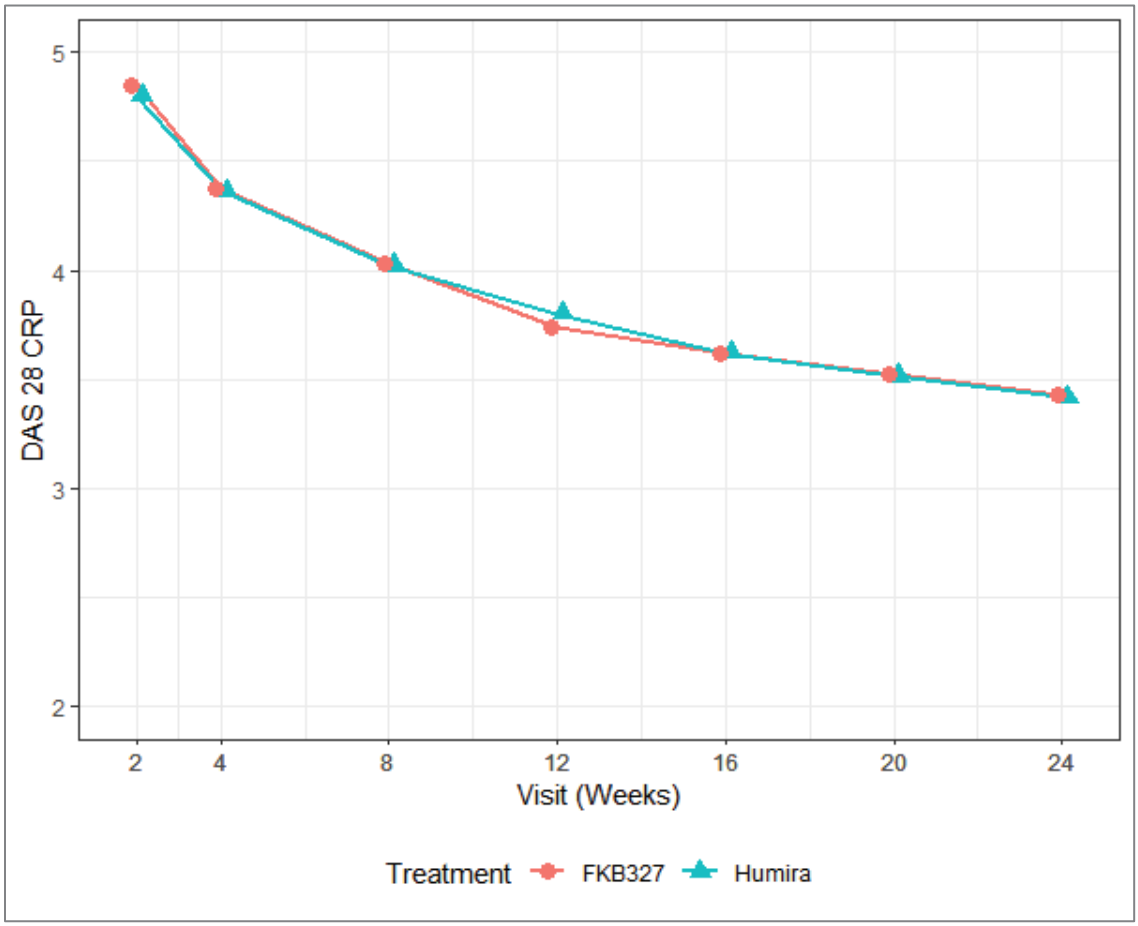
Table 32: Analysis of the DAS28-CRP at Week 24 in Study FKB327-002

Treatment	n/N	Least Square Mean (LSM)	LSM Difference	95% CI	90% CI
FKB327	340/363	3.43	0.01	(-0.16, 0.18)	(-0.13, 0.15)
US-Humira	339/358	3.42			
Total	679/721	73.4			

ACR=American College of Rheumatology; CI=confidence interval; FAS=Full Analysis Set; N= Total number of patients in the analysis population; n= total number of patients with an observation at Week 24, RA=rheumatoid arthritis.
Source: Statistical Reviewer

DAS28-CRP scores declined over time during the study period, trending towards improvement, (Figure 10) and found to be similar across treatment groups. However, US-Humira group showed a slightly higher DAS28-CRP response compared to FKB327.

Figure 10: DAS28-CRP Score (LS Means) over Time

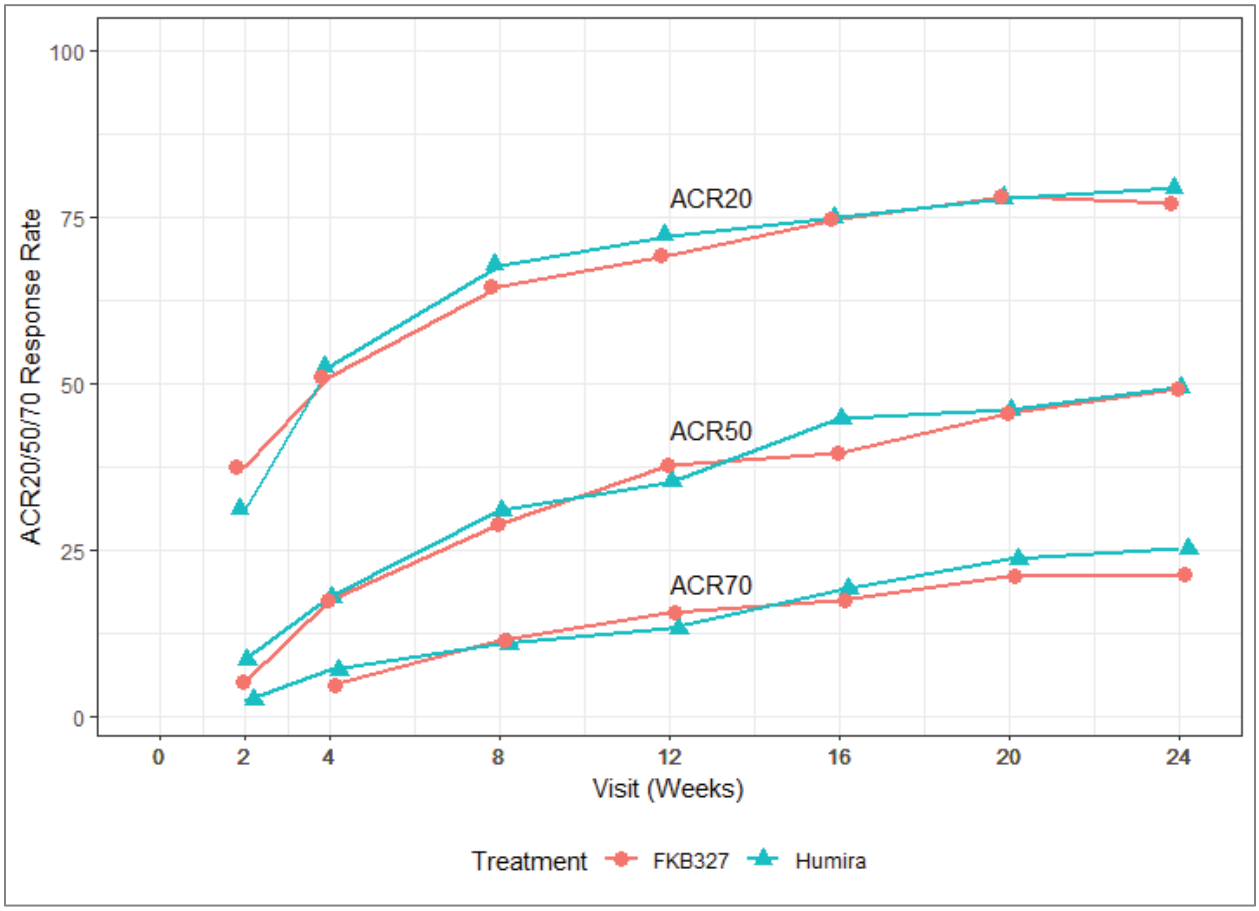


Source: Statistical Reviewer

ACR50 and ACR70 Response Rates

The proportion of ACR responders increased over time in both of the two treatment arms and the trend was largely similar between FKB327 and US-Humira treatment groups. At Week 24, patients in the US-Humira group showed a slightly higher response rate compared to FKB327 patients. However, such a difference was not observed in the ACR50 endpoint.

Figure 11: ACR20/50/70 response rate over Time



Source: Statistical Reviewer

Assay Sensitivity and the Constancy Assumption

To reliably evaluate whether the experimental treatment retains a certain proportion of the effect of the reference product versus placebo, the constancy assumption must be reasonable, i.e., that estimates of the effect of the reference product from historical, placebo-controlled studies used to calculate the similarity margins reflect those of the current comparative clinical study.

The design and patient population of FKB327-002 are largely similar to the historical randomized, double-blind, parallel-group, placebo-controlled clinical studies used to define the

similarity margins (Table 33). All three studies evaluated the impacts of treatment in TNF inhibitor naïve patients with active RA despite treatment with methotrexate, who were at least 18 years of age, manifested RA with at least six swollen and tender joint counts the time of enrollment, and received treatment as an add-on to a stable dose of methotrexate.

Table 33: Key Characteristics of Study SB4-G31-RA and Two Historical Randomized, Placebo-Controlled Clinical Studies of Adalimumab in RA

	Keystone, et al., 2004	Weinblatt, et al., 2003	Kim, et al., 2007	Chen, et al., 2009	Study FKB327-002
Selected inclusion/ exclusion criteria	SJ≥6, TJ≥9, CRP >1 mg/dL, RF+, ≥1 joint erosion	SJ≥6, TJ≥9	SJ≥6, TJ≥9	SJ≥6, TJ≥9	SJ≥6, TJ≥6
Anti-TNF allowed?	No	No	No	No	No
Concomitant DMARDs	Stable MTX, corticosteroids, NSAIDs	Stable MTX, corticosteroids, NSAIDs	Stable MTX	Stable MTX	Stable MTX, Oral Steroids, NSAIDs
Region/ Country	US & Canada	US & Canada	Korea	Taiwan	Europe, US, Canada, South America
Baseline characteristics	SJ: 19; TJ: 27; dur: 11 yrs; HAQ: 1.5	SJ: 17; TJ: 28; dur: 12 yrs; HAQ: 1.6	SJ: 12; TJ: 19; dur: 6 yrs; HAQ: 1.4	SJ: 22; TJ: 33; dur: 6 yrs; HAQ: 1.7	SJ: 16; TJ: 26; HAQ: 1.8
Time of ACR20 Evaluation	Week 24	Week 24	Week 24	Week 12	Week 24
ACR20 response on adalimumab	63%	67%	62%	54%	73%
Withdrawal Rates	22% (Week 52)	7% (Week 16)	9%	NA	10%

Source: Statistical Reviewer

Completion rates were similar in the historic and current study. Keystone, et al., showed a higher withdrawal rate of 22% and the data is not available in Chen, et. al. Withdrawal rates of the remaining studies were comparable with that from FKB327-002, in which 90% of the patients enrolled in the study completed at Week 24.

However, ACR20 outcomes on study FKB327-002 were higher in compared to other historical studies. At Week 24, the ACR20 response rate for the adalimumab group was 73% in FKB327-002 and around 54-65% in other 24 Week studies. However, we note that in biosimilar studies, subjects are aware that they are receiving active treatment (i.e., either FKB327 or US-Humira).

This information may explain the increased response rate in comparison to the historical, placebo-controlled studies.

In summary, the important aspects of the historical and current studies, including key inclusion criteria, prior medications, add-on medications, baseline disease severity, and dropout rates were largely similar and support the assumption of constancy.
In addition to the constancy assumption, to reliably evaluate whether there are clinically meaningful differences between two products, a comparative clinical study must also have assay sensitivity, or the ability to detect meaningful differences if such differences exist. The absence of a placebo arm in the present active-controlled study makes it difficult to determine whether the assumptions of assay sensitivity and constancy have been met. As discussed in the ICH E10 guidelines and in the literature, historical evidence of sensitivity to drug effects and appropriate study conduct may be used to support the presence of assay sensitivity and a conclusion that the treatments are similarly effective.

The withdrawal rates were low (10%) in study FKB327-002 which argues in favor of proper study conduct. Furthermore, the majority of subjects continued with collection of data regardless of treatment adherence, as specified in the study protocol.

The Applicant planned to enroll an adequate number of patients in study FKB327-002 to rule out clinically meaningful differences between two treatments with sufficient power (88%). In addition to the originally planned sample size, 50 more patients were enrolled in the study, which provided increased power to detect the treatment difference. Although there was a slightly higher enrollment rate in one month in the last phase of the study, its impact on the efficacy results was found to be minimal. Randomized treatment allocation of patients in to the two groups minimized bias and provided an assurance of comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease.

In summary, the design, conduct, and within-group responses rates of study FKB327-002 strongly support its assay sensitivity.

Subgroup analyses

The subgroup analyses compared efficacy results across treatment arms within different subgroups defined by sex, region, age, race and BMI values. The analyses were conducted on the SAS, which included all randomized patients who received at least one dose of randomized treatment. The results given below (Figure 12) shows that estimated differences between subgroups were largely centered around similarity, and there were no striking trends between FKB327 and US-Humira. However, patients in the US-Humira group showed greater improvement compared to FKB327 group in the older age category (>=65 years).

Analysis showed that the confidence interval of some subgroups (North America, >=65 years of age, “other” race, etc) exceeded the similarity margin. However, the size of those subgroups

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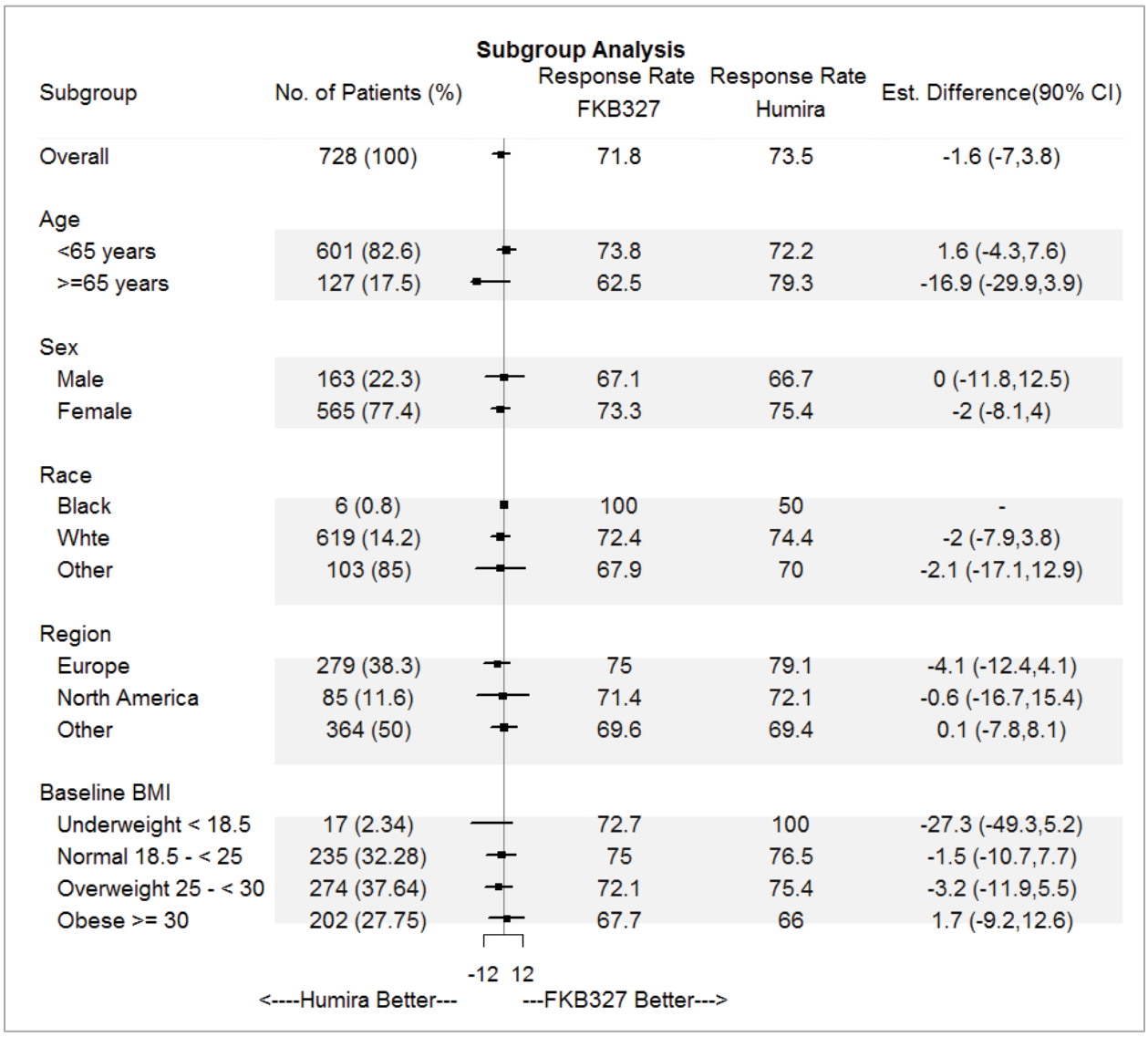
was found to be small, which may have resulted in wider confidence intervals. As such, we do not feel these subgroup analyses preclude a conclusion of no clinically meaningful differences.

Figure 12: Estimated differences between FKB327 and US-Humira in ACR20 response at Week 24, stratified by selected subgroups, in study FKB327-002.



CI=confidence interval
Source: Statistical Reviewer

Statistical Issues

During this statistical review, we identified the following important issues:

- *Primary analysis population*

Efficacy analyses were performed using the FAS, which was defined as the set of patients who received at least one dose of the randomized treatment and who had at least one evaluable primary efficacy measurement after their first dose of randomized treatment. In particular, 9 patients (1%) were excluded from the FAS, either because they did not receive study drug or because they did not have a primary efficacy measurement after the first study drug dose. We do not agree with this approach as it conditions on a post-randomization variable. However, independent analyses of the primary endpoint in all randomized patients showed consistent results.

- *Margin selection and evidence of similarity*
  The applicant's original proposal was to conduct the primary analysis with similarity margins of (b) (4) evaluated at the two-sided 95% level of confidence. Following the advice given by FDA , the Applicant amended the protocol and proposed a revised margin of (-12%, +15%) with some justification on the relaxed upper bound. However, this wider upper bound is not a concern because the primary analysis successfully ruled out the ±12% margin, initially recommended by FDA.

- *Potential effect of missing data on the reliability of efficacy results*
  As discussed in detail above, there was some missing data in this study: Up to Week 24, 69 (10%) patients had withdrawn from the study: 34 (9%) patients from FKB327 and 35 (10%) patients from US-Humira treatment group. Tipping point sensitivity analyses, however, largely supported the findings of similarity between FKB327 and US-Humira.

- *Assay sensitivity and the constancy assumption*
  As discussed in detail, it is critical that a comparative clinical study have assay sensitivity, the ability to detect any meaningful differences between products and that constancy assumption holds. ACR20 outcome on study FKB327-002 was found to be higher compared to other historical studies. At Week 24, the ACR20 response rate for the adalimumab group was 73% in FKB327-002 and around 65% in other 24 Week studies. However, it was found that biosimilar studies often have higher rates because subjects know they are getting new, potentially effective treatment. Therefore, the totality of available information largely supports constancy as well as sufficient assay sensitivity in the current evaluation of similarity.

- *Higher ACR20 response rate in US-Humira group in older patients*
  Subgroup analyses showed that greater improvement in ACR20 response rate for US-Humira patients compared to FKB327 patients in the older age category (63 vs. 79). Considering the smaller sample size in the subgroup, it is difficult to draw conclusions on whether this difference in the ACR20 response rate indicates a true difference in the overall population.

Collective Evidence

The collective evidence from this comparative clinical study in rheumatoid arthritis supports the conclusion of no clinically meaningful differences between FKB327 and US-Humira. The adjusted treatment difference in ACR20 response rates between the FKB327 and US-Humira treatment groups in the FAS population was -1.8 with a 90% CI of (-7.3%, 3.6%), which was contained within the similarity margin of [−12%, +15%] recommended by FDA. Furthermore, ACR20, ACR50, and ACR70 responses over time, mean changes from baseline in the components of the ACR composite endpoint and the disease activity score (DAS28), and other secondary efficacy endpoint results, showed no obvious differences between FKB327 and US-Humira. There was some missing data in important analyses, but tipping point analyses largely supported the finding of similarity. In addition, the totality of available information largely supports the assay sensitivity of study FKB327-002 as well as the constancy assumption.

7.3.3. Study FKB327-003

FKB327-003 was an open-label extension study to compare the long-term efficacy, safety, immunogenicity, and pharmacokinetics of FKB327 and US-Humira in patients with RA.

Study Design and Endpoints

Participants who completed Study FKB327-002 were invited to participate in Study FKB327-003. A maximum of 4 weeks was allowed to elapse between the two studies, with an ideal start of Study FKB327-003 at the final visit (Week 24) of Study FKB327-002.

Of the patients that completed Study FKB327-002, 645 elected to enroll in the OLE study. This study was conducted in two periods. In Period I, patients were randomized to 40 mg every other week of US-Humira or FKB327 from Week 0 to Week 28. Patients who had received FKB327 in Study FKB327-002 received FKB327 or US-Humira in a 2:1 ratio; patients who received US-Humira in Study FKB327-002 received US-Humira or FKB327 in a 2:1 ratio. As such, some patients continued on therapy from FKB327-002 or were switched to the other therapy under investigation, yielding four different exposures (FKB327-Humira, denoted F-H; FKB327-FKB327, denoted F-F; Humira-Humira, denoted H-H; and Humira-FKB327, denoted H-F; Figure 8). Period II, which enrolled 572 patients, consisted of a single, open-label FKB327 treatment arm, also yielding four different exposures (F-F-F, F-H-F, H-F-F, and H-H-F). Period II was considered to be from Week 30 to Week 79, followed by a 4-week Follow-up period (Figure 8).

There was no primary efficacy endpoint for this study. The primary objective of the study was to compare the safety of long-term treatment with FKB327 and US-Humira in patients with RA.

Study location: This was a multi-national study. Patients were enrolled from 92 sites across 11 countries. The proportion of patients recruited in each region was similar for the FKB327 and US-Humira treatment groups as outlined in Table 34.

Study subjects: Participants completed all 24 weeks of study procedures and received a minimum of 9 doses of drug during Study FKB327-002. In order to be eligible for participation in Study FKB327-003, the patient had to have shown a clinical response to treatment during Study FKB327-002. Patients with an SAE ongoing from the previous study were excluded, as were patients with active TB and/or untreated latent TB. Presence of a serious, uncontrolled disease was also a reason for exclusion. Patients that required antibiotic treatment in the two weeks prior to Week 0 dosing were also excluded.

Study treatment: Patients received study medications in an open-label fashion in Study FKB327-003. Patients received 40 mg FKB327 or US-Humira every other week via PFS during Period 1. From Week 30 (Period II), patients received FKB327 via AI, with the exception of participants in the US who continued to receive study medication via PFS.

Concomitant medications: Permitted medications were the same as Study FKB327-002, with the following exceptions:

- Corticosteroid: ≤10 mg/day prednisone or equivalent was permitted. An increase in oral steroid dose was permitted to treat a concomitant condition, but the dose was to be tapered back down to a stable dose as soon as medically viable. Dose may also be increased in the setting of RA flare, though attempts to taper dose down were encouraged. A short course of steroids was also possible in patients who had not previously been taking them if an RA flare occurred. Inhaled and topical steroids were permitted. Intra-articular steroids were permitted, though repeated injections were considered lack of efficacy and a consideration for participant withdrawal. Injected joints were excluded from joint counts.
- NSAIDs: Oral NSAID up to the maximum approved dose were permitted. An increase in dose was permitted, though attempts to taper were encouraged. Topical NSAIDs were also permitted. Analgesics up to the maximum approved dose were permitted during the study but were not to be taken 24 hours prior to efficacy evaluations.
- Anti-mycobacterial treatment: Patients with latent TB upon completion of Study FKB327-002 were to be given treatment.

Subject Disposition

Following completion of Study FKB327-002, 645 patients were enrolled and randomized to treatment.

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Table 34: Disposition of Patients, Study FKB327-003, Period 1

	F-F-F n (%)	F-H-F n (%)	H-F-F n (%)	H-H-F n (%)	Total n (%)
Patients enrolled in the study, N	-	-	-	-	645
Patients randomized to treatment	216 (100%)	108 (100%)	108 (100%)	213 (100%)	645 (100%)
Patients with study drug administered	216 (100.0)	108 (100.0)	108 (100.0)	213 (100.0)	645 (100.0)
Patients completed the study	174 (80.6)	88 (81.5)	81 (75.0)	172 (80.8)	515 (79.8)
Period I:	**F-F**	**F-H**	**H-F**	**H-H**	
Patients completed Period I	189 (87.5)	100 (92.6)	93 (86.1)	190 (89.2)	572 (88.7)
Patients discontinued from Period I	27 (12.5)	8 (7.4)	15 (13.9)	23 (10.8)	73 (11.3)
Primary reason for premature discontinuation[a]					
Adverse event	8 (29.6)	0	3 (20.0)	7 (30.4)	18 (24.7)
Medical reason	1 (3.7)	1 (12.5)	0	1 (4.3)	3 (4.1)
Screen failure[b]	1 (3.7)	0	1 (6.7)	0	2 (2.7)
Withdrawal of consent	9 (33.3)	1 (12.5)	3 (20.0)	4 (17.4)	17 (23.3)
Other[C]	8 (29.6)	6 (75.0)	8 (53.3)	11 (47.8)	33 (45.2)
Period II:	**F-F-F**	**F-H-F**	**H-F-F**	**H-H-F**	
Patients entered Period II[d]	189 (100.0)	100 (100.0)	93 (100.0)	190 (100.0)	572 (100.0)
Patients who started the AI[d]	165 (87.3)	91 (91.0)	83 (89.2)	168 (88.4)	507 (88.6)
Patients completed Period II[d]	174 (92.1)	88 (88.0)	81 (87.1)	172 (90.5)	515 (90.0)
Patients discontinued from Period II[d]	15 (7.9)	12 (12.0)	12 (12.9)	18 (9.5)	57 (10.0)
Primary reason for premature discontinuation[a]					
Adverse event	3 (20.0)	5 (41.7)	4 (33.3)	11 (61.1)	23 (40.4)
Medical reason	0	1 (8.3)	0	0	1 (1.8)
Pregnancy	0	0	1 (8.3)	0	1 (1.8)
Withdrawal of consent	7 (46.7)	4 (33.3)	0	3 (16.7)	14 (24.6)
Other[c]	5 (33.3)	2 (16.7)	7 (58.3)	4 (22.2)	18 (31.6)

Source: FDA reviewer; Table 10-3, FKB327-003 Report Body, page 68
AI=auto-injector; F=FKB327; H=US-Humira; n=total number of patients with observation.
Percentages based on the number of randomized patients, unless otherwise specified.
[a]Percentages for discontinuation reasons based on the number of patients who discontinued from the study during that period.
[b]Patients were identified as ineligible after starting study drug administration.
[c]The category 'other' encompassed several different causes of patient discontinuation, the most common being non-compliance with study visits, positive or indeterminate QuantiFERON™ tests and study drug being interrupted for >4 weeks.
[d]Percentages based on the number of patients who started Period II.

Demographics and Baseline Characteristics

FKB327-003 was an OLE study and therefore the demographic characteristics of participants closely mirrors those of FKB327-002. In Period I, participants were on average 53 years old, and were mostly female and white (Table 34). Participants in both treatment groups had similar baseline disease characteristics (Table 35). These demographic and disease characteristics mirror those in Period II.

Table 35: Demographics Characteristics, Study FKB327-003, Period I (Safety Analysis Set)

Demographic	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Totals N=645
Age (years)					
mean (SD)	52.7 (12.4)	52.1 (11.4)	52.3 (11.9)	54 (12.6)	53 (12.2)
range	18, 85	24, 77	23, 82	21, 93	18, 93
Sex – n, %					
Female	162 (75%)	85 (79%)	83 (77%)	171 (80%)	501 (78%)
Male	54 (25%)	23 (21%)	25 (23%)	42 (20%)	144 (22%)
Race – n, %					
White	187 (87%)	90 (83%)	90 (83%)	185 (87%)	552 (86%)
Other	26 (12%)	17 (16%)	15 (14%)	25 (12%)	83 (13%)
Black or African American	1 (1%)	1 (1%)	2 (2%)	2 (1%)	6 (1%)
American Indian or Alaska Native	1 (1%)	0 (0%)	0 (0%)	1 (1%)	2 (0.3%)
Asian	1 (1%)	0 (0%)	1 (1%)	0 (0%)	2 (0.3%)
Region – n, %					
Rest of World	111 (51%)	56 (52%)	54 (50%)	106 (50%)	327 (51%)
Europe	80 (37%)	40 (37%)	41 (38%)	81 (38%)	242 (38%)
North America	25 (12%)	12 (11%)	13 (12%)	26 (12%)	76 (12%)
Height at Baseline (cm)					
mean (SD)	164.2 (10.3)	163.3 (9.2)	163.7 (8.4)	162.3 (9.1)	163.3 (9.4)
range	141, 193	141, 189	144, 180	144, 192	141, 193
Weight at Baseline (kg)					
mean (SD)	74.3 (16)	74.9 (15.9)	75.4 (16.6)	74.3 (15.4)	74.6 (15.9)
range	41.3, 116.3	42.5, 122.7	44, 115.5	41, 122.2	41, 122.7

N=Total number of patients in the safety population; n=total number of patients with observation; SD=standard deviation
Source: Generated by FDA reviewer

Table 36: Rheumatoid Arthritis Disease Characteristics, Study FKB327-003, Period I (Safety Analysis Set)

Patient Characteristic	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Totals N=645
Rheumatoid factor status, n (%)					
Positive	164 (76%)	82 (76%)	85 (79%)	159 (75%)	490 (76%)
Negative	52 (24%)	25 (23%)	23 (21%)	52 (24%)	152 (24%)
Missing	0 (0%)	1 (1%)	0 (0%)	2 (1%)	3 (0%)
Serum MMP-3 concentration (ng/mL)					
n	213	108	105	207	633
Mean (SD)	42.8 (43.6)	42.9 (51)	44.1 (38.2)	37.1 (37.3)	41.2 (42.2)
Range	4, 281	6, 330	4.3, 176	4, 288	4, 330
Anti-CCP antibody concentration					
n	168	90	84	168	510
Mean (SD)	1842.7 (3781.2)	1840.9 (1897.7)	1598.4 (1716)	1732.5 (2175.4)	1765.8 (2713.2)
Range	18, 41728	20, 7648	27, 7488	24, 13888	18, 41728
CRP level (mg/L)					
n	215	108	108	213	644

Mean (SD)	9.7 (13.8)	13.7 (21.4)	12 (19.2)	11.5 (18.8)	11.4 (17.9)
Range	0.9, 92.2	0.9, 105.4	0.9, 117.6	0.9, 165.1	0.9, 165.1
ESR (mm/hr)					
n	216	108	108	213	645
Mean (SD)	21.8 (15.4)	23.5 (17.8)	23.4 (17.9)	24.5 (18.4)	23.3 (17.3)
Range	1, 80	2, 74	0, 85	2, 110	0, 110
Tender joint count (68 joint count)					
n	216	108	108	213	645
Mean (SD)	8.5 (10.6)	8.6 (10.6)	8.7 (9.2)	7.8 (9.6)	8.3 (10)
Range	0, 58	0, 60	0, 48	0, 52	0, 60
Swollen joint count (66 joint count)					
N	216	108	108	213	645
Mean (SD)	3.5 (5.2)	4.3 (7.5)	4.2 (6.1)	3 (4.6)	3.6 (5.6)
Range	0, 38	0, 48	0, 31	0, 37	0, 48
Patient's assessment of disease activity					
n	216	108	108	213	645
Mean (SD)	36.5 (24.3)	33.8 (23.4)	36.1 (22.6)	31.4 (23.2)	34.3 (23.6)
Range	0, 100	1, 90	1, 99	0, 94	0, 100
Physician's assessment of disease activity					
N	216	108	108	212	644
Mean (SD)	21.8 (17.8)	20.3 (16.3)	22.1 (16.5)	20.2 (16)	21 (16.7)
Range	0, 84	0, 67	0, 75	0, 70	0, 84
Patient's assessment of pain					
n	216	108	108	212	644
Mean (SD)	36.1 (24.4)	32.6 (22.5)	35.2 (23.5)	32.3 (23.5)	34.1 (23.6)
Range	0, 99	0, 93	1, 99	0, 93	0, 99
Health Assessment Questionnaire					
n	216	108	108	212	644
Mean (SD)	1.2 (0.7)	1.3 (0.7)	1.3 (0.7)	1.2 (0.7)	1.2 (0.7)
Range	0, 2.6	0, 2.8	0, 2.5	0, 2.8	0, 2.8
DAS28-CRP					
n	215	108	108	213	644
Mean (SD)	3.5 (1.3)	3.5 (1.3)	3.7 (1.4)	3.4 (1.3)	3.5 (1.3)
Range	1.2, 7.3	1.3, 7.4	1.2, 7.2	1.2, 7	1.2, 7.4
DAS28-ESR					
n	216	108	107	213	644
Mean (SD)	3.8 (1.4)	3.8 (1.4)	4 (1.4)	3.8 (1.3)	3.8 (1.4)
Range	0, 7.6	0.7, 7.5	0.5, 7.8	1, 7.1	0, 7.8

Source: FDA Reviewer, Table 10-7, FKB327-003 Report Body, Page 73
N=Number of patients in Safety Analysis Set, n=Number patients in the subgroup
ESR=erythrocyte sedimentation rate; CCP=cyclic citrullinated peptide; CRP=C-reactive protein, DAS=disease activity score, MMP-3=matrix metalloproteinase-3, SD=standard deviation
The rheumatoid factor values are categorized as "negative" if <12 kU/l and "positive if >12 kU/l.

7.3.4. Study FKB327-005

FKB327-005 was a phase I, randomized, open-label, single-dose study to assess the relative bioavailability of a subcutaneous dose of FKB327 when administered using either a PFS, AI, or a vial with disposable syringe in healthy subjects.

Study Design and Endpoints

Given that vial, PFS, and AI presentations were used throughout the phase 3 clinical program, Study FKB327-005 was conducted as a bridging study to show relative bioequivalence. Study FKB327-005 enrolled 195 healthy male and females individuals, age 18 to 64 years. Participants with significant medical history, or a history of adalimumab use, were excluded.

Participants were randomized 1:1:1 to receive 40 mg subcutaneous FKB327 via vial, PFS, or AI presentations. Doses were administered to the anterior abdominal wall or to the thigh, depending on randomization. All doses were administered to participants in a fasted state. Patients were randomized based on weight strata (50-75 kg and >75-100 kg). Subjects were screened within 28 days prior to dosing of Day 1. Participants were domiciled starting on Day -1 until Day 2 (24 hours post-dose). Subjects returned for evaluation on Days 3, 4, 5, 6, 7, 8, 9, 16, 23, 30, 37, 44, 51, and 65.

The prespecified primary PK endpoints were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

Study location: This study was conducted at a single site in London, England.

Study subjects: Participants were healthy males or females who had not previously received adalimumab.

- Participants deems healthy on the basis of medical history, physical examination, ECG, vital signs, and laboratory testing.
- Male volunteers were required to use contraception for 4 months after dosing
- Age 18 to 64 years
- Body weight 50 to 1000 kg and BMI 18 – 30 kg/m^2

Study treatment: Subjects received a single dose of 40 mg FKB327 in a volume of 0.8 mL by subcutaneous injection to either thigh or abdomen. FKB327 was provided in vials, PFS or AI.

Concomitant medications: Participants were not permitted to use any systemic or topical medications, unless it was determined by the Investigator that it would not interfere with study procedures. Immunization with live vaccines was prohibited for 3 months prior to drug administration, as well as 3 months after.

Statistical Methodologies

Reference ID: 4635331

Given that FKB327-005 was a phase 1 study, there were no pre-specified efficacy endpoints. For a discussion of the statistical analysis of the primary PK endpoints, see Section 6.3.

Subject Disposition

One hundred ninety-five participants were randomized and dosed with FKB327 (66 with vial presentation, 63 with PFS, and 66 with AI). All participants completed the study, except for 1 participant that was lost to follow-up.

Demographics and Baseline Characteristics

Volunteers were 38 years old on average, and were mostly male and white. The average participants was 76 kg, 174 cm, and had a BMI of 25 kg/m^2 (Table 36).

Table 37: Demographic Characteristics, Study FKB327-005 (Safety Analysis Set)

Demographic	FKB327 - vial n=66	FKB327 - PFS n=63	FKB327 - AI n=66	Total n=195
Age (years)				
mean (SD)	37.5 (13.6)	40 (12.9)	36.6 (12.5)	38 (13.0)
Range	19, 63	19, 63	19, 63	19, 63
Sex – n, %				
Male	50 (76%)	45 (71%)	50 (76%)	145 (74%)
Female	16 (24%)	18 (29%)	16 (24%)	50 (26%)
Race – n, %				
White	62 (94%)	58 (92%)	53 (80%)	173 (89%)
Black or African American	2 (3%)	1 (2%)	9 (14%)	12 (6%)
Asian	2 (3%)	4 (6%)	3 (5%)	9 (5%)
Other	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Height at Baseline (cm)				
mean (SD)	174.1	172.6	174	173.6
Range	155, 195	154, 192	156, 191	154, 195
Weight at Baseline (kg)				
mean (SD)	76.2	75.3	75.5	75.6
Range	56.7, 95.4	53.7, 96.7	51.2, 99.4	51.2, 99.4
BMI (kg/m^2)				
Mean (SD)	25.2 (3.1)	25.2 (2.6)	24.8 (2.9)	25.1 (2.8)
Range	18.6, 29.7	19.9, 29.9	19.2, 29.9	18.6, 29.9

Source: Generated by FDA reviewer
N= Total number of patients in the safety population; n=total number of observations

7.4. Review of Safety Data

7.4.1. Methods

To characterize safety, adverse events, laboratory examination, vital signs, hypersensitivity, and immunogenicity were reviewed. The primary study used to evaluate safety was the comparative clinical study FKB327-002, as it provided controlled and blinded comparisons between US-Humira and FKB327 in patients with RA for 24 weeks. Additionally, the safety of longer term use of FKB327, as well the safety of switching between products, was assessed in Study FKB327-003. Safety data from Studies FKB327-001 and FKB327-005 were also reviewed as supportive of the primary safety assessment. Two additional single-dose, supplemental studies (FKB327-004 and FKB327-006) in healthy Japanese individuals were also briefly reviewed for completeness, as these were submitted by the Applicant as studies conducted to enable a local product license application.

Clinical Studies Used to Evaluate Safety

The Applicant has submitted safety data from six clinical studies in support of the BLA, as listed in Table 3and summarized below. In all studies, patients received 40 mg of either FKB327 or US-Humira. The primary safety data were derived through the conduct of Studies FKB327-002 and FKB327-003. The remaining four studies are single-dose PK similarity and usability studies and were conducted in healthy volunteers; two of these studies exclusively enrolled Japanese patients. As such, limited safety data for the intended population can be obtained from these four studies.

FKB327-001 was a randomized, double-blind, parallel-group, 3-arm comparative PK study that enrolled healthy volunteers. Sixty subjects were randomized to each arm and received a single-dose of FKB327, US-Humira and EU-Humira.

FKB327-005 was a randomized, open-label, single-dose study to assess the relative bioavailability of a subcutaneous dose of FKB327 when administered using either a PFS (n=63), AI (n=66), or a vial (n=66) with a disposable syringe. It is meant to serve as a bridging study, as all three presentations of FKB327 were used during the clinical development program.

Studies FKB327-004 and 006 were randomized, single blind, active control, parallel group, two arm PK, immunogenicity, and safety studies conducted in healthy Japanese adults to enable local product license application. One hundred thirty patients received FKB327 and 130 patients received US-Humira as a comparator. Safety data from these studies are included for completeness.

The primary safety data were derived through the conduct of Studies FKB327-002 and FKB327-003. These were phase 3 studies that were designed to assess efficacy, safety, immunogenicity and pharmacokinetics of FKB327 compared to US-Humira in patients with RA. Study FKB327-

Reference ID: 4635331

002 was a randomized, double-blind, equivalence trial of 24 weeks that enrolled 730 patients with moderate to severe RA while on methotrexate. In this study, 366 patients received at least one dose of FKB327 and 362 patients received at least one dose of US-Humira. FKB327-003 was a OLE study that was designed to study the long-term use of FKB327, as well as the effect of switching between the two therapies. Of the patients that completed Study FKB327-002, 645 elected to enroll in Period I of the OLE study; 572 patients participated in Period II. The design of the two phase 3 studies represents a possible 100 weeks of exposure for patients who received FKB327 continuously throughout Studies FKB327-002 and FKB327-003. In addition to providing long-term safety data, the OLE study (FKB327-003) also provides information related to the effect of switching between the two therapies in the above mentioned parameters.

Extent of exposure: The safety database includes a total of 751 participants who received at least one dose of FKB327 (385 healthy individuals and 366 patients with RA) and is adequate to support a comparative safety assessment.

- Healthy subjects: 635 participants received a single dose of 40 mg/0.8mL product subcutaneously, with a follow-up visit on Day 65.
    - FKB327 n=385
    - US-Humira n=190
    - EU-Humira n=60
- Patients with RA: 728 patients received at least one dose of 40mg/0.8mL product subcutaneously every other week for up to 100 weeks (Studies FKB327-002 and OLE FKB327-003).
    - FKB327 n=366
    - US-Humira n=362

Median treatment durations were comparable across the treatment groups in StudyFKB327-002 (Table 37). A higher proportion of patients in the US-Humira treatment group received all 12 dose of the study medication (74%), compared to the FKB327 (70%) group. The mean number of doses received was 11.4 and 11.3 for the FKB327 and Humira treatment groups, respectively.

Table 38: Exposure to Study Medications, FKB327-002 (Safety Analysis Set)

	FKB327 N=366	US-Humira N=362	Totals N=728
Patients fully dosed, n (%)			
Baseline	366 (100%)	361 (100%)	727 (100%)
Week 2	358 (98%)	349 (96%)	707 (97%)
Week 4	358 (98%)	345 (95%)	703 (97%)
Week 6	356 (97%)	345 (95%)	701 (96%)
Week 8	348 (95%)	343 (95%)	691 (95%)
Week 10	349 (95%)	347 (96%)	696 (96%)
Week 12	345 (94%)	336 (93%)	681 (94%)

Week 14	344 (94%)	338 (93%)	682 (94%)
Week 16	337 (92%)	331 (91%)	668 (92%)
Week 18	340 (93%)	341 (94%)	681 (94%)
Week 20	338 (92%)	333 (92%)	671 (92%)
Week 22	330 (90%)	334 (92%)	664 (91%)
Number of patients who received all doses (12), n (%)[a]	255 (70%)	269 (74%)	524 (72%)
Number of doses received			
Mean (SD)	11.4 (1.6)	11.3 (1.9)	11.4 (1.8)
Range	1, 12	1, 12	1, 12
Duration of treatment (days)			
Mean (SD)	163.2 (22.3)	162.1 (25.8)	162.6 (24.1)
Range	14, 191	14, 185	14, 191

Source: FDA reviewer; Table 12-1, FKB327-002 Report Body, Page 127
[a]Does not include patients who received their dose of study drug at an unscheduled visit
N= Number of patients in Safety Analysis Set, n= Number patients in this subgroup

Approximately 87% of participants completed Period I and 80% completed Period II in Study FKB327-003 (Table 38). Sixty percent of participants received all doses as scheduled, with 34 out of possible 40 doses being received, on average. Overall, treatment exposure was approximately equivalent between groups.

During Period II, patients enrolled in centers outside of the US were transitioned from PFS to the AI presentation. Of the 572 patients who continued treatment in Period II, 507 where switched to AI from PFS. The remaining 65 patients at US sites continued to receive FKB327 via PFS.

Table 39: Summary of Treatment Compliance, FKB327-003 (Safety Analysis Set)

	F-F-F n=216	F-H-F n=108	H-F-F n=108	H-H-F n=213	Total n=645
Patients fully dosed, n (%)					
Start of Period I					
Week 0	215 (100%)	108 (100%)	108 (100%)	213 (100%)	644 (100%)
Week 2	211 (98%)	105 (97%)	107 (99%)	206 (97%)	629 (98%)
Week 4	208 (96%)	106 (98%)	106 (98%)	206 (97%)	626 (97%)
Week 8	199 (92%)	102 (94%)	103 (95%)	198 (93%)	602 (93%)
Week 12	198 (92%)	102 (94%)	101 (94%)	200 (94%)	601 (93%)
Week 24	193 (89%)	99 (92%)	93 (86%)	193 (91%)	578 (90%)
Week 28	188 (87%)	97 (90%)	91 (84%)	187 (88%)	563 (87%)
Start of Period II					
Week 30	184 (85%)	98 (91%)	92 (85%)	187 (88%)	561 (87%)
Week 32	187 (87%)	97 (90%)	90 (83%)	186 (87%)	560 (87%)
Week 34	184 (85%)	98 (91%)	91 (84%)	188 (88%)	561 (87%)
Week 42	180 (83%)	95 (88%)	90 (83%)	179 (84%)	544 (84%)
Week 54	175 (81%)	93 (86%)	87 (81%)	176 (83%)	531 (82%)
Week 66	174 (81%)	89 (82%)	82 (76%)	172 (81%)	517 (80%)
Week 76	174 (81%)	89 (82%)	81 (75%)	173 (81%)	517 (80%)

Patients who received all doses	135 (63%)	65 (60%)	57 (53%)	132 (62%)	389 (60%)
Patients who received delayed or interrupted dosing	74 (34%)	38 (35%)	43 (40%)	69 (32%)	224 (35%)
Number of doses received					
Mean (SD)	33.8 (10.8)	34.9 (9.3)	33.2 (11)	34.4 (10.1)	34.1 (10.3)
Range	1, 39	2, 39	2, 40	1, 40	1, 40

Source: Generated by FDA reviewer; Table 10-17, FKB327-003 Report Body, page 83
N= Number of patients in Safety Analysis Set, n= Number patients in this subgroup
Percentages relative to the number of participants in safety population

Population Demographics

Trials FKB327-001 and FKB327-005 enrolled healthy subjects. The demographics are presented in Table 23 and Table 36. Studies FKB327-004 and FKB327-006 enrolled healthy Japanese subjects.

The baseline patient demographics for Studies FKB327-002 are shown in Table 26. Participants were mostly female (78%) and white (85%), with an average age of 53 years. Twelve percent of the participants were from North America. Baseline rheumatoid arthritis characteristics are presented in Table 27. The demographic and disease characteristics are similar across the two treatment arms.

Given that Study FBK327-003 is an extension of FBK327-002, the demographics for both Period I and Period II are similar (Table 34). Baseline RA assessments for Study FKB327-003 were assessed at the Week 24 visit of Study FKB327-002, prior to Week 0 dosing for Study FKB327-003. Baseline RA characteristics for Periods I and II were improved compared to those of Study FKB327-002, reflecting the effect of treatment during that study. Baseline characteristics remained similar across treatment groups in Study FKB327-003 (Table 35).

Categorization of Adverse Events

AEs and SAEs were appropriately defined by the Applicant during the course of the FKB327 development program. AEs were monitored from time of Screening or informed consent, until End of Study or Early Termination. In Studies FKB327-001, FKB327-002, FKB327-003, and FKB327-005, AEs were elicited by asking the patient a non-leading questions such as “how are you feeling?” Spontaneously reported AEs were also recorded and documented, as well as significant clinical changes appreciated during clinical assessments. As per the Report Body for Studies FKB327-004 and FKB327-006, “investigators were to establish a sufficient monitoring system for the safety of the subject and appropriateness of the study continuation for the subject.” Throughout the development program, clinically significant changes seen at safety examinations were to be considered AEs, including changes in signs and symptoms, vital signs, EKGs, and clinical laboratory test results.

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In Study FKB327-001, SAEs were followed until resolution, the event was unlikely to resolve, or if the subject was lost to follow-up. In Study FKB327-005, AEs were followed until resolution or could be "clinically explained." AEs were followed until recovery or stabilization for Trials FKB327-004 and FKB327-006.

In Study FKB327-002, AEs were monitored from signing of informed consent until Week 24 (for patients who entered the OLE), Week 26 (for patients that did not enter the OLE), or the Early Termination visit. All AEs were followed until resolution, were no longer a clinical concern, had stabilized or were otherwise explained, or the patient was lost to follow-up. AEs ongoing at the final visit were to be followed for as long as necessary to adequately evaluate the safety of the patient, had stabilized, resolved, or was no longer a clinical concern. AEs ongoing from Study FKB327-002 were considered to be medical history for participants in Study FLB327-003; any new or worsening AE occurring after Study FKB327-003 randomization was considered an AE for that study. AEs were followed until resolution, the investigator confirmed the event was unlikely to resolve, or the patient was lost to follow-up. AEs ongoing at the final visit were followed until resolution, they were no longer a clinical concern, had stabilized, or the patient was lost to follow-up.

Verbatim terms were appropriately converted to preferred terms using MedDRA Version 16.1 (FKB327-001), 17.1 (FKB327-002 & FKB327-003), 18 (FKB327-005), 19 (FKB327-004), and 20.1 (FKB327-006).

The severity of AEs was characterized by investigators as mild (did not interfere with daily routine and did not require intervention), moderate (interfered with some aspect of daily routine, or required intervention, but was not damaging to health), or severe (resulted in alteration, discomfort or disability that was damaging to health) throughout the clinical development program.

Safety Analyses

The Safety Analysis Set for each study was defined as those participants who received at least one dose of study medication. Patient safety data were analyzed according to the treatment actually received.

The safety analyses submitted by the Applicant were from the individual studies and not from pooled studies. The differences in study population and conduct of the studies made pooling of the clinical studies inappropriate.

7.4.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

The safety database submitted for assessment of comparative safety between FKB327 and US-Humira included six clinical studies (four single-dose comparative PK studies and two

comparative clinical studies) as summarized above. Due to differences in clinical study design and study population, no pooled analyses by demographic subgroups were performed. The comparative clinical studies, FKB327-002 and FKB327-003, were conducted in patients with active RA who are representative of the target patient population. The study design was not powered for any subgroup analyses of safety.

Overall AE profile

The phase 3 clinical program provides the main comparative data for the safety review. No new safety signals were identified. During Study FKB327-002, TEAEs were more commonly seen in the US-Humira treatment group (62%) compared to the FKB327 treatment group (56%) (Table 39). SAEs were also more commonly seen in the US-Humira treatment group (5%), compared to those exposed to FKB327 (4%). Patients in the FKB327 treatment group were more likely to discontinue treatment due to an AE, though the reasons for discontinuation were mostly singular events (Table 42).

Table 40: Safety Summary for Study FKB327-002 (Safety Analysis Set)

	FKB327 N=366	US-Humira N=362	Total N=728
Number of subjects with ≥1 TEAE, n (%)	203 (56%)	223 (62%)	426 (59%)
Number of subjects with ≥1 SAE, n (%)	15 (4%)	19 (5%)	34 (5%)
Death, n (%)	1 (0.3%)	0 (0%)	1 (0.1%)
Discontinuation due to AE, n (%)	14 (4%)	10 (3%)	23 (3%)

Source: Generated by FDA reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

Period I of FKB327-003 allows for a safety evaluation of longer term FKB327 therapy compared to US-Humira treatment, as well as the safety of switching between the two products (Table 40). Patients in the F-F treatment group were less commonly found to have an TEAE (44%) compared to those in the H-H treatment group (55%). Rates of SAEs were comparable, though slightly less in the F-F treatment group. Patients in the F-F and H-H treatment groups were equally likely to discontinue study medication due to a TEAE (Table 40). Switching from US-Humira treatment to FKB327 (H-F) did not result in a higher proportion of reported TEAEs compared to patients who continued on US- Humira therapy in Period I from Trial FB327-002 (H-H), though SAEs were more common in the H-F group. Rates of discontinuation due to AEs were comparable between the H-F and H-H treatment groups (Table 40).

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Table 41: Safety Summary for Study FKB327-003, Period I (Safety Analysis Set)

	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Total N=645
Number of subjects with ≥1 TEAE, n (%)	103 (48%)	59 (55%)	59 (55%)	117 (55%)	338 (52%)
Number of subjects with ≥1 SAE, n (%)	5 (2%)	7 (7%)	5 (5%)	7 (3%)	24 (4%)
Death, n (%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	2 (0.3%)
Discontinuation due to AE, n (%)	10 (5%)	0 (0%)	4 (4%)	11 (5%)	25 (4%)

Source: Generated by FDA reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

Comparable rates of TEAEs and SAEs were seen between the treatment groups in Period II (Table 41). The use of longer term FKB327 therapy (F-F-F treatment group) was not associated with an increased risk of TEAEs, SAEs, death or rate of discontinuation compared to the other exposure groups.

Table 42: Safety Summary for Study FKB327-003, Period II (Safety Analysis Set)

	F-F-F N=189	F-H-F N=100	H-F-F N=93	H-H-F N=190	Total N=572
Number of subjects with ≥1 TEAE, n (%)	114 (60%)	61 (61%)	51 (55%)	114 (60%)	340 (59%)
Number of subjects with ≥1 SAE, n (%)	8 (4%)	8 (8%)	6 (7%)	11 (6%)	33 (6%)
Death, n (%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	2 (0.3%)
Discontinuation due to AE, n (%)	4 (2%)	5 (5%)	6 (7%)	10 (5%)	25 (4%)

Source: Generated by FDA reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

When considering individual AEs, some minor numerical differences were observed, However, these differences are likely due to chance alone and do not indicate meaningful differences between FKB327 and US-Humira (see below in Table 47, Table 48, Table 49).

Overall, there were no major differences in deaths, SAEs, TEAEs, AEs leading to discontinuation, between the treatment groups during the phase 3 clinical program. In addition, the safety observed in the single-dose PK studies in healthy subjects further support the comparable safety profile between FKB327 and US-Humira.

Deaths

There were 5 deaths during the clinical development program of FKB327.

Reference ID: 4635331

One patient died during Study FKB327-002:

- A 72-year-old white female (Patient (b) (6)) from Romania receiving FKB327 died from disseminated tuberculosis. This patient had a negative QuantiFERON test at screening, but tested positive at routine screening at Week 22. Pulmonary radiography revealed multiple opacities. She was subsequently hospitalized and diagnosed with pulmonary and peritoneal TB. She was treated with oral isoniazid, ethambutol, and rifampin, but then was transitioned to IV formulations following the development of melena and hematemesis. Within the first week of her hospitalization, this patient developed hepatic and renal insufficiency and subsequently died.

Four patients died during Study FKB327-003:

- Patient (b) (6), a 69-year-old female from Russia, died on Day 202 of Period I. This patient received US-Humira during FKB327-002 and was then randomized to receive FKB327 during Period I of Study FKB327-003. She received 13 doses of FKB327 and was then diagnosed with cervical carcinoma on Day 190. The patient also developed hydronephrosis, acute pyelonephritis, and lymphostasis, all of which were thought to be related to obstruction of the left ureter and lymphatics of the left leg by the tumor. The patient did not return for a scheduled site visit on Day 202, and it was subsequently determined that the patient died suddenly at home on that day, though the exact cause of death was unknown.
- Patient (b) (6), a 62-year old white male from Russia with a past medical history of hypertension and ischemic heart disease, died on Day 89 in Period I from a cerebrovascular accident. This patient received US-Humira during FKB327-002 and was re-randomized to continue US-Humira during Period of Study FKB327-003.
- Patient (b) (6), a 63 year old white female from the Czech Republic, received US-Humira during Study FKB327-002. This patient developed pneumonia during that time but recovered and continued participation in the clinical program. During Period I, she received 14 out of 15 doses of FKB327 and 11 doses in Period II. On Day 384, the patient developed moderate bronchitis, with elevated CRP and leukocytosis on Day 389. A month later, the patient developed phlebothrombosis of the right leg and thrombosis of the left leg. A chest x-ray performed at that time was notable for basal atelectasis. The patient was reportedly started on antibiotics and anticoagulants. On Day 445 in Period II, the patient died of pneumonia and sepsis.
- Patient (b) (6) was a 68-year old white male from Poland with past medical history of coronary artery disease, cardiac extrasystoles, hypercholesterolemia and hypertension. He received US-Humira during FKB327-002, during which time he experienced an AE of cardiac extrasystoles, which resolved. He received 15 out of 15 doses of US-Humira in Period I and 15 doses of FKB327 in Period II. This patient died suddenly at home of unknown causes on Day 407.

Serious Adverse Events (SAEs)

Healthy Volunteers: Three SAEs occurred during the single-dose PK studies that were conducted in healthy volunteers. In Study FKB327-001, 1 participant in the FKB327 treatment group experienced loss of consciousness 11 days after study drug administration. The other SAE, a psychotic event, occurred 8 days after US-Humira administration. A subject in the US-Humira treatment group experienced frontal bone fracture/skull fracture 41 days after dosing in Study FKB327-006. No SAEs occurred during the conduct of Study FKB327-004 and FKB327-005.

Patients with RA: In Study FKB327-002, the number of SAEs were comparable between the FKB327 and US-Humira treatment groups (Table 42). Infectious and infestations were the most common SAEs, with more events seen in the FKB327 treatment group. Of note, however, the events seen were rare, occurring in ≤1% of patients.

Table 43: Treatment-Emergent Serious Adverse Events, FKB327-002 (Safety Analysis Set)

Organ Systems Class Preferred Term	FKB327 N=366	US-Humira N=362	Totals N=728
Number of patients with at least 1 TESAE	**15 (4%)**	**19 (5%)**	**34 (5%)**
Infections and infestations	**10 (3%)**	**5 (1%)**	**15 (2%)**
Pneumonia	3 (1%)	0 (0%)	3 (0.4%)
Pulmonary tuberculosis	0 (0%)	2 (1%)	2 (0.3%)
Disseminated tuberculosis	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cervicitis	1 (0.3%)	0 (0.0%)	1 (0.1%)
Erysipelas	1 (0.3%)	0 (0.0%)	1 (0.1%)
Gangrene	1 (0.3%)	0 (0.0%)	1 (0.1%)
Latent tuberculosis	1 (0.3%)	0 (0.0%)	1 (0.1%)
Bronchopneumonia	1 (0.3%)	0 (0.0%)	1 (0.1%)
Sepsis	1 (0.3%)	0 (0.0%)	1 (0.1%)
Urinary tract infection	1 (0.3%)	0 (0.0%)	1 (0.1%)
Pyelonephritis acute	0 (0%)	1 (0.3%)	1 (0.1%)
Osteomyelitis chronic	0 (0%)	1 (0.3%)	1 (0.1%)
Injury, poisoning and procedural complications	**0 (0%)**	**5 (1%)**	**5 (1%)**
Hip fracture	0 (0%)	2 (1%)	2 (0.3%)
Spinal compression fracture	0 (0%)	1 (0.3%)	1 (0.1%)
Traumatic fracture	0 (0%)	1 (0.3%)	1 (0.1%)
Femoral neck fracture	0 (0%)	1 (0.3%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (1%)**	**3 (1%)**	**5 (1%)**
Squamous cell carcinoma	1 (0.3%)	1 (0.3%)	2 (0.3%)
Lymphoma	0 (0%)	1 (0.3%)	1 (0.1%)
Plasma cell myeloma	1 (0.3%)	0 (0.0%)	1 (0.1%)
Uterine leiomyoma	0 (0%)	1 (0.3%)	1 (0.1%)
Vascular disorders	**1 (0.3%)**	**2 (1%)**	**3 (0.4%)**
Thrombosis	0 (0%)	1 (0.3%)	1 (0.1%)

Thrombophlebitis	1 (0.3%)	0 (0%)	1 (0.1%)
Aortic aneurysm	0 (0%)	1 (0.3%)	1 (0.1%)
Nervous system disorders	**1 (0.3%)**	**1 (0.3%)**	**2 (0.3%)**
Cerebrovascular accident	1 (0.3%)	1 (0.3%)	2 (0.3%)
Renal and urinary disorders	**1 (0.3%)**	**1 (0.3%)**	**2 (0.3%)**
Nephrotic syndrome	1 (0.3%)	0 (0%)	1 (0.1%)
Renal colic	0 (0%)	1 (0.3%)	1 (0.1%)
Immune system disorders	**1 (0.3%)**	**0 (0%)**	**1 (0.1%)**
Amyloidosis	1 (0.3%)	0 (0%)	1 (0.1%)
Skin and subcutaneous tissue disorders	**1 (0.3%)**	**0 (0%)**	**1 (0.1%)**
Lichen sclerosis	1 (0.3%)	0 (0%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	**0 (0%)**	**1 (0.3%)**	**1 (0.1%)**
Lung infiltration	0 (0%)	1 (0.3%)	1 (0.1%)
Hepatobiliary disorders	**0 (0%)**	**1 (0.3%)**	**1 (0.1%)**
Cholelithiasis	0 (0%)	1 (0.3%)	1 (0.1%)
Gastrointestinal disorders	**1 (0.3%)**	**0 (0%)**	**1 (0.1%)**
Anal fistula	1 (0.3%)	0 (0%)	1 (0.1%)

Source: Generated by FDA reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

During Period I of FKB327-003, patients in the F-F treatment group were less likely to experience an SAE (2%), compared to those in the H-H (3%) group. The highest rates of SAEs were in patients that changed treatment (F-H and H-F), though all SAEs were singular by preferred term (Table 43).

Table 44: Treatment-Emergent Serious Adverse Events, Period I, FKB327-003 (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Totals N=645
Number of subjects with ≥1 SAE	**5 (2%)**	**7 (7%)**	**5 (5%)**	**7 (3%)**	**24 (4%)**
Infections and infestations	**2 (1%)**	**3 (3%)**	**1 (1%)**	**2 (1%)**	**8 (1%)**
Pyelonephritis acute	1 (0%)	0 (0%)	1 (1%)	1 (0%)	3 (0%)
Appendicitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Pneumonia	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Pyelonephritis	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Erysipelas	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Pulmonary mycosis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Bronchitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Musculoskeletal and connective tissue disorders	**2 (1%)**	**1 (1%)**	**1 (1%)**	**1 (0%)**	**5 (1%)**
Osteoarthritis	1 (0%)	1 (1%)	0 (0%)	0 (0%)	2 (0%)
Synovitis	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Rotator cuff syndrome	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Spondylolisthesis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Renal and urinary disorders	**1 (0%)**	**0 (0%)**	**1 (1%)**	**1 (0%)**	**3 (0%)**

Hydronephrosis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Renal failure chronic	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Nephrolithiasis	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Surgical and medical procedures	**0 (0%)**	**1 (1%)**	**1 (1%)**	**1 (0%)**	**3 (0%)**
Knee arthroplasty	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Joint surgery	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Hip arthroplasty	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Cardiac disorders	**0 (0%)**	**1 (1%)**	**1 (1%)**	**0 (0%)**	**2 (0%)**
Acute myocardial infarction	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Cardiac failure congestive	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
General disorders and administration site conditions	**0 (0%)**	**1 (1%)**	**1 (1%)**	**0 (0%)**	**2 (0%)**
Pyrexia	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Sudden death	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Hepatobiliary disorders	**1 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**	**2 (0%)**
Cholangitis	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Cholelithiasis	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Injury, poisoning and procedural complications	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**
Tendon rupture	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Nervous system disorders	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**	**1 (0%)**
Cerebrovascular accident	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Reproductive system and breast disorders	**0 (0%)**	**1 (1%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Endometrial hyperplasia	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**
Cervix carcinoma	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Vascular disorders	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**
Lymphostasis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)

Source: Generated by FDA reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

The rate of SAEs were comparable across the four exposure groups in Period II, with all SAEs as singular events, with the exception of pneumonia in the H-F-F exposure group (n=2) (Table 44).

Table 45: Treatment-Emergent Serious Adverse Events, Period II, FKB327-003 (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F-F N=189	F-H-F N=100	H-F-F N=93	H-H-F N=190	Totals N=572
Number of subjects with ≥1 SAE	**8 (4%)**	**8 (8%)**	**6 (7%)**	**11 (6%)**	**33 (6%)**
Infections and infestations	**1 (0%)**	**1 (1%)**	**3 (3%)**	**2 (1%)**	**7 (1%)**
Pneumonia	0 (0%)	1 (1%)	2 (2%)	1 (0%)	4 (1%)
Pyelonephritis acute	0 (0%)	0 (0%)	1 (1%)	1 (0%)	2 (0%)
Sepsis	0 (0%)	0 (0%)	1 (1%)	1 (0%)	2 (0%)
Pyelonephritis	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Bronchitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)

Urinary tract infection	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Meningitis	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Musculoskeletal and connective tissue disorders	**1 (0.5%)**	**3 (3%)**	**1 (1%)**	**2 (1%)**	**7 (1%)**
Back pain	0 (0%)	1 (1%)	0 (0%)	1 (0%)	2 (0%)
Back disorder	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Intervertebral disc degeneration	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Rheumatoid arthritis	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Bursitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Spinal column stenosis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Injury, poisoning and procedural complications	**0 (0%)**	**2 (2%)**	**1 (1%)**	**1 (0%)**	**4 (1%)**
Maternal exposure during pregnancy	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Fracture	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Femur fracture	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Muscle rupture	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Reproductive system and breast disorders	**2 (1%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**	**3 (0%)**
Cervical dysplasia	1 (0%)	0 (0%)	0 (0%)	1 (0%)	2 (0%)
Endometrial hyperplasia	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Respiratory, thoracic and mediastinal disorders	**1 (0%)**	**2 (2%)**	**0 (0%)**	**0 (0%)**	**3 (0%)**
Chronic obstructive pulmonary disease	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Lung disorder	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Pulmonary mass	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Nervous system disorders	**0 (0%)**	**0 (0%)**	**0 (0%)**	**2 (1%)**	**2 (0%)**
Anterior spinal artery syndrome	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Sciatica	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Cardiac disorders	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**	**2 (0%)**
Acute myocardial infarction	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Myocardial infarction	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Angina unstable	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
General disorders and administration site conditions	**0 (0%)**	**0 (0%)**	**1 (1%)**	**1 (0%)**	**2 (0%)**
Death	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Non-cardiac chest pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Hepatobiliary disorders	**0 (0%)**	**1 (1%)**	**1 (1%)**	**0 (0%)**	**2 (0%)**
Hepatocellular injury	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Cholecystitis chronic	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**	**2 (0%)**
Basal cell carcinoma	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Breast cancer	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Surgical and medical procedures	**1 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Synovectomy	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Renal and urinary disorders	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**
Calculus urinary	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)

Pregnancy, puerperium and perinatal conditions	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**
Pregnancy	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Gastrointestinal disorders	**1 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Esophageal rupture	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Metabolism and nutrition disorders	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**	**1 (0%)**
Hyponatremia	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)

Source: Generated by FDA reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

Overall, there were no meaningful difference in the types and frequencies of SAEs between FKB327 and US-Humira during the phase 3 development program. These findings support a similar safety profile between the two products.

Treatment Emergent Adverse Events

Healthy Volunteers: The frequency of TEAEs were comparable across treatment groups in single-dose studies that enrolled healthy volunteers. In Study FKB327-001, 58% of participants experienced at least 1 TEAE, compared to 60% in the US-Humira group (Table 45). The rates of individual AEs were also similar across treatment groups, though injection site hematoma was seen at a notably higher rate in the FKB327 group (7%) compared to US-Humira (3%). In addition, headache, upper respiratory tract infection, toothache, oropharyngeal pain, dysphonia, neutropenia, and tooth repair were seem more commonly in the FKB327-treatment group compared to the US-Humira treatment group. Given that these AEs were following a single dose of FKB327 or US-Humira, their clinical significance is unclear, and are likely not reflective of a clinically meaningful difference between the two products.

Table 46: Treatment-Emergent Adverse Events Reported for ≥2% for Any Treatment Group, FKB327-001 (Safety Analysis Set)

System Organ Class Preferred Term	FKB327 N=60	US-Humira N=60	Totals N=180
Number of subjects with ≥1 TEAE	**35 (58%)**	**36 (60%)**	**110 (61%)**
Nervous system disorders	**13 (22%)**	**11 (18%)**	**35 (19%)**
Headache	12 (20%)	10 (17%)	33 (18%)
Dizziness	0 (0%)	1 (2%)	4 (2%)
Infections and Infestations	**8 (13%)**	**13 (22%)**	**34 (19%)**
Upper respiratory tract infection	5 (8%)	4 (7%)	15 (8%)
Nasopharyngitis	2 (3%)	3 (5%)	7 (4%)
Gastroenteritis	0 (0%)	3 (5%)	5 (3%)
Oral herpes	0 (0%)	0 (0%)	2 (1%)
Gastrointestinal Disorders	**4 (7%)**	**9 (15%)**	**23 (13%)**
Nausea	0 (0%)	1 (2%)	4 (2%)
Toothache	2 (3%)	1 (2%)	3 (2%)
Vomiting	0 (0%)	2 (3%)	2 (1%)
Gastroesophageal reflux disease	0 (0%)	0 (0%)	2 (1%)

Respiratory, Thoracic, and Mediastinal Disorders	**9 (15%)**	**6 (10%)**	**19 (11%)**
Oropharyngeal pain	4 (7%)	3 (5%)	9 (5%)
Nasal congestion	1 (2%)	2 (3%)	4 (2%)
Dysphonia	2 (3%)	0 (0%)	2 (1%)
Musculoskeletal and Connective Tissue Disorders	**4 (7%)**	**6 (10%)**	**18 (10%)**
Back pain	0 (0%)	2 (3%)	5 (3%)
Pain in extremity	1 (2%)	1 (2%)	5 (3%)
Arthralgia	0 (0%)	2 (3%)	2 (1%)
General Disorders and Administration Site Conditions	**8 (13%)**	**5 (8%)**	**16 (9%)**
Injection site hematoma	4 (7%)	2 (3%)	7 (4%)
Injury, Poisoning, and Procedural Complications	**4 (7%)**	**3 (5%)**	**11 (6%)**
Arthropod sting	0 (0%)	2 (3%)	2 (1%)
Skin and Subcutaneous Tissue Disorders	**1 (2%)**	**4 (7%)**	**8 (4%)**
Rash	1 (2%)	2 (3%)	6 (3%)
Investigations	**2 (3%)**	**3 (5%)**	**6 (3%)**
Liver function test abnormal	2 (3%)	3 (5%)	5 (3%)
Blood and Lymphatic Disorders	**4 (7%)**	**2 (3%)**	**6 (3%)**
Neutropenia	3 (5%)	2 (3%)	5 (3%)
Surgical and Medical Procedures	**2 (3%)**	**0 (0%)**	**3 (2%)**
Tooth repair	2 (3%)	0 (0%)	3 (2%)

Source: Generated by FDA reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

The AEs seen in Studies FKB327-004 and FKB327-006 are similar to those seen in Study FKB327-001, and are overall consistent with the known safety profile of adalimumab.

All participants were administered FKB327 in Study FKB327-005, though various presentations (vial, PFS, and AI) were used. While this study does not provide comparative safety data relative to US-Humira, it is consistent with the types of AEs seen in the other single-dose studies, supporting the overall safety of FKB327 (Table 46). While AEs were generally comparable across presentations, it is notable that AEs related to the General Disorders and Administration Site Conditions SOC were more common in the AI treatment group, relative to the vial and PFS presentations.

Table 47: Treatment-Emergent Adverse Events Reported for ≥2% for Any Treatment Group, FKB327-005 (Safety Analysis Set)

Organ Systems Class Preferred Term	FKB327 (vial) N=66	FKB327 (PFS) N=63	FKB327 (AI) N=66	Totals N=180
Infections and infestations	**18 (27%)**	**18 (29%)**	**22 (33%)**	**58 (30%)**
Nasopharyngitis	14 (21%)	15 (24%)	20 (30%)	49 (25%)
Influenza	3 (5%)	0 (0%)	0 (0%)	3 (2%)
Oral herpes	2 (3%)	0 (0%)	0 (0%)	2 (1%)

Respiratory, thoracic and mediastinal disorders	**9 (14%)**	**11 (17%)**	**11 (17%)**	**31 (16%)**
Cough	5 (8%)	1 (2%)	3 (5%)	9 (5%)
Oropharyngeal pain	4 (6%)	3 (5%)	1 (2%)	8 (4%)
Rhinorrhea	1 (2%)	2 (3%)	3 (5%)	6 (3%)
Nasal congestion	0 (0%)	2 (3%)	2 (3%)	4 (2%)
Nervous system disorders	**10 (15%)**	**11 (17%)**	**6 (9%)**	**27 (14%)**
Headache	7 (11%)	9 (14%)	2 (3%)	18 (9%)
Dizziness	1 (2%)	1 (2%)	3 (5%)	5 (3%)
Paresthesia	0 (0%)	2 (3%)	0 (0%)	2 (1%)
General disorders and administration site conditions	**6 (9%)**	**5 (8%)**	**14 (21%)**	**25 (13%)**
Fatigue	2 (3%)	0 (0%)	3 (5%)	5 (3%)
Injection site pain	0 (0%)	1 (2%)	3 (5%)	4 (2%)
Injection site rash	0 (0%)	0 (0%)	4 (6%)	4 (2%)
Injection site bruising	2 (3%)	2 (3%)	0 (0%)	4 (2%)
Vessel puncture site pain	0 (0%)	0 (0%)	3 (5%)	3 (2%)
Vessel puncture site bruise	0 (0%)	0 (0%)	2 (3%)	2 (1%)
Gastrointestinal disorders	**7 (11%)**	**6 (10%)**	**9 (14%)**	**22 (11%)**
Diarrhea	2 (3%)	2 (3%)	2 (3%)	6 (3%)
Abdominal pain upper	1 (2%)	1 (2%)	2 (3%)	4 (2%)
Toothache	2 (3%)	0 (0%)	1 (2%)	3 (2%)
Vomiting	2 (3%)	0 (0%)	1 (2%)	3 (2%)
Nausea	1 (2%)	0 (0%)	2 (3%)	3 (2%)
Abdominal pain	0 (0%)	2 (3%)	0 (0%)	2 (1%)
Musculoskeletal and connective tissue disorders	**6 (9%)**	**5 (8%)**	**8 (12%)**	**19 (10%)**
Back pain	3 (5%)	1 (2%)	2 (3%)	6 (3%)
Pain in extremity	0 (0%)	2 (3%)	2 (3%)	4 (2%)
Arthralgia	2 (3%)	1 (2%)	0 (0%)	3 (2%)
Myalgia	0 (0%)	0 (0%)	2 (3%)	2 (1%)
Injury, poisoning and procedural complications	**2 (3%)**	**4 (6%)**	**5 (8%)**	**11 (6%)**
Laceration	0 (0%)	3 (5%)	3 (5%)	6 (3%)
Skin and subcutaneous tissue disorders	**5 (8%)**	**0 (0%)**	**4 (6%)**	**9 (5%)**
Rash	2 (3%)	0 (0%)	3 (5%)	5 (3%)
Investigations	**2 (3%)**	**0 (0%)**	**3 (5%)**	**5 (3%)**
Aspartate aminotransferase increased	0 (0%)	0 (0%)	2 (3%)	2 (1%)
Metabolism and nutrition disorders	**0 (0%)**	**2 (3%)**	**1 (2%)**	**3 (2%)**
Decreased appetite	0 (0%)	2 (3%)	1 (2%)	3 (2%)

Source: Generated by FDA reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

Patients with RA: The comparative safety of chronic use of FKB327 relative to US-Humira relies on data from Study FKB327-002, where patients with RA were exposed to either product for up to 22 weeks. The rate of AEs seen this study was higher in the US-Humira treatment group

compared to the FKB327 treatment group (Table 47). TEAEs in the Infections and Infestations, Gastrointestinal Disorders, and Musculoskeletal and Nutrition disorders SOCs were the most numerous, with comparative rates between the two treatment groups. The most commonly reported AEs were nasopharyngitis, respiratory tract infection and urinary tract infection, with similar incidence rates across the two treatment groups. AEs seen at a rate of ≥2% and more commonly with FKB327 treatment included urinary tract infection, respiratory tract infection, latent tuberculosis, rheumatoid arthritis, back pain, and hypercholesterolemia. These events are consistent with the safety profile of US-Humira and likely does not represent a clinically meaningful difference between the two products (Table 47).

Table 48: Treatment-Emergent Adverse Events Reported for ≥2% for Any Treatment Group, FKB327-002 (Safety Analysis Set)

Organ Systems Class Preferred Term	FKB327 N=366	US-Humira N=362	Totals N=728
Number of subjects with ≥1 TEAE	**203 (55%)**	**223 (62%)**	**426 (59%)**
Infections and infestations	**106 (29%)**	**108 (30%)**	**214 (29%)**
Nasopharyngitis	26 (7%)	29 (8%)	55 (8%)
Respiratory tract infection[a]	19 (5%)	18 (5%)	31 (4%)
Urinary tract infection	17 (5%)	11 (3%)	28 (4%)
Bronchitis	4 (1%)	14 (4%)	18 (2%)
Pharyngitis	5 (1%)	9 (2%)	14 (2%)
Latent tuberculosis	8 (2%)	4 (1%)	12 (2%)
Gastrointestinal disorders	**34 (9%)**	**41 (11%)**	**75 (10%)**
Diarrhea	11 (3%)	13 (4%)	24 (3%)
Musculoskeletal and connective tissue disorders	**33 (9%)**	**38 (10%)**	**71 (10%)**
Rheumatoid arthritis	12 (3%)	9 (2%)	21 (3%)
Back pain	9 (2%)	5 (1%)	14 (2%)
Metabolism and nutrition disorders	**32 (9%)**	**24 (7%)**	**56 (8%)**
Hypercholesterolemia	15 (4%)	11 (3%)	26 (4%)
Nervous system disorders	**18 (5%)**	**23 (6%)**	**41 (6%)**
Headache	6 (2%)	10 (3%)	16 (2%)
General disorders and administration site conditions	**19 (5%)**	**22 (6%)**	**41 (6%)**
Injection site erythema	5 (1%)	8 (2%)	13 (2%)
Vascular disorders	**17 (5%)**	**17 (5%)**	**34 (5%)**
Hypertension	7 (2%)	14 (4%)	21 (3%)
Blood and lymphatic system disorders	**17 (5%)**	**17 (5%)**	**34 (5%)**
Anemia	9 (2%)	10 (3%)	19 (3%)

Source: Generated by FDA reviewer
[a]"respiratory tract infection" and "upper respiratory tract infection" pooled
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

The design of Study FKB327-003 allows for an assessment of safety that compares continuous treatment to that of switching products. As show in Table 48, the F-F treatment group had the lowest incidence of AEs (48%). Pharyngitis, urinary tract infection, rheumatoid arthritis, and

headache were reported more frequently and at rates >2% in the F-F group compared to the H-H group (Table 48). Overall, these events were relatively rare, and are consistent with the known safety profile of adalimumab, further supporting that there an absence of clinical difference between these two products.

Those that switched from US-Humira to FKB327 (H-F) experienced the same incidence of AEs as that of the treatment group that continued on US-Humira from Study FKB327-002 (H-H) and those that switched from FKB327 in Study FKB327-002 to US-Humira (F-H; 55% in all three groups). While some individual AE preferred terms were seen at higher rates in the H-F group compared to the H-H group, there were all at a rate of ≤2%, with the exception of RA flare (H-F: 5% vs. H-H: 4%) (Table 48). In Period II, rates of AEs were comparable between the four different exposure groups (Table 49). As such, data from Study FKB327-003 does not indicate an increased safety risk when switching between the two products.

Table 49: Treatment-Emergent Adverse Events Reported for ≥2% for Any Treatment Group, Period I, FKB327-003 (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Totals N=645
Number of subjects with ≥1 TEAE	**103 (48%)**	**59 (55%)**	**59 (55%)**	**117 (55%)**	**338 (52%)**
Infections and infestations	**45 (21%)**	**27 (25%)**	**27 (25%)**	**63 (30%)**	**162 (25%)**
Nasopharyngitis	7 (3%)	9 (8%)	6 (6%)	13 (6%)	35 (5%)
Bronchitis	10 (5%)	3 (3%)	2 (2%)	11 (5%)	26 (4%)
Pharyngitis	6 (3%)	3 (3%)	3 (3%)	4 (2%)	16 (2%)
Urinary tract infection	6 (3%)	3 (3%)	3 (3%)	4 (2%)	16 (2%)
Upper respiratory tract infection	3 (1%)	2 (2%)	3 (3%)	7 (3%)	15 (2%)
Latent tuberculosis	3 (1%)	0 (0%)	4 (4%)	4 (2%)	11 (2%)
Sinusitis	3 (1%)	0 (0%)	2 (2%)	1 (1%)	6 (1%)
Cystitis	1 (1%)	2 (2%)	0 (0%)	1 (1%)	4 (1%)
Musculoskeletal and connective tissue disorders	**28 (13%)**	**15 (14%)**	**17 (16%)**	**16 (8%)**	**76 (12%)**
Rheumatoid arthritis	12 (6%)	7 (7%)	5 (5%)	8 (4%)	32 (5%)
Arthralgia	2 (1%)	0 (0%)	3 (3%)	1 (1%)	6 (1%)
Back pain	2 (1%)	1 (1%)	2 (2%)	1 (1%)	6 (1%)
Muscle spasms	1 (1%)	2 (2%)	1 (1%)	0 (0%)	4 (1%)
Osteochondrosis	0 (0%)	2 (2%)	0 (0%)	0 (0%)	2 (0%)
Investigations	**23 (11%)**	**6 (6%)**	**7 (7%)**	**15 (7%)**	**51 (9%)**
Mycobacterium tuberculosis complex test positive	7 (3%)	2 (2%)	2 (2%)	6 (3%)	17 (3%)
Alanine aminotransferase increased	3 (1%)	2 (2%)	0 (0%)	1 (1%)	6 (1%)
Gastrointestinal disorders	**11 (5%)**	**7 (7%)**	**6 (6%)**	**10 (5%)**	**34 (5%)**
Diarrhea	2 (1%)	2 (2%)	0 (0%)	3 (1%)	7 (1%)
Abdominal pain upper	1 (1%)	2 (2%)	0 (0%)	0 (0%)	3 (1%)
Gastritis	0 (0%)	2 (2%)	0 (0%)	0 (0%)	2 (0%)
Injury, poisoning and procedural complications	**11 (5%)**	**5 (5%)**	**6 (6%)**	**7 (3%)**	**29 (4%)**

Contusion	2 (1%)	0 (0%)	2 (2%)	2 (1%)	6 (1%)
Skin and subcutaneous tissue disorders	**7 (3%)**	**6 (6%)**	**4 (4%)**	**11 (5%)**	**28 (4%)**
Erythema	0 (0%)	2 (2%)	0 (0%)	1 (1%)	3 (1%)
Nervous system disorders	**8 (4%)**	**5 (5%)**	**4 (4%)**	**6 (3%)**	**23 (4%)**
Headache	4 (2%)	1 (1%)	1 (1%)	2 (1%)	8 (1%)
Renal and urinary disorders	**7 (3%)**	**3 (3%)**	**6 (6%)**	**6 (3%)**	**22 (3%)**
Nephrolithiasis	3 (1%)	1 (1%)	2 (2%)	1 (1%)	7 (1%)
Hematuria	1 (1%)	0 (0%)	2 (2%)	2 (1%)	5 (1%)
General disorders and administration site conditions	**9 (4%)**	**7 (7%)**	**2 (2%)**	**4 (2%)**	**22 (3%)**
Injection site reaction	1 (1%)	2 (2%)	0 (0%)	0 (0%)	3 (1%)
Metabolism and nutrition disorders	**4 (2%)**	**6 (6%)**	**3 (3%)**	**8 (4%)**	**21 (3%)**
Hypercholesterolemia	3 (1%)	3 (3%)	2 (2%)	3 (1%)	11 (2%)
Blood and lymphatic system disorders	**8 (4%)**	**2 (2%)**	**2 (2%)**	**8 (4%)**	**20 (3%)**
Anemia	3 (1%)	1 (1%)	2 (2%)	3 (1%)	9 (1%)
Vascular disorders	**3 (1%)**	**4 (4%)**	**4 (4%)**	**8 (4%)**	**19 (3%)**
Hypertension	2 (1%)	3 (3%)	3 (3%)	4 (2%)	12 (2%)
Respiratory, thoracic and mediastinal disorders	**5 (2%)**	**5 (5%)**	**4 (4%)**	**3 (1%)**	**17 (3%)**
Rhinorrhea	0 (0%)	2 (2%)	0 (0%)	0 (0%)	2 (0%)
Eye disorders	**2 (1%)**	**3 (3%)**	**2 (2%)**	**1 (1%)**	**8 (1%)**
Blepharitis	0 (0%)	2 (2%)	0 (0%)	0 (0%)	2 (0%)
Reproductive system and breast disorders	**2 (1%)**	**2 (2%)**	**3 (3%)**	**1 (1%)**	**8 (1%)**
Hepatobiliary disorders	2 (1%)	1 (1%)	2 (2%)	3 (1%)	8 (1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0%)**	**0 (0%)**	**4 (4%)**	**3 (1%)**	**7 (1%)**
Uterine leiomyoma	0 (0%)	0 (0%)	2 (3%)	0 (0%)	2 (0%)

Source: Generated by FDA reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation
AEs are counted under the treatment arm and period in which the event started

Table 50: Treatment-Emergent Adverse Events Reported for ≥2% for Any Treatment Group, Period II, FKB327-003 (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F-F N=189	F-H-F N=100	H-F-F N=93	H-H-F N=190	Totals N=572
Number of subjects with ≥1 TEAE	**114 (60%)**	**61 (61%)**	**51 (55%)**	**114 (60%)**	**340 (59%)**
Infections and infestations	**68 (36%)**	**26 (26%)**	**34 (37%)**	**61 (32%)**	**189 (33%)**
Nasopharyngitis	23 (12%)	8 (8%)	11 (12%)	18 (9%)	60 (10%)
Upper respiratory tract infection	14 (7%)	1 (1%)	3 (3%)	6 (3%)	24 (4%)
Urinary tract infection	9 (5%)	3 (3%)	5 (5%)	7 (4%)	24 (4%)
Bronchitis	5 (3%)	3 (3%)	5 (5%)	8 (4%)	21 (4%)
Pharyngitis	5 (3%)	2 (2%)	6 (6%)	4 (2%)	17 (3%)
Latent tuberculosis	3 (2%)	1 (1%)	2 (2%)	4 (2%)	10 (2%)
Pneumonia	0 (0%)	2 (2%)	3 (3%)	1 (1%)	6 (1%)
Sinusitis	1 (1%)	2 (2%)	1 (1%)	2 (1%)	6 (1%)
Gastroenteritis	0 (0%)	2 (2%)	1 (1%)	2 (1%)	5 (1%)

Musculoskeletal and connective tissue disorders	**22 (12%)**	**21 (21%)**	**10 (11%)**	**21 (11%)**	**74 (13%)**
Rheumatoid arthritis	7 (4%)	6 (6%)	4 (4%)	8 (4%)	25 (4%)
Back pain	7 (4%)	2 (2%)	0 (0%)	4 (2%)	13 (2%)
Arthralgia	0 (0%)	3 (3%)	0 (0%)	2 (1%)	5 (1%)
Osteoarthritis	0 (0%)	3 (3%)	1 (1%)	0 (0%)	4 (1%)
Costochondritis	0 (0%)	2 (2%)	0 (0%)	0 (0%)	2 (0%)
Investigations	**11 (6%)**	**11 (11%)**	**6 (7%)**	**13 (7%)**	**41 (7%)**
Alanine aminotransferase increased	5 (3%)	2 (2%)	2 (2%)	1 (1%)	10 (2%)
C-reactive protein increased	0 (0%)	4 (4%)	0 (0%)	4 (2%)	8 (1%)
Aspartate aminotransferase increased	5 (3%)	1 (1%)	0 (0%)	1 (1%)	7 (1%)
Mycobacterium tuberculosis complex test positive	0 (0%)	2 (2%)	0 (0%)	2 (1%)	4 (1%)
Blood creatinine increased	1 (1%)	2 (2%)	0 (0%)	0 (0%)	3 (1%)
Transaminases increased	1 (1%)	0 (0%)	2 (2%)	0 (0%)	3 (1%)
Injury, poisoning and procedural complications	**8 (4%)**	**7 (7%)**	**6 (7%)**	**15 (8%)**	**36 (6%)**
Contusion	1 (1%)	1 (1%)	2 (2%)	2 (1%)	6 (1%)
Nervous system disorders	**11 (6%)**	**8 (8%)**	**2 (2%)**	**11 (6%)**	**32 (6%)**
Headache	7 (4%)	2 (2%)	1 (1%)	8 (4%)	18 (3%)
Sciatica	1 (1%)	3 (3%)	0 (0%)	1 (1%)	5 (1%)
Metabolism and nutrition disorders	**6 (3%)**	**8 (8%)**	**1 (1%)**	**8 (4%)**	**23 (4%)**
Dyslipidemia	3 (2%)	4 (4%)	0 (0%)	1 (1%)	8 (1%)
Gastrointestinal disorders	**8 (4%)**	**1 (1%)**	**3 (3%)**	**9 (5%)**	**21 (4%)**
Nausea	1 (1%)	0 (0%)	2 (2%)	0 (0%)	3 (1%)
Hiatus hernia	0 (0%)	0 (0%)	2 (2%)	0 (0%)	2 (0%)
Blood and lymphatic system disorders	**5 (3%)**	**5 (5%)**	**1 (1%)**	**7 (4%)**	**18 (3%)**
Anemia	1 (1%)	4 (4%)	0 (0%)	6 (3%)	11 (2%)
Vascular disorders	**4 (2%)**	**4 (4%)**	**4 (4%)**	**1 (1%)**	**13 (2%)**
Hypertension	2 (1%)	2 (2%)	3 (3%)	1 (1%)	8 (1%)
Renal and urinary disorders	**1 (1%)**	**2 (2%)**	**2 (2%)**	**2 (1%)**	**7 (1%)**
Hematuria	0 (0%)	2 (2%)	0 (0%)	0 (0%)	2 (0%)
Endocrine disorders	**0 (0%)**	**2 (2%)**	**0 (0%)**	**0 (0%)**	**2 (0%)**
Hypothyroidism	0 (0%)	2 (2%)	0 (0%)	0 (0%)	2 (0%)

Source: Generated by FDA Reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation
AEs are counted under the treatment arm and period in which the event started

Dropouts and/or Discontinuations

Healthy volunteers: There were no discontinuations due to AEs in any of the studies conducted in healthy volunteers.

Patients with RA: Twenty-four participants in Study FKB327-002 discontinued treatment due to an AE (Table 50). Infections and Infestations were the most common cause for discontinuation, with tuberculosis cases being the most numerous within the SOC. This is consistent with the known safety profile of adalimumab products, and is not particularly alarming given that this

study was primarily conducted in parts of the world with a higher prevalence of TB than the US. Rates of discontinuation were overall comparable between the treatment groups.

Table 51: Treatment-Emergent Adverse Events Leading to Discontinuation, Study FKB327-002 (Safety Analysis Set)

Organ Systems Class Preferred Term	FKB327 N=366	US-Humira N=362	Totals N=728
Patients with ≥1 AE leading to treatment discontinuation	**14 (4%)**	**10 (3%)**	**24 (3%)**
Infections and infestations	**5 (1%)**	**5 (1%)**	**10 (1%)**
Latent tuberculosis	2 (1%)	1 (0%)	3 (1%)
Pulmonary tuberculosis	0 (0%)	2 (1%)	2 (0%)
Disseminated tuberculosis	1 (0%)	1 (0%)	2 (0%)
Pneumonia	1 (0%)	0 (0%)	1 (0%)
Sepsis	1 (0%)	0 (0%)	1 (0%)
Ophthalmic herpes simplex	1 (0%)	0 (0%)	1 (0%)
Bronchopneumonia	1 (0%)	0 (0%)	1 (0%)
Osteomyelitis chronic	0 (0%)	1 (0%)	1 (0%)
Investigations	**2 (1%)**	**0 (0%)**	**2 (0%)**
Mycobacterium tuberculosis complex test positive	2 (1%)	0 (0%)	2 (0%)
Vascular disorders	**1 (0%)**	**1 (0%)**	**2 (0%)**
Vasculitis	0 (0%)	1 (0%)	1 (0%)
Raynaud's phenomenon	1 (0%)	0 (0%)	1 (0%)
Skin and subcutaneous tissue disorders	**2 (1%)**	**0 (0%)**	**2 (0%)**
Urticaria	1 (0%)	0 (0%)	1 (0%)
Rash generalized	1 (0%)	0 (0%)	1 (0%)
Injury, poisoning and procedural complications	**0 (0%)**	**2 (1%)**	**2 (0%)**
Hip fracture	0 (0%)	1 (0%)	1 (0%)
Synovial rupture	0 (0%)	1 (0%)	1 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0%)**	**1 (0%)**	**2 (0%)**
Lymphoma	0 (0%)	1 (0%)	1 (0%)
Squamous cell carcinoma	1 (0%)	0 (0%)	1 (0%)
Nervous system disorders	**1 (0%)**	**0 (0%)**	**1 (0%)**
Cerebrovascular accident	1 (0%)	0 (0%)	1 (0%)
Immune system disorders	**1 (0%)**	**0 (0%)**	**1 (0%)**
Drug hypersensitivity	1 (0%)	0 (0%)	1 (0%)
Respiratory, thoracic and mediastinal disorders	**0 (0%)**	**1 (0%)**	**1 (0%)**
Lung infiltration	0 (0%)	1 (0%)	1 (0%)
Gastrointestinal disorders	**1 (0%)**	**0 (0%)**	**1 (0%)**
Anal fistula	1 (0%)	0 (0%)	1 (0%)

Renal and urinary disorders	**1 (0%)**	**0 (0%)**	**1 (0%)**
Nephrotic syndrome	1 (0%)	0 (0%)	1 (0%)

Source: Generated by FDA Reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

Five percent of participants in the F-F and H-H treatment groups in Study FKB327-003 discontinued treatment due to an AE (Table 51). Rates of discontinuation due to AE were similar in patients that continued US-Humira therapy (H-H) compared to those that transitioned from US-Humira to FKB327 (H-F). No patients in the H-F discontinued due to an AE.

Table 52: Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Period I, Study FKB327-003 (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Totals N=645
Patients with ≥1 AE leading to treatment discontinuation	**10 (5%)**	**0 (0%)**	**4 (4%)**	**11 (5%)**	**25 (4%)**
Infections and infestations	**3 (1%)**	**0 (0%)**	**1 (1%)**	**5 (2%)**	**9 (1%)**
Latent tuberculosis	2 (1%)	0 (0%)	0 (0%)	2 (1%)	4 (1%)
Pneumonia	0 (0%)	0 (0%)	1 (1%)	2 (1%)	3 (0%)
Hemophilus infection	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Herpes zoster	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Pneumonia pneumococcal	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Investigations	**3 (1%)**	**0 (0%)**	**0 (0%)**	**3 (1%)**	**6 (1%)**
Mycobacterium tuberculosis complex test positive	2 (1%)	0 (0%)	0 (0%)	3 (1%)	5 (1%)
Weight decreased	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Musculoskeletal and connective tissue disorders	**1 (1%)**	**0 (0%)**	**2 (2%)**	**2 (1%)**	**5 (1%)**
Rheumatoid arthritis	1 (1%)	0 (0%)	0 (0%)	2 (1%)	3 (0%)
Arthralgia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Joint swelling	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Neck pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Nervous system disorders	**0 (0%)**	**0 (0%)**	**1 (1%)**	**1 (0%)**	**2 (0%)**
Paresthesia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Cerebrovascular accident	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Respiratory, thoracic and mediastinal disorders	**1 (1%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**2 (0%)**
Asthma	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Alveolitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Skin and subcutaneous tissue disorders	**1 (1%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Pruritus generalized	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
General disorders and administration site conditions	**1 (1%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Asthenia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Gastrointestinal disorders	**1 (1%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Dyspepsia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Eye disorders	**1 (1%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**

Eye inflammation	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Blood and lymphatic system disorders	**1 (1%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Neutropenia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Psychiatric disorders	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**
Insomnia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)

Source: Generated by FDA Reviewer
N=Number of patients in Safety Analysis Set, n=Number of patients with observation
AEs are counted under the treatment arm and period in which the event started

In Period II, 4% of participants discontinued due to an AE. Those who were continuously exposed to FKB327 (F-F-F) had the lowest rates of discontinuation due to an AE compared to the other exposure groups (Table 52).

Table 53: Treatment-Emergent Adverse Events Leading to Discontinuation, Period II, FKB327-003 (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F-F N=189	F-H-F N=100	H-F-F N=93	H-H-F N=190	Totals N=572
Patients with ≥1 AE leading to treatment discontinuation	**4 (2%)**	**5 (5%)**	**6 (7%)**	**10 (5%)**	**25 (4%)**
Infections and infestations	**2 (1%)**	**0 (0%)**	**4 (4%)**	**5 (3%)**	**11 (2%)**
Herpes zoster	0 (0%)	0 (0%)	0 (0%)	2 (1%)	2 (0%)
Urinary tract infection	0 (0%)	0 (0%)	1 (1%)	1 (1%)	2 (0%)
Pyelonephritis acute	0 (0%)	0 (0%)	1 (1%)	1 (1%)	2 (0%)
Sepsis	0 (0%)	0 (0%)	1 (1%)	1 (1%)	2 (0%)
Gingivitis	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Latent tuberculosis	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Upper respiratory tract infection	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Pneumonia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Nasopharyngitis	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Herpes virus infection	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Pyelonephritis	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Meningitis	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Blood and lymphatic system disorders	**0 (0%)**	**1 (1%)**	**0 (0%)**	**2 (1%)**	**3 (1%)**
Leukopenia	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Lymphadenopathy	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Anemia	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Reproductive system and breast disorders	**1 (0%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**2 (0%)**
Cervical dysplasia	1 (0%)	0 (0%)	0 (0%)	1 (1%)	2 (0%)
Musculoskeletal and connective tissue disorders	**0 (0%)**	**2 (2%)**	**0 (0%)**	**0 (1%)**	**2 (0%)**
Bursitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Rheumatoid arthritis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Injury, poisoning and procedural complications	**0 (0%)**	**1 (1%)**	**1 (1%)**	**0 (0%)**	**2 (0%)**
Muscle rupture	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Maternal exposure during pregnancy	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)

Skin and subcutaneous tissue disorders	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (1%)**	**2 (0%)**
Toxic skin eruption	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Erythema	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**2 (0%)**
Breast cancer	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Basal cell carcinoma	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Gastrointestinal disorders	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**1 (0%)**
Gastric ulcer	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Eye disorders	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**1 (0%)**
Eyelid edema	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Erythema of eyelid	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Pregnancy, puerperium and perinatal conditions	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**
Pregnancy	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Investigations	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**1 (0%)**
Mycobacterium tuberculosis complex test positive	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Metabolism and nutrition disorders	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**1 (0%)**
Hyponatremia	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Hepatobiliary disorders	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**
Cholecystitis chronic	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Vascular disorders	**1 (1%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Thrombophlebitis	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Respiratory, thoracic and mediastinal disorders	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (0%)**
Tonsillar hypertrophy	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)

Source: Generated by FDA reviewer and Table 12-19, FKB327-003 Report Body, page 168
N=Number of patients in Safety Analysis Set, n=Number of patients with observation

Product Specific Safety Concerns

Adverse Events of Special Interest (AESI) for Studies FKB327-002 and FKB327-003 were compiled based on the prescribing information for US-Humira.

Infections and Serious Infections

As shown in Table 47, both treatment groups in Study FKB327-002 showed similar rates of infection overall. Only urinary tract infection, latent tuberculosis, and respiratory tract infection were seen more commonly in the FKB327 treatment group compared to the US-Humira treatment group. While SAEs related to infection were more commonly seen in the FKB327 group compared to the US-Humira group (Table 42), most of the SAE were singular, with the exception of pneumonia (3 FKB327 patients, 0 US-Humira patients), pulmonary TB (0 FKB327 patients, 2 US-Humira patients), and disseminated tuberculosis (1 FKB327 patient, 1 US-Humira patient). These difference likely do not represent clinically meaningful differences between the two products.

The four cases of active tuberculosis in Study FKB327-002 were from Romania, Peru, and the Ukraine. An investigation conducted by the sponsor's medical advisor determined that the higher than expected rate of active tuberculosis infection was likely related to the high incidence of TB in the general population of the countries included in the study. Once the study was unblinded, the incidence of active TB was determined by the sponsor to be 0.61 per 100 patient years in the FKB327 treatment group and 1.87 per 100 patient years in the US-Humira treatment group.

Infections and infestations were reported at a rate of 25% during Period I of Study FKB327-003. The F-F treatment group saw the lowest rate of infections (21%), compared to the other exposure groups. Pharyngitis and urinary tract infections were seen at higher rate in the F-F group compared to the H-H group. Switching between products (F-H or H-F) did not result in increased rates of infection compared to continued therapy with one medication (F-F or H-H; Table 48). Infections that were considered serious were rare, with comparable rates of infection across treatment groups and each preferred term reported at a rate of ≤1% (Table 43). Thirty-three percent of participants in Period II reported infections or infestations. The rate of infection was similar across the exposure groups. Prolonged exposure to FKB327 across both studies FKB327-002 and FKB327-003 did not result in a higher rate of infection compared to other exposures (Table 49). Rates of serious infections were also similar across exposure groups in Period II (Table 44).

Injection Site Reaction to Study Drug

AEs related to injection site reactions were more common in the US-Humira treatment group compared to the FKB327 treatment group in Study FKB327-002 (Table 53). It should be noted, however, that patients received FKB327 from a vial and US-Humira from a pre-filled syringe in this study.

Table 54: AEs Related to Injection Site Reactions, Study FKB327-002 (Safety Analysis Set)

Organ Systems Class Preferred Term	FKB327 N=366	US-Humira N=362	Totals N=728
Patients with ≥1 AE related to injection site reactions	**8 (2%)**	**14 (4%)**	**22 (2%)**
General disorders and administration site conditions	**8 (2%)**	**14 (4%)**	**22 (2%)**
Injection site erythema	5 (1%)	8 (2%)	13 (1%)
Injection site reaction	3 (1%)	5 (1%)	8 (1%)
Injection site pruritus	1 (0%)	1 (0%)	2 (0%)
Administration site rash	0 (0%)	1 (0%)	1 (0%)
Administration site reaction	1 (0%)	0 (0%)	1 (0%)
Injection site swelling	0 (0%)	1 (0%)	1 (0%)

Source: Table 12-12, FKB327-002 Report Body, page 145
N= number of patients in Safety Analysis Set, n=number of patients with observation

During Period I of Study FKB327-003, all patients received FKB327 or US-Humira via PFS. Rates of injection site reactions were highest in the F-H treatment group, though overall the rates were similar across groups (Table 54).

Table 55: AEs Related to Injection Site Reactions, Study FKB327-003, Period I (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Totals N=645
Patients with ≥1 AE related to injection site reaction	**3 (1%)**	**2 (2%)**	**1 (1%)**	**3 (1%)**	**9 (1%)**
General disorders and administration site conditions	**3 (1%)**	**2 (2%)**	**1 (1%)**	**3 (1%)**	**9 (1%)**
Injection site erythema	2 (1%)	0 (0%)	0 (0%)	3 (1%)	5 (1%)
Injection site reaction	1 (1%)	2 (2%)	0 (0%)	0 (0%)	3 (1%)
Injection site laceration	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Injection site edema	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Injection site pruritis	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)

Source: FDA Reviewer
N= number of patients in Safety Analysis Set, n=number of patients with observation

In Period II, patients in the US continued to receive FKB327 via PFS, while the rest of the participants received FKB327 by AI (Table 55).

Table 56: AEs Related to Injection Site Reactions, Study FKB327-003, Period II (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F-F N=189	F-H-F N=100	H-F-F N=93	H-H-F N=190	Totals N=572
Patients with ≥1 AE related to injection site reactions	**3 (2%)**	**2 (2%)**	**1 (1%)**	**1 (1%)**	**7 (1%)**
General disorders and administration site conditions	**3 (2%)**	**2 (2%)**	**1 (1%)**	**1 (1%)**	**7 (1%)**
Injection site erythema	2 (1%)	1 (1%)	1 (1%)	1 (1%)	5 (1%)
Injection site reaction	1 (1%)	1 (1%)	0 (0%)	0 (0%)	2 (0%)

Source: FDA Reviewer
N= number of patients in Safety Analysis Set, n=number of patients with observation

Hypersensitivity Reactions and Anaphylaxis

Data submitted from the Applicant regarding this AESI focused on events that were thought to be related to study treatment. When all events irrespective of causality were assessed, AEs related to hypersensitivity were more commonly reported in the FKB327 group than the US-Humira group (Table 56). There were no events of anaphylaxis and none of the events listed in Table 56 were considered to be a SAE. Hypersensitivity to the study drugs was reported at comparable incidence rates, though events of drug hypersensitivity, rash, and urticaria in the FKB327 treatment group resulted in discontinuation (Table 50).

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Table 57: AEs Related to Hypersensitivity or Anaphylaxis, Study FKB327-002 (Safety Analysis Set)

Organ Systems Class Preferred Term	FKB327 N=366	US-Humira N=362	Totals N=728
Patients with ≥1 AE related to hypersensitivity or anaphylaxis	**33 (9%)**	**26 (7%)**	**59 (8%)**
Skin and subcutaneous tissue disorders	**24 (7%)**	**17 (5%)**	**41 (6%)**
Rash	6 (2%)	4 (1%)	10 (1%)
Eczema	2 (1%)	4 (1%)	6 (1%)
Dermatitis allergic	3 (1%)	2 (1%)	5 (1%)
Urticaria	3 (1%)	1 (0%)	4 (1%)
Pruritus	2 (1%)	2 (1%)	4 (1%)
Rash erythematous	1 (0%)	2 (1%)	3 (0%)
Dermatitis contact	1 (0%)	1 (0%)	2 (0%)
Skin exfoliation	0 (0%)	2 (1%)	2 (0%)
Rash vesicular	0 (0%)	1 (0%)	1 (0%)
Pruritus generalized	1 (0%)	0 (0%)	1 (0%)
Erythema nodosum	1 (0%)	0 (0%)	1 (0%)
Blister	1 (0%)	0 (0%)	1 (0%)
Dermatitis	1 (0%)	0 (0%)	1 (0%)
Rash generalized	1 (0%)	0 (0%)	1 (0%)
Rash maculo-papular	1 (0%)	0 (0%)	1 (0%)
Rash morbilliform	1 (0%)	0 (0%)	1 (0%)
Respiratory, thoracic and mediastinal disorders	**5 (1%)**	**4 (1%)**	**9 (1%)**
Rhinitis allergic	1 (0%)	2 (1%)	3 (0%)
Allergic sinusitis	2 (1%)	0 (0%)	2 (0%)
Asthma	0 (0%)	2 (1%)	2 (0%)
Interstitial lung disease	1 (0%)	0 (0%)	1 (0%)
Allergic bronchitis	1 (0%)	0 (0%)	1 (0%)
Immune system disorders	**2 (1%)**	**3 (1%)**	**5 (1%)**
Drug hypersensitivity	1 (0%)	2 (1%)	3 (0%)
Hypersensitivity	1 (0%)	1 (0%)	2 (0%)
Gastrointestinal disorders	**4 (1%)**	**1 (0%)**	**5 (1%)**
Stomatitis	2 (1%)	1 (0%)	3 (0%)
Mouth ulceration	2 (1%)	0 (0%)	2 (0%)
General disorders and administration site conditions	**1 (0%)**	**1 (0%)**	**2 (0%)**
Face edema	1 (0%)	0 (0%)	1 (0%)
Administration site rash	0 (0%)	1 (0%)	1 (0%)
Investigations	**1 (0%)**	**0 (0%)**	**1 (0%)**
Eosinophil count increased	1 (0%)	0 (0%)	1 (0%)
Eye disorders	**0 (0%)**	**1 (0%)**	**1 (0%)**
Eyelid edema	0 (0%)	1 (0%)	1 (0%)

Source: FDA Reviewer
N= number of patients in Safety Analysis Set, n=number of patients with observation

Anaphylaxis was also not seen during the conduct of Study FKB327-003. During Period I, AEs related to hypersensitivity were most commonly reported in the F-H treatment group. Neither prolonged FKB327 therapy (F-F) nor switching from US-Humira to FKB327 (H-F) were associated with an increased rate of AEs related to hypersensitivity compared to other exposure groups (Table 57).

Table 58: AEs Related to Hypersensitivity or Anaphylaxis, Study FKB327-003, Period I (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Totals N=645
Patients with ≥1 AE related to hypersensitivity or anaphylaxis	**8 (4%)**	**8 (7%)**	**2 (2%)**	**10 (5%)**	**28 (4%)**
Skin and subcutaneous tissue disorders	**5 (2%)**	**6 (6%)**	**0 (0%)**	**8 (4%)**	**19 (3%)**
Rash	3 (1%)	1 (1%)	0 (0%)	0 (0%)	4 (1%)
Erythema	0 (0%)	2 (2%)	0 (0%)	1 (0%)	3 (0%)
Urticaria	0 (0%)	0 (0%)	0 (0%)	2 (1%)	2 (0%)
Pruritus generalized	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Skin erosion	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Dermatitis allergic	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Angioedema	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Dermatitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Dermatitis atopic	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Pruritus	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Eczema nummular	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Rash maculo-papular	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Rash erythematous	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Respiratory, thoracic and mediastinal disorders	**2 (1%)**	**1 (1%)**	**1 (1%)**	**1 (0%)**	**5 (1%)**
Interstitial lung disease	1 (0%)	1 (1%)	0 (0%)	0 (0%)	2 (0%)
Rhinitis allergic	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Alveolitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Asthma	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Immune system disorders	**1 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**2 (0%)**
Drug hypersensitivity	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Seasonal allergy	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Infections and infestations	**0 (0%)**	**1 (1%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Conjunctivitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Investigations	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**	**1 (0%)**
Eosinophil percentage increased	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)

Source: FDA Reviewer
N= number of patients in Safety Analysis Set, n=number of patients with observation

In Period II, rate of AEs related to hypersensitivity was highest in the F-H-F group. Overall, AEs related to hypersensitivity were rare.

Table 59: AEs Related to Hypersensitivity or Anaphylaxis, Study FKB327-003, Period II (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F-F N=189	F-H-F B=100	H-F-F N=93	H-H-F N=190	Totals N=572
Patients with ≥1 AE related to hypersensitivity or anaphylaxis	**4 (2%)**	**6 (6%)**	**1 (1%)**	**8 (4%)**	**19 (3%)**
Skin and subcutaneous tissue disorders	**0 (0%)**	**4 (4%)**	**1 (1%)**	**6 (3%)**	**11 (2%)**
Erythema	0 (0%)	0 (0%)	0 (0%)	3 (2%)	3 (1%)
Dermatitis contact	0 (0%)	1 (1%)	0 (0%)	1 (1%)	2 (0%)

Dermatitis allergic	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Toxic skin eruption	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Dermatitis atopic	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Skin erosion	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Rash	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Rash macular	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Rash erythematous	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Respiratory, thoracic and mediastinal disorders	**3 (2%)**	**1 (1%)**	**0 (0%)**	**0 (0%)**	**4 (1%)**
Bronchial hyperreactivity	1 (1%)	1 (1%)	0 (0%)	0 (0%)	2 (0%)
Asthma	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Rhinitis allergic	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Immune system disorders	**1 (1%)**	**0 (0%)**	**0 (0%)**	**3 (2%)**	**4 (1%)**
Seasonal allergy	1 (1%)	0 (0%)	0 (0%)	1 (1%)	2 (0%)
Hypersensitivity	0 (0%)	0 (0%)	0 (0%)	2 (1%)	2 (0%)
Infections and infestations	**0 (0%)**	**1 (1%)**	**0 (0%)**	**0 (0%)**	**1 (0%)**
Conjunctivitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Eye disorders	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**1 (0%)**
Eyelid edema	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)

Source: FDA Reviewer
N= number of patients in Safety Analysis Set, n=number of patients with observation

Malignancies and Lymphoproliferative Disorders

Malignancies and lymphoproliferative disorders were rare in Study FKB327-002 and were seen at comparable rates between the two treatment groups (Table 59). Of the three patients who reported squamous cell carcinoma, one was *in situ*.

Table 60: AEs Related to Malignancy or Lymphoproliferative Disorder, Study FKB327-002 (Safety Analysis Set)

Organ Systems Class Preferred Term	FKB327 N=366	US-Humira N=362	Totals N=728
Patients with ≥1 AE related to malignancy or lymphoproliferative disorder	**3 (1%)**	**2 (1%)**	**5 (1%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (1%)**	**2 (1%)**	**5 (0%)**
Squamous cell carcinoma of skin[a]	2 (1%)	1 (0%)	3 (0.4%)
Lymphoma	0 (0%)	1 (0%)	1 (0%)
Plasma cell myeloma	1 (0%)	0 (0%)	1 (0%)
Basal cell carcinoma[b]	0 (0%)	1 (0%)	1 (0%)

Source: FDA Reviewer
N= number of patients in Safety Analysis Set, n=number of patients with observation
[a]"Squamous cell carcinoma" (n=2) were located in skin. These events were grouped with "Squamous cell carcinoma of the skin" to make a total of n=3.
[s]Superficial basal cell carcinoma event was erroneously not entered into eCRF

Malignancy or lymphoproliferative disorders were rare in Study FKB327-003, occurring in less than 1% of patients (Table 60 Table 61)

Table 61: AEs Related to Malignancy or Lymphoproliferative Disorder, Study FKB327-003, Period I (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Totals N=645
Number of subjects with ≥1 AE related to malignancy or lymphoproliferative disorder	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Cervix carcinoma	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)

Source: FDA Reviewer
N= number of patients in Safety Analysis Set, n=number of patients with observation

Table 62: AEs Related to Malignancy or Lymphoproliferative Disorder, Study FKB327-003, Period II (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F-F n=189	F-H-F n=100	H-F-F n=93	H-H-F n=190	Totals n=572
Number of subjects with ≥1 AE related to malignancy or lymphoproliferative disorder	**1 (1%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**2 (0%)**
Basal cell carcinoma	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0.2%)
Breast cancer	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)

Source: FDA reviewer

Aplastic Anemia and Pancytopenia
There were no events of aplastic anemia or pancytopenia during the phase 3 development program.

Neutropenia
A 49-year-old white female developed mild neutropenia on Day 62 following exposure to FKB327. Her neutropenia ranged from 1.41 GI/L to 4.27 GI/L during the course of treatment (reference range 1.8 to 8 GI/L). She continued therapy, completed Study FKB327-002, and went on to enroll in the OLE.

In Study FKB327-003, neutropenia was appreciated in 1% of participants, with the F-F exposure group having the highest rate, 2% (Table 62).

Table 63: AEs Related to Neutropenia, StudyFKB327-003, Period I (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F N=216	F-H N=108	H-F N=108	H-H N=213	Totals N=645
Number of subjects with ≥1 AE related to neutropenia	**3 (1%)**	**0 (0%)**	**1 (1%)**	**1 (1%)**	**5 (1%)**
Neutropenia[a]	**3 (1%)**	**0 (0%)**	**1 (1%)**	**1 (1%)**	**5 (1%)**

Source: FDA Reviewer
N= number of patients in Safety Analysis Set, n=number of patients with observation
[a]"Neutropenia" and "neutrophil count decreased" pooled together
Source: FDA Reviewer

Similar rates of neutropenia were seen during Period II (Table 63). Overall, events of neutropenia were rare and do not represent a clinically meaningful difference between FKB327 and US-Humira treatment.

Table 64: AEs Related to Neutropenia, Study FKB327-003, Period II (Safety Analysis Set)

Organ Systems Class Preferred Term	F-F-F n=189	F-H-F n=100	H-F-F n=93	H-H-F n=190	Totals n=572
Number of subjects with ≥1 AE related to neutropenia	**2 (1%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**	**3 (1%)**
Neutropenia[a]	2 (1%)	0 (0%)	0 (0%)	1 (1%)	3 (1%)

Source: FDA Reviewer
N= number of patients in Safety Analysis Set, n=number of patients with observation
[a]"Neutropenia" and "neutrophil count decreased" pooled together

Thrombocytopenia
Thrombocytopenia was seen in two patients during Study FKB327-002. A 49-year old white female exposed to FKB327 was noted to have a platelet count of 87 GI/L at Week 16. At Week 22, her platelet count was 139 and this event was considered to be resolved by study investigators. A 73-year old white male exposed to US-Humira with a baseline platelet count of 149 GI/L was observed to have thrombocytopenia at Week 4 with a platelet count of 104 GI/L. He ultimately discontinued US-Humira therapy due to moderate thrombocytopenia at Week 16.

There were no events of thrombocytopenia during the conduct of Study FKB327-003.

New or Worsening Congestive Heart Failure
Two patients in the FKB327 treatment group were noted to have congestive heart failure during the conduct of Study FKB327-002. During Study FKB327-003, one patient in the F-H treatment group, who then went on to be in the F-H-F treatment group, developed heart failure. Given the rarity of these events, it is likely that there is no clinically significant difference between FKB-327 and US-Humira treatment with regards to the development of heart failure.

Demyelination
There were no events of demyelination during Studies FKB327-002 and FKB327-003.

Lupus-like reaction
There were no events of a lupus-like reaction during Studies FKB327-002 and FKB327-003.

7.4.3. Additional Safety Evaluations

Not applicable.

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7.5. 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 patients with RA (multiple dose up to 100 weeks), and an assessment of the impact of ADA on PK, efficacy and safety. It is concluded that FKB327 was similar to US-Humira in the production of ADA/NAb and their impact on PK, efficacy and safety. Refer to Section 6.4 *Clinical Immunogenicity Studies* for results of the immunogenicity assessments.

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7.6. Extrapolation to Support Licensure of Non-Studied Indications

The collective evidence from the comparative clinical study supports a demonstration of no clinically meaningful differences between FKB327 and US-Humira in the studied indication (RA). In addition to the RA indication, the Applicant is seeking licensure for following 6 indications, for which US-Humira has been previously approved and for which FKB327 has not been directly studied:

1. Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age and older
2. Psoriatic Arthritis (PsA)
3. Ankylosing Spondylitis (AS)
4. Adult Crohn's Disease (CD)
5. Ulcerative Colitis (UC)
6. Plaque Psoriasis (Ps)

The Applicant provided a justification for extrapolation of data and information submitted in the application to support licensure of FKB327 as a biosimilar for each indication for which licensure is sought and for which US-Humira has been previously approved.

First, the Applicant's extensive analytical characterization data support a demonstration that FKB327 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components. In addition, the data support a demonstration there are no clinically meaningful differences between FKB327 and US-licensed Humira in terms of safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in RA.

Further, the additional points considered in the scientific justification for extrapolation of data and information to support licensure of FKB327 for the treatment of JIA in patients 4 years of

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age and older, PsA, AS, adult CD, UC, and PsO, as referenced in Section 7.6.1 and Section 7.6.2, include:

- Similar PK was demonstrated between FKB327 and US-Humira as discussed in the section on Clinical Pharmacology. Importantly, FKB327 was demonstrated to be highly similar to US-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 FKB327 and US-Humira in the indications sought for licensure. Thus, a similar PK profile would be expected between FKB327 and US-Humira in patients across all the indications being sought for licensure.

- In general, immunogenicity of US-Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used[4]. As stated elsewhere in this document, the Agency has concluded that there are sufficient data to support similar immunogenicity between FKB327 and US-Humira with repeat dosing in patients with RA, and between FKB327 and US-Humira, after a single dose in healthy subjects. Accordingly, similar immunogenicity would be expected between FKB327 and US-Humira in patients with JIA, PsA, AS, adult CD, UC, and PsO.

- The Applicant demonstrated that there are no clinically meaningful differences between FKB327 and US-Humira in patients with RA, and between FKB327 and US-Humira following single doses in healthy subjects. Additionally, in controlled clinical studies of US-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 FKB327 and US-Humira, support the conclusion that a similar safety profile would be expected between FKB327 and US-Humira in patients with JIA, PsA, AS, adult CD, UC, and PsO.

- The Applicant addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that FKB327 and US-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.

Therefore, based on the above considerations, DRTM, DDD, and DG review teams have concluded (see also Sections 7.6.1 and 7.6.2) that the Applicant has provided adequate data and information to support licensure of FKB327 for each of the following indications for which US-licensed Humira has been previously licensed and for which Mylan is seeking licensure of FKB327: RA, JIA in patients 4 years and older, PsA, AS, PsO, adult CD, and UC.

[4] FDA-approved US-Humira labeling

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7.6.1. Division of Gastroenterology

Executive Summary: Consistent with the principles of the FDA Guidance - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)[5], 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 FKB327 as a biosimilar, under section 351(k) of the PHS Act, for the inflammatory bowel disease (IBD) indications of adult Crohn's disease and ulcerative colitis (non-studied indications). As previously noted in section 2.2., the Applicant is not seeking an indication for the treatment of pediatric Crohn's disease at this time because US- Humira has unexpired orphan drug exclusivity for this indication. As stated in its May 29, 2020 response to a May 22, 2020 information request, the Applicant is requesting a deferral of the pediatric assessment for pediatric CD (6-17 years of age). US-Humira is not approved for use in pediatric ulcerative colitis. The scientific justifications 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 RA (the studied clinical study population) are also relevant to IBD. The Applicant provided data to support that FKB327 has the same known and potential mechanisms of action as US-Humira, which supports extrapolation to indications not directly studied in the FKB327 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 (RA), 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 inhibitors in 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 mechanisms of action involving the Fc region of the antibody.[6,7] Table 37 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

[5] Guidance for Industry – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
[6] Oikonomopoulos A, et al., Current Drug Targets 2013; 14:1421-32.
[7] Tracey D, et al., Pharmacology & Therapeutics 2008; 117:244–79.

Reference ID: 4635331

antibody, while the other plausible mechanisms of action involve the fragment crystallizable (Fc region) region of the antibody.

Table 65 - 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 [7,7,8]

The biological activities of FKB327 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. TNF-α binding and neutralization, believed to be 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 were found to be similar between FKB327 and US-Humira. These data support the conclusion that FKB327 and US-Humira utilize the same mechanism(s) of action, to the extent such mechanism(s) are known.

Pharmacokinetics (PK): Study FKB327-001 was a randomized, double-blind, parallel group, single dose, PK similarity study conducted in healthy adult male and female subjects. The clinical pharmacology reviewers concluded that the data from study FKB327-001 support a demonstration of PK similarity of FKB327 to US-Humira in healthy subjects (refer to Section 6.0 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 FKB327 is expected to be similar between patients with RA (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

[8] Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

been shown to be higher in patients who developed anti-drug-antibodies (ADA). Immunogenicity considerations are discussed further below.

Immunogenicity: In the FKB327 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (RA and healthy subjects). Immunogenicity was found to be similar when comparing FKB327 and US-Humira in the PK similarity study FKB327-001 in healthy subjects, and between FKB327 and US-Humira in the comparative clinical study FKB327-002 conducted in patients with RA. Specifically, the rates of binding and neutralizing anti-drug antibodies were found to be similar between FKB327 and US-Humira. These results support a demonstration of no clinically meaningful differences between FKB327 and US-Humira. In the open-label extension study FKB327-003, patients who received US-Humira in the preceding study FKB327-002 were re-randomized to either continue on US-Humira or switch to FKB327, while patients randomized to FKB327 were re-randomized to either continue on FKB327 or switch to US-Humira, 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 US-Humira to FKB327. There were no meaningful differences in the rates of binding and neutralizing antidrug antibodies in those subjects that underwent a single transition from US-Humira to FKB327, compared to those that remained on their randomized treatment (US-Humira or FKB327). Therefore, it is reasonable to conclude that immunogenicity in patients with IBD receiving FKB327 would be similar to that observed in patients with IBD receiving US-Humira.

Safety: The safety of FKB327 compared to US-Humira was assessed in comparative clinical studies (FKB327-002 and FKB327-003) conducted in patients with RA, and supported by a single dose, PK similarity study (FKB327-001) conducted in healthy subjects. Safety assessments in the two clinical studies included adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory testing, and immunogenicity assessments. The clinical reviewers of this BLA have concluded that overall the data support a similar safety profile between the FKB327 and US-licensed Humira, and that the frequency of TEAEs, SAEs, and events leading to discontinuation of study drug had no meaningful differences between the treatment arms (refer to Section 7.4 – Review of Safety Data). In addition, as previously noted a single transition from US-Humira to FKB327 was assessed as part of the open-label extension study FKB327-003. No meaningful differences in the incidence of adverse events, including hypersensitivity, were observed in patients with RA that underwent a single transition from US-Humira to FKB327, compared to those that remained on their randomized treatment (FKB327 or US-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 FKB327 has been shown to be similar to that of US-Humira in patients with RA, and given the similar product quality attributes, PK, and immunogenicity, we expect that the safety profile in the IBD population is unlikely to be different from that observed in patients with RA.

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Regulatory Recommendation: DG concludes that sufficient scientific justification was provided to support licensure of FKB327 for the following IBD indications:

- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab products, and
- Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers.

Authors:

Sandhya Apparaju, Ph.D.	Juli Tomaino, M.D.	Jessica Lee, M.D.
Clinical Analyst	Clinical Team Leader	Acting Division Director

7.6.2 Division of Dermatology and Dental

The Division of Dermatology and Dental has concluded that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of this data and information submitted, including clinical data from the studied population (rheumatoid arthritis), to support licensure of FKB327 as a biosimilar, under section 351(k) of the PHS Act, for plaque psoriasis (see section 7.6 – Extrapolation to Support Licensure of Non-Studied Indications). Although the applicant did not conduct a clinical study in plaque psoriasis patients, the Applicant has provided adequate scientific justification to support extrapolation of the data and information submitted, to support licensure under section 351(k) of the PHS Act of FKB327 as a biosimilar for plaque psoriasis (see section 7.6). The proposed adult dosing and the recommended posology of FKB327 is the same as approved for US-Humira in the treatment of moderate to severe chronic plaque psoriasis: 80 mg initial dose, followed by 40 mg every other week starting one week after the initial dose.

US-licensed Humira is not approved for chronic moderate to severe plaque psoriasis in the pediatric population.

It is the Division's conclusion that sufficient scientific justification is presented for use of FKB327 for "the treatment of adult patients with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy."

Authors:
Denise Cook, M.D.
Medical Officer

Gordana Diglisic, M.D.
Clinical Team Leader

8. Labeling Recommendations

8.1. Proper Name

The Applicant's nonproprietary name, adalimumab-fkjp was found to be conditionally accepted by the Agency.

8.2. Proprietary Name

The Applicant's proposed proprietary name for FKB327, Hulio, has been conditionally approved. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded that the name is acceptable (DMEPA review dated October 4, 2019).

8.3. Other Labeling Recommendations

FKB327 is a proposed biosimilar to US-Humira. The Applicant is proposing the following dosage forms and strengths:

- Injection: 40 mg/0.8 mL in a single-dose prefilled autoinjector
- Injection: 40 mg/0.8 mL in a single-dose prefilled plastic syringe
- Injection: 20 mg/0.4 mL in a single-dose prefilled plastic syringe

The proposed FKB327 prescribing information incorporated relevant data and information from the US-Humira prescribing information, with appropriate modifications. The Applicant is seeking licensure for the following indications, for which US-Humira has been previously approved: rheumatoid arthritis, juvenile idiopathic arthritis in patients 4 years of age and older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis.

The Applicant is not seeking licensure for the following indications for which US-Humira has been previously approved: juvenile idiopathic arthritis in patients 2 to less than 4 years of age, pediatric Crohn's disease, hidradenitis suppurativa, and uveitis. The Applicant's proposed labeling does not include these indications and certain information relating to them.

The Applicant is also proposing that the dosage and administration information relating to the JIA indication be limited to patients weighing more than 15 kg and to include a statement in the labeling that there is no dosage form of the product that allows weight-based dosing for pediatric patients below 15 kg.

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

The Applicant agreed to changes requested by the Division to improve readability, clarity, and accuracy of the prescribing information.

Authors:
Natalie Pica, M.D., Ph.D.
Clinical Reviewer

Miya Paterniti, M.D.
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:
Miya Paterniti, M.D.
Cross Discipline Team Leader

10. Pediatrics

As communicated on May 29, 2020 in a response to an information request sent by the Division on May 22, 2020, the Applicant is requesting a deferral of the pediatric assessment for pediatric CD (6-17 years of age).

The Applicant's iPSP was then discussed at the PeRC meeting on June 9, 2020. The PeRC agreed with the requested deferrals for JIA (2 to less than 4 years of age), CD (6-17 years of age), and UC (5-17 years of age). PeRC agreed with the September 2021 deferral dates for JIA (2 to less than 4 years of age) and CD (6-17 years of age). In addition, PeRC and the review divisions determined that the pediatric assessment of pediatric UC (5-17 years of age) should be deferred until September 2021. The Applicant will also be required to develop a formulation (presentation) that can be used to accurately administer FKB327 to pediatric patients who weigh less than 15 kg, with the final report submission in December 2023 . See Section 11.2.

The Agency has determined at this time that, with respect to the following indications, no pediatric studies will be required under the Pediatric Research Equity Act (PREA) for the

Applicant's BLA:
- JIA in 0 to less than 2 years of age;
- PsA;
- AS;
- CD in 0 to less than 6 years of age;
- UC in 0 to less than 5 years of age; and
- PsO.

Refer to memo dated June 19, 2020.

Authors:
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Clinical Reviewer

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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 current FKB327 presentations are not designed to allow for accurate administration of doses less than 20 mg, which impacts children who weigh less than 15 kg. For accurate weight-based dosing, an age-appropriate formulation (presentation) is required by PREA. Therefore, a PREA PMR is recommended for the development of a formulation (presentation) that can be used to administer FKB327 in patients who weigh less than 15 kg.

The Applicant is required to submit a pediatric assessment under PREA for the following:
- Patients with JIA 2 to <4 years of age
- Patients with CD 6 to 17 years of age
- Patients with UC 5 to 17 years of age.

The following four PREA PMRs were agreed upon by the Applicant on June 18 (PMRs 2 & 3) and June 26, 2020 (PMRs 1&4).

> PMR-1: Assessment of Hulio (adalimumab-fkjp) for the treatment of polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 to less than 4 years of age.
> Final Report Submission Date: September 2021
>
> PMR-2: Assessment of Hulio (adalimumab-fkjp) for the treatment of pediatric Crohn's

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disease (CD) in pediatric patients 6 years to 17 years of age.
Final Report Submission Date: September 2021

The Applicant may fulfill these PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate justification under the BPCI Act for extrapolating the pediatric information from US-Humira to FKB327.

PMR-3: Assessment of Hulio (adalimumab-fkjp) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age.
Final Report Submission Date: September 2021

US-Humira is not licensed for the treatment of pediatric ulcerative colitis in patients 5 to 17 years of age. The Applicant may fulfill this PREA requirement by seeking to update its labeling, supported by biosimilar extrapolation or appropriate data, that includes relevant pediatric information after the labeling of US-Humira is updated with that information.

PMR-4: Develop a presentation that can be used to accurately administer Hulio (adalimumab-fkjp) to pediatric patients who weigh less than 15 kg.
Final Report Submission Date: December 2023

In addition, the following postmarketing commitments (PMCs) were agreed upon by the Applicant on June 18, 2020:

PMC-1: Mylan commits to develop and implement test in appropriate format (functional bioassays or the use of FcγRIIIa and C1q binding as surrogates) for the Fc-domain-mediated effector functions of antibody-dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) of FKB327; and to add these tests to the drug substance release specification. The updated drug substance release specification, test methods and supporting validation data will be submitted to FDA following 21 CFR 601.12 (b).
Final Report Submission Date: September 2022

Authors:

Natalie Pica, M.D., Ph.D.
Clinical Reviewer

Miya Paterniti, M.D.
Clinical Team Leader

12. Division Director/Designated Signatory Comments

I concur with the review and conclusions by the review team. The regulatory action is approval.

Author:

Nikolay Nikolov, M.D.
DRTM Designated Signatory

13. Appendices

13.1. References

1 Korswagen, L. A. *et al.* Venous and arterial thromboembolic events in adalimumab-treated patients with antiadalimumab antibodies: a case series and cohort study. *Arthritis Rheum* **63**, 877-883, doi:10.1002/art.30209 (2011).

2 van Schouwenburg, P. A., Rispens, T. & Wolbink, G. J. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol* **9**, 164-172, doi:10.1038/nrrheum.2013.4 (2013).

3 Vincent, F. B. *et al.* Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. *Ann Rheum Dis* **72**, 165-178, doi:10.1136/annrheumdis-2012-202545 (2013).

13.2. Financial Disclosure

Covered Clinical Study: FKB327-001 & FKB327-005

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: FKB327-002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 118		
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	Yes ☐	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: FKB327-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 97		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Appendices

13.3.1. Nonclinical Pharmacology

FKB327 is a human monoclonal immunoglobulin G (IgG1 κ subtype). It was demonstrated that FKB327 binds to human TNFα with high affinity and produced a dose-dependent inhibition of TNFα in in vitro assays. Based on the information submitted during discussions prior to submission of the IND, secondary and safety pharmacology studies were not necessary for this biosimilar development program.

13.3.2. Nonclinical Pharmacokinetics and Pharmacodynamics

Cynomolgus Monkey Single Dose Pharmacokinetics

The following study was reviewed under IND 116471.

Study Title: Pharmacokinetics of FKB327 and EU-Humira after a single subcutaneous administration in cynomolgus monkeys

Study no.	r-fkb327-01
Study report location	Module 4.2.2.2
Conducting laboratory and location	(b) (4)
Date of study initiation	Aug, 2011
GLP compliance	No
QA statement	No
Drug, lot #, and % purity	FKB327, Lot 164P110627NM, 69.24 mg/mL EU-Humira, Lot No 88031LT40, 46.48 mg/mL

A pharmacokinetic (PK) study was conducted in monkeys (n=4/group) to obtain blood samples for assay development and validation for the quantification of FKB327 and EU-Humira in serum by electrochemiluminescent assay. Male cynomolgus monkeys were administered 3 mg/kg of either FKB327 or EU-Humira, SC, as a single dose, then followed for 29 days. Blood samples were collected on day 1 (4 hours after dosing), and on days 2, 3, 4, 6, 8, 15, 22, and 29.

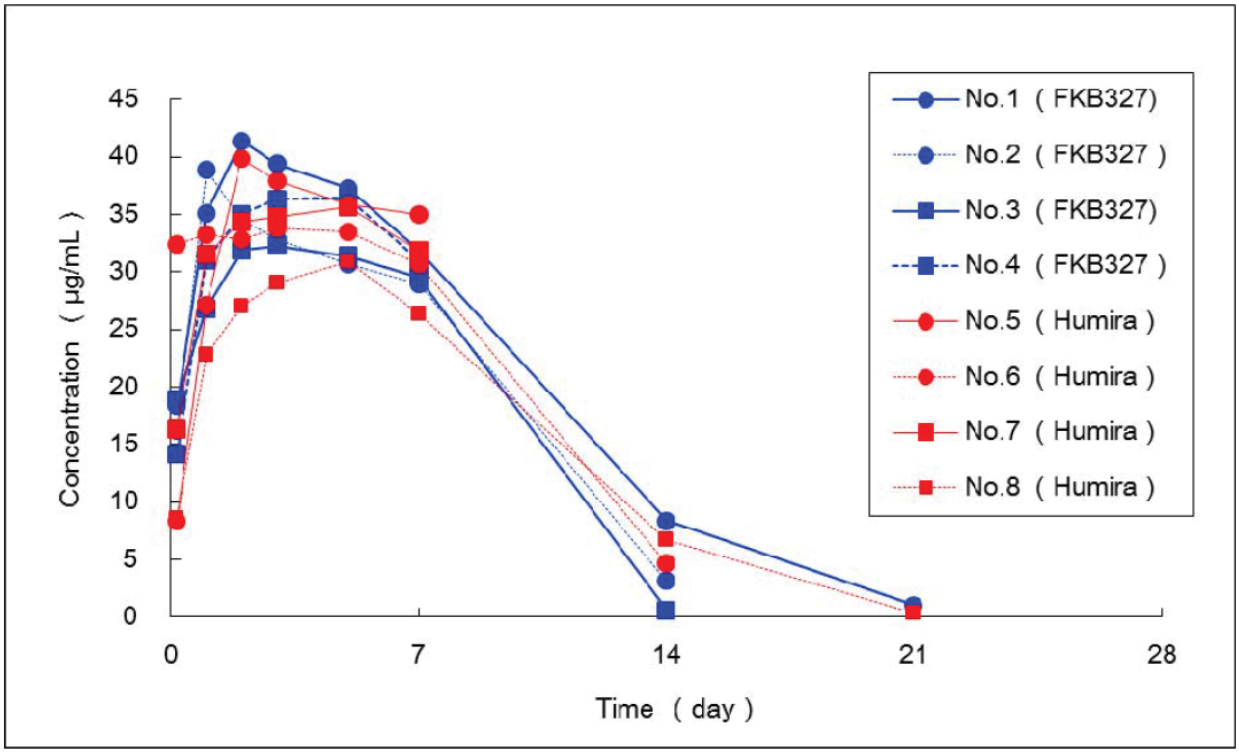
Most samples collected on days 22 and 29 after administration had concentrations below the detectable limit of the assay (<0.1 µg/mL). The PK parameters of T_{max}, C_{max} and AUC_{0-168} for both FKB327 and EU-Humira are presented in the summary table and figure of individual concentration profiles below.

Reference ID: 4635331

Summary of Pharmacokinetic parameters of FKB327 and EU-Humira after a single subcutaneous administration at a dose of 3 mg/kg to male cynomolgus monkeys (mean ± SD)

	FKB327	EU-Humira
Tmax (h)	66.0 ± 41	90.0 ± 36
Cmax (μg/mL)	37.3 ± 3.9	35.0 ± 3.7
AUC0-168 (μg-h/mL)	5410 ± 430	5230 ± 540

Individual serum concentrations of FKB327 and EU-Humira after a single subcutaneous administration of 3 mg/kg to male cynomolgus monkeys



13.3.3. General Toxicology

Based on the information submitted during discussions prior to submission of the IND, genetic toxicology, reproductive and developmental toxicity and carcinogenicity studies were not necessary for this biosimilar development program. This section contains the review of a toxicity and PK/TK study of FKB327 and EU-Humira in cynomolgus monkeys, followed by a summary of the toxicology assessment of the excipient, monosodium glutamate. While SBL330-011 included the use EU-Humira, the data generated using EU-Humira was not used to support the demonstration of biosimilarity

Reference ID: 4635331

Repeat-Dose Toxicity/Toxicokinetics

The following study was reviewed under IND 116471.

Study title: Comparative Toxicity Study of FKB327 and EU-Humira in Cynomolgus Monkeys with 4-Week Intermittent Subcutaneous Dosing Followed by an 8-Week Recovery Period

Study no	SBL330-001
Study report location	SD-6, November 29, 2013
Conducting laboratory and location	(b) (4)
Date of study initiation	September 18, 2012
GLP compliance	Yes
QA statement	Yes
Drug, lot #, and % purity	FKB327, Lot TVK120117, (53.92 mg/mL) Purity 99.5% EU-Humira, Lot 10220XD01 (52.50 mg/mL)

Key Study Findings

- Male cynomolgus monkeys were administered 30 mg/kg FKB327 or EU-Humira, subcutaneously, once weekly for 4 weeks. A control group was administered the vehicle for FKB327. Recovery animals were followed for an additional 8 weeks.
- There were no mortalities during the treatment period.
- There was no effect of FKB327 on clinical observations, body temperature, blood pressure, body weight, feed consumption, ophthalmoscopy, ECG parameters, hematology, bone marrow nucleated cell count, clinical chemistry, C-reactive protein, serum cytokines, urinalysis, macroscopic findings, or organ weights.
- There was very slight perivascular mononuclear cell infiltration in the subcutis at the injection site in all 3 main study animals (#11, 13, and 14) of the FKB327 treatment group. This finding was not present in the other treatment groups. This finding was also not present in the FKB327 recovery animals, 8 weeks later.
- In the FKB327 group, there were decreases in the staining (compared to control staining), with anti-CD21 in the follicle of the spleen, mesenteric lymph node, and submandibular lymph node at the end of the dosing period, and in the follicle of the spleen, mesenteric lymph node, and submandibular lymph node at the end of the recovery period. This occurred in 1 to 3 animals for each tissue and treatment group.
- Anti-drug antibodies were detected in 1 FKB327 animal but did not appear to affect plasma FKB327 values.

Reference ID: 4635331

Methods

Doses:	0 (FKB327 vehicle), 30 mg/kg (FKB327), 30 mg/kg (EU-Humira)
Frequency of dosing	Once weekly for 4 weeks (on days 1, 8, 15, and 22)
Route of administration	Subcutaneous, into the interscapular region
Dose volume	0.6 mL/kg
Formulation/Vehicle	10 mmol/L sodium L-glutamate, 262 mmol/L D-sorbitol, 5 mmol/L L-methionine, 1 mg/mL Polysorbate 80, pH 5.2
Species/Strain	*Macaca fascicularis* (cynomolgus monkey, purpose-bred, anti-B virus antibody negative); Origin: (b) (4)
Number/Sex/Group	Males: 3/dose in the main study, 2/dose in the recovery phase
Age	3 to 4 years
Weight	3.22 to 3.99 kg
Satellite groups:	Recovery animals were followed for 8 weeks after dosing was terminated.
Unique study design:	Selection of the administered dose was based on a repeated subcutaneous dose administration of Humira (it was unclear if this study was newly conducted by the sponsor or based on public information in the Humira approval package)
Deviation from study protocol:	There were no deviations that affected the interpretation and conclusions of the study

Observations and Results

Mortality

Animals were monitored at least twice daily.

There were no mortalities during the treatment period.

Clinical Signs

Animals were checked at least twice daily and subjected to a physical examination (including pulse oximetry and respiratory rate) on days -6, 23, and on recovery day 51 (week 8 of recovery). For exams, animals were sedated by intramuscular injection (0.2 mL/kg, 10 mg/kg) of ketamine hydrochloride, and examined by a veterinarian.

There was no effect of FKB327 or EU-Humira on clinical observations.

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Body Weights

Animal weights were monitored once weekly.

There was no effect of FKB327 or EU-Humira on body weight.

Feed Consumption

Feed Consumption was monitored daily. The number of pieces provided to each animal and the number remaining were recorded daily, and food consumption per day (g) was calculated.

There was no effect of FKB327 or EU-Humira on feed consumption.

Ophthalmoscopy

Eyes were examined after instillation of a mydriatic agent and as part of the physical examination under ketamine sedation and after on days -6, 23 and on recovery day 51 (week 8 of recovery). Gross observations and pupillary light reflex examinations were performed using a portable slit lamp. The anterior ocular segment and optic media were examined with a portable slit lamp, and the ocular fundi was examined with an indirect ophthalmoscope.

There was no effect of FKB327 or EU-Humira on ophthalmic findings.

ECG

ECG recordings were made on day -10, 1, 22, and on recovery day 51 (week 8 of recovery) at approximately 4 hours after dosing or corresponding to this time of day for non-dosing days. The animals were unanesthetized and positioned in a sitting position in procedure cages. Data was analyzed from lead II to provide heart rate (beats/min), PR interval (ms), QRS duration (ms), QT interval (ms), and QTc (Bazett's formula, ms).

Body temperature and blood pressure was measured on days -10, 1, 22, and on recovery day 50 (week 8 of recovery), approximately 4 hours after dosing. Blood pressure was measured using an automatic blood pressure monitor at the brachium.

There was no effect of FKB327 or EU-Humira on ECG parameters, blood pressure, or body temperature.

Hematology

Blood was sampled from the femoral vein on days -13, -6, 14, 28, and on recovery days 15, 29, and 56 (week 8). The morphology of white blood cells was also evaluated from blood smears. Immunophenotyping was also conducted (refer to the special evaluations section, below). Standard hematology parameters were evaluated.

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There was no effect of FKB327 or EU-Humira on hematology parameters, and there were no morphologically abnormal cells observed in blood smears.

There were two animals, one from the EU-Humira and one from the FKB327 treatment groups with increased WBC cells during the study compared with predose values or vehicle control values, however these values were not greatly elevated and returned to control values the following week or during the recovery period. Animal #7 of the EU- Humira group had higher WBC counts than other animals in the group on all sampling days, and on day 14 this was 77 10^3/uL compared to predose values of 15 and 13 10^3/uL. The value returned to 20 10^3/uL on day 28 and during the recovery period, values ranged from 19-23 10^3/uL for this animal. The FKB327 animal #15 had WBC values of 36 10^3/uL on day 28 compared to values of 11 and 6 10^3/uL prior to the start of study dosing, and recovery values ranged from 10 to 14 10^3/uL.

Peripheral Blood Immunophenotyping

Blood was collected on days -13, -6, 14, 28, and on recovery days 15, 29, and 56. Lymphocytes were stained with antibodies against CD3, CD4, CD8, CD16, and CD20 antigenic sites, then analyzed by flow cytometry.

There were no overall effects of treatment on blood cell populations determined by immunophenotyping. In two animals (EU-Humira treated animal #7 on dosing day 14 and FKB327-treated animal #15 on dosing day 28) increases in CD3+, CD3+CD4+, CD3+CD8+, and CD3-CD20+ cell populations were noted that corresponded to the increase in lymphocytes noted in the hematology analysis.

Clinical Chemistry

Blood was sampled from the femoral vein on days -13, -6, 14, 28, and on recovery days 15, 29, and 56 (week 8). Standard clinical chemistry parameters were evaluated along with C-reactive protein.

There was no effect of FKB327 or EU-Humira on hematology or C-reactive protein levels. One animal in each treatment group had an elevated C-reactive protein concentration on day 14 (FKB327 animal #13: 3.9 mg/dL, and EU-Humira animal #9: 1.9 mg/dL).

Serum Cytokine Measurement

Blood was collected from the femoral vein on days -13, -6, 14, 28, and on recovery days 29 and 56. Serum cytokines IL-2, IL-4, IL-5, IL-6, TNF, and IFN- γ were quantified with a commercially available kit for non-human primates.

Except for IL-6, serum cytokines (IL-2, IL-4, IL-5, TNF, and IFN-γ) were below the detection limit at all time points in all groups. For IL-6, there was no effect on FKB327 or EU-Humira on IL-6 concentrations compared to control levels.

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Urinalysis

Urine was collected on days −14, −7, 13, 27, and in the recovery period on days 28 and 55. Urine was collected in trays during a 2 hr morning period for fresh urine and during a 16 hour overnight period for preserved urine. Standard parameters were evaluated. Total electrolyte excretion was calculated from electrolyte concentration and urine volume, however only total electrolyte excretion was evaluated.

There was no effect of FKB327 on urinalysis parameters. Occult blood of 1+ severity was detected in 2 EU-Humira-treated animals, #7 on day 27 and #9 on days 13 and 27, but no red blood cells or WBC were observed in the urine of these animals.

Gross Pathology

At the end of the dosing phase and the end of the recovery phase, animals were anesthetized by an intravenous injection of sodium pentobarbital, weighed, and euthanized by exsanguination. External appearance, and internal organs and tissues were examined macroscopically. An adequate list of tissues was examined for organ weights and histopathology.

There were no effects of FKB327 or EU-Humira on macroscopic findings. All males were probably sexually immature based on testis weight and histopathology.

Organ Weights

Organs weights were expressed in terms of absolute weight and percentage of body weight.

There was no effect of FKB327 or EU-Humira on organ weights. All animals, except 1 FKB327 group animal (#13) were probably sexually immature based on testis weight (right or left testis: ≤2.1 g vs 7.3 for animal #13) and histopathology.

Histopathology

Adequate Battery: Yes. There was no written pathology report, only data tables were provided.
(The left thyroid and parathyoid were absent in 2 animals (#13 and #15), a congenital defect)

Peer Review: Yes, a signed statement by (b) (4)

There was perivascular mononuclear cell infiltration in the subcutis at the injection site in all 3 main study animals (#11, 13 and 14) of the FKB327 treatment group, which was not present in the other treatment groups. The severity was minimal. This finding was not present in the two FKB327 recovery animals, 8 weeks later. There were no other treatment-related effects.

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Histopathology Summary

		Vehicle of FKB327	EU-Humira	FKB327
n		**3**	**3**	**3**
recovery n		**2**	**2**	**2**
	Severity			
Injection site, interscapular in back				
mononuclear infiltration, perivascular, subcutis	no abnormal change very slight change	**3** **0**	**3** **0**	**0** **3**
Recovery	no abnormal change	0	0	0

Immunohistochemistry

Frozen and paraffin-embedded tissues of the spleen, thymus, submandibular lymph nodes (right), and mesenteric lymph nodes were used for immunohistochemical analysis using antibodies against cellular antigens CD2, CD3, CD4, CD8, CD20, CD21, and immunoglobulins IgM and IgG.

Although there were no histopathology changes observed in lymphoid tissues with routine H and E staining methods, or changes in overall cell populations between EU- Humira and FKB327 treatments, there was a very slight reduction in CD21 immunostaining, a B cell marker, in some individual animals. It was not clear if the decrease in staining indicated only a reduction in CD21 antigen or reduction in cells expressing CD21.

Tissue Immunohistochemistry Summary

		Vehicle of FKB327	EU-Humira	FKB327
n		3	3	3
recovery n		2	2	2
Lymph Node CD21 Immunostaining				
Mesenteric, positive reaction follicle	no abnormality very slight decrease	3 0	1 2	2 1
Recovery	no abnormality very slight decrease	2 0	0 2	1 1
Submandibular, positive reaction follicle	no abnormality very slight decrease	3 0	2 1	2 1
Recovery	no abnormality very slight decrease	2 0	0 2	1 1
Spleen, positive reaction follicle	no abnormality very slight decrease	3 0	0 3	1 2
Recovery	no abnormality very slight decrease	2 0	0 2	1 1

Bone Marrow Examination

Bone marrow was obtained from the sternum of all animals at necropsy. Nucleated cell counts were determined and bone marrow smears were prepared. Only cell counts were conducted, smears were not analyzed.

There were no effects of FKB327 or EU-Humira on bone marrow nucleated cell counts.

Toxicokinetics

Blood was obtained from the femoral vein on each of the dosing days and at the following times:

Day 1: Before dosing, and at 8, 24, 48, 72, 96, 120, and 144 hours after dosing (corresponding to days 2, 3, 4, 5, 6, and 7)

Day 8: Before dosing which is 168 hours after 1st dose, and 48 hours after dosing (day 10 of dosing)

Day 15: Before dosing, and 48 hours after dosing day 17 of dosing

Day 22: Before dosing, and at 8 hours and 24, 48, 72, 120, and 168 hours after dosing, (corresponding to days 23, 24, 25, and 27 and recovery day 1)

Recovery period: Days 3, 8, 15, 29, 43, and 56 of recovery

For the negative control group, only samples from before each dosing and 48 hours after each dosing were analyzed during the dosing period. Analysis was performed by a validated electrochemiluminescent assay (ECLA). The lower limit of quantification was 100 ng/mL (0.1 µg/mL).

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Anti-Drug Antibodies were quantified also by electrochemiluminescent assay from samples collected on days -13, 15 (before dosing), recovery day 1 (including all main study animals that were necropsied), and on recovery days 29 and 56.

The toxicokinetic parameters (C_{max}, $AUC_{0\text{-}168h}$, $t_{1/2}$, CL/F, and Vz/F) of FKB327 and EU-Humira were similar. There was no anti-human TNFα detected in control samples.

Anti-Drug Antibodies
Anti-FKB327 antibody was detected in 1 animal (#12) on day 56 of recovery, which did not appear to substantially alter plasma levels of FKB327 compared with the other animals in this recovery group. There were no anti-EU-Humira antibody positive animals.

Toxicokinetic Parameters

Parameters	Humira		FKB327	
	1st dosing	4th dosing	1st dosing	4th dosing
C_{max} (μg/mL)	282 ± 42	611 ± 84	309 ± 20	599 ± 40
$AUC_{0\text{-}168h}$ (μg·h/mL)	40500 ± 4600	90000 ± 12500	43900 ± 5100	88600 ± 6800
T_{max} (h)	77 ± 26	53 ± 11	101 ± 39	48 ± 0
$t_{1/2}$ (h)	NC	316 ± 123	NC	293 ± 84
CL/F (mL/h/kg)	NC	0.115 ± 0.053	NC	0.115 ± 0.035
Vz/F (mL/kg)	NC	46.0 ± 6.5	NC	45.2 ± 2.5

Values are expressed as mean ± S.D. (Number of animals: 5 animals/group).
NC: Not calculated.

Dosing Solution Analysis

Stability: Stability information came from sponsor studies conducted earlier on the same lot of FKB327. FKB327 (Lot TVK120117) stored at 5 ± 3°C was stable for 9 months, the longest time tested. There was no change in % main peak (99.5%), HMWS (0.4%), or LMWS (0.1%) at storage times of 0, 3, 6, and 9 months. Protein concentration
increased slightly at the 9 month timepoint (53.84 at 0 months, 54.47 at 9 months).

Homogeniety: Not assessed

Dosing Concentration: Not assessed. Although the dosing concentration was not assessed, the toxicokinetic analysis indicated similar parameter results as with EU- approved Humira. Other toxicity and pharmacodynamic parameters evaluated were also similar. There is no obvious

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reason for not accepting the study, despite the lack of verification of the dosing solution concentration.

Toxicology Assessment of Monosodium Glutamate (MSG)

The following conclusions are based on the information submitted by the Applicant and additional literature regarding MSG, used as excipient in FKB327:

- Neurotoxicity in infant animals was noted in the late 1960's and was the subject of intensive investigation for the next 15 years or so. This had implications for MSG use as a dietary flavoring and was the subject of numerous FDA and international regulatory agency reviews. A maximal human dose containing 6 mg of MSG (a one-time loading dose for certain indications) at a frequency of once every other week and administered subcutaneously for a potential lifetime duration, would be equivalent to approximately 0.1 mg/kg (for a 60 kg individual). This amount is 5,000-fold less compared to the doses that induced lesions in neonatal mice, the most sensitive species, (500 mg/kg, SC, Reynolds et al, 1979). The maximum human dose is also 10,000-fold below the dose that induced lesions in infant monkeys (1000 mg/kg, SC, Olney et al, 1972).
- The Applicant presented an analysis of MSG exposure in adult and pediatric subjects based on the assumption that MSG is immediately absorbed and distributed throughout the vasculature, using an adult blood volume of 4.7 L. For a 160 mg FKB327 loading dose containing 6 mg of MSG, the MSG amount would contribute approximately 7.5 µM to the blood glutamate pool of approximately 150-300 µM, a 2.5 to 5.0% increase over endogenous glutamate levels. Based on animal studies this level of increase is far below the increase needed to induce neurotoxicity and it is given one time. Lower maintence doses of 40 mg FKB327 every other week would be expected to be 25% of this value.
- MSG was not mutagenic or clastogenic in almost all studies, including those conducted by Litton Bionetics for the FDA (1973 to 1977) and more recently under OECD guidelines (Taakumi et al., 2019). Only a study by Ataseven et al (2016) that used doses exceeding regulatory guidances in some assays found MSG to be mutagenic. The study's methodology and conclusions were the subject of a commentary by Rogers (2016).
- MSG is unlikely to be carcinogenic, based on 2-year bioassays in the mouse and rat (Little 1974) and mouse (Ebert 1979). Specific details of the analysis and tissues findings were not as well described as would be expected today and it was conducted prior to implementation of GLP regulations. The Little (1974) series of studies were the subject of discussion for GRAS recommendation in 1977.
- The few studies of reproductive toxicity were not conducted to current standards. In studies of monkeys, usually no adverse effects were found, but effects were noted in female mice and rats (Yu et al 1979; Eweka et al 2010; Das and Ghosh 2011; and Hermanussen et al 2006) and male mice and rats (Mosseir et al 2010; Das and Ghosh 2011). The administered doses were sufficiently high that lesions of the hypothalamic areas would be expected. These areas that regulate pituitary secretion of follicle

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stimulating hormone and luteinizing hormone, as well as prolactin and growth hormone, are essential for the growth and maintence of reproductive-related organs and tissues. Thus, the effects on reproductive tissues were probably secondary to brain lesions.

- Developmental studies were also not conducted to current standards. A few studies examined the potential of neurotoxicity but did not address teratogenicity other than to state the animals were born healthy and grew as expected. The 2-year carcinogenicity of Ebert (1979) included a mutigenerational assessment of reproduction and development in rats and found no significant effects. There is little change in fetal glutamate exposure after maternal plasma glutamate levels are highly elevated through dietary MSG, or intragastric or intravenous administration of MSG (Ohara et al 1970; Stegink et al 1975; Pitkin et al 1979). Evidence suggests the placenta metabolizes glutamate readily (Stegink et al 1975), thus acting as barrier to fetal glutamate exposure.
- Safety from local toxicity due to subcutaneous injection of MSG was established by the Applicant's toxicity study. Histopathology conducted 1 week after the 4th subcutaneous dose found perivascular mononuclear cell infiltration in the subcutis at the injection site in 3 of 3 animals treated with FKB327 and no adverse findings at the end of the 8-week recovery period. A comparison of the amount of MSG administered in the 4-week cynomolgus monkey PK/toxicity study (Report SBL330-001), to the human dose for various indications is presented in the 2 tables below. Even with a 160 mg load dose (4 doses over 1 or 2 days), the human dose per kg is approximately 1.5- to 2-fold less than that administered to monkeys based on body weight with minimal toxicity observed. For a 40 mg dose of FKB327, there is a 10-fold margin based on body weight (glutamate levels were not measured).
- Clinical experience did not find an increase in signs of injection site toxicity compared to control groups (Refer to Clinical Safety in Section 7.4, and Tables 38-40).

While the majority of studies available from published literature do not meet current regulatory standards, the studies have been discussed extensively by international regulatory agencies including the FDA, albeit for food flavoring additive safety. The Applicant has provided sufficient nonclinical information to support the safety of MSG as an excipient in Hulio.

Table 66: MSG administered to cynomolgus monkey (Report SBL330-001)

	FKB327 Dose	Frequency	MSG/dose[1]			MSG/animal[+]	
			mg	µmol*		mg/kg	µmol/kg*
4-week PK/Toxicity Monkey (Report SBL330-00)	30 mg	Once weekly	3-4	18-24		0.75-1.1	4.5-6.0
* MSG 169 g/mole [+] male cynomolgus monkeys were 3.5 to 4 kg body weight [1] 10 mM MSG at 0.6 mL/kg							

Table 67: Amounts of MSG administered to subjects for various indications

	FKB327 Dose	Frequency	MSG/dose			MSG/subject[+]	
			mg	µmol*		mg/kg	µmol/kg*
Adult	40 mg/vial	Once every 2 weeks	1.5	8.9		0.025	0.15
Pediatric	20 mg/vial	Once every 2 weeks	0.75	4.4		0.025	0.15[#]
Loading dose (some indications)	160 mg; Next dose 80 mg; Next dose 40 mg	Once every 2 weeks	6.0	35.5		0.100	0.59[+]
* MSG 169 g/mole [+] adult human = 60 kg [#] if 30 kg child							

Additional References

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13.4. Office of Clinical Pharmacology Appendices

13.4.1. Summary of Bioanalytical Method Validation and Performance

13.4.1.1. Pharmacokinetics

For the PK similarity study (Study FKB327-001), serum FKB327 and US-Humira concentrations measured using a validated electrochemiluminescence (ECL) method were suitable for assessment of PK similarity. In this method, recombinant human TNF-α was used as the capture protein and a ruthenylated anti-human kappa light chain mAb (Ruthenylated-KM4455) was used as the detection antibody. FKB327 was used to establish the standard curves and the accuracy and precision (± 20.0%, ± 25.0% for lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ)) was evaluated using FKB327 and US-Humira as QC samples. Both the method validation (Reports 327-PK12-001 and 327-PK13-009) and sample analysis for Study FKB327-001 were performed at Kyowa Kirin Pharmaceutical Research, Inc. (La Jolla, CA). The same assay was then transferred to (b) (4) and used for serum FKB327 and US-Humira concentration measurement for Studies FKB327-002, FKB327-003, and Study FKB327-005 (Validation report 8380.083014.1). All study samples were analyzed within the duration with long-term stability established. The assay validation were summarized in the tables as below.

Table 68. Summary of the bioanalytical method validation (327-PK12-001 and 327-PK13-009) and in-study performance for measurement of FKB327 and US-Humira in human serum (Study FKB327-001)

Parameter	Criterion	Result FKB327	Result US-Humira	Result EU-Humira
Assay range (ng/mL)	NA	100-10000		
ACCURACY AND PRECISION				
INTRA-ASSAY PARAMETERS ABS (%RE) of mean of 6 runs Mean %CV of 6 runs	 ≤20 (≤25 at LLOQ) ≤20 (≤25 at LLOQ)	 0.1 to 7.8 4.0 to 8.6	 0.9 to 3.0 3.8 to 7.4	 0.0 to 7.5 6.2 to 9.1
INTER-ASSAY PARAMETERS ABS (%RE) of the cumulative mean %CV of the cumulative mean Total error	 ≤20 (≤25 at LLOQ) ≤20 (≤25 at LLOQ) ≤30 (≤40 at LLOQ & ULOQ)	 0.1 to 7.8 6.7 to 11.9 6.8 to 19.4	 0.9 to 3.0 6.7 to 10.5 7.7 to 12.2	 0.0 to 7.5 9.2 to 16.7 10.2 to 21.3
SELECTIVITY				
ABS (%RE) of individuals spiked at 100 ng/mL	≤25 in at least 80% of individuals	≤25 in 100% of individuals	≤25 in 80% of individuals	≤25 in 90% of individuals
Observed concentration of individual blank matrix	<LLOQ	<LLOQ in all individuals	<LLOQ in all individuals	<LLOQ in all individuals
HOOK EFFECT				
MSD Signal Count at a concentration of Humira 5, 10 and 100-fold greater than ULOQ	NA	No hook effect observed		
DILUTIONAL LINEARITY				
ABS (%RE) for corrected determinations of dilutions between LLOQ and ULOQ	≤20	1.0 to 9.0	8 pass (-8.7 to 18.0), 1 fail (24.0) Acceptable up to 500-fold dilution	1.6 to 13.0
%CV of cumulative mean of corrected determinations between LLOQ and ULOQ	≤20	5.2	8.7	7.5
BENCH TOP STABILITY				
ABS (%Diff) of mean observed concentration when prepared in 100% matrix	≤20 when kept at room temperature for up to 24 hours	0.4 to 9.9	1.5 to 5.0	2.3 to 8.6
FREEZE-THAW STABILITY				
ABS (%Diff) of mean observed concentration after 1, 3 and 5 freeze/thaw cycles at −80°C	≤20	0.3 to 11.5	3.0 to 14.1	0.0 to 6.3
LONG-TERM STABILITY				
ABS (%Diff) of mean observed concentration after 1, 3, 5, 9 and 12 months at −20°C and −80°C	≤20	0.8 to 13.9	0.1 to 12.9	0.2 to 18.2

ABS (%RE) = absolute % relative error; ABS (%Diff) = absolute % difference; %CV = % coefficient of variation
Matrix effect was evaluated as selectivity evaluation using ten lots of individual human serum (five males and five females).
Source: Table 5 of Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 69. Summary of the bioanalytical method validation (8380.083014.1) and in-study performance for measurement of FKB327 and US-Humira in human serum (Studies FKB327-002, FKB327-003, and FKB327-005)

	FKB327	US-Licensed Humira
ACCURACY AND PRECISION		
Precision and Accuracy Run's Calibration Standards		
Inter-batch Precision (%CV)	≤ 6.34%	
Inter-batch Accuracy (%RE)	−1.80% to 2.00%	
Total Error	≤ 8.20%	
Non-Precision and Accuracy Run's Calibration Standards		
Inter-batch Precision (%CV)	≤ 3.92%	
Inter-batch Accuracy (%RE)	−1.00% to 1.60%	
Run-qualifying QCs		
Inter-batch Precision (%CV)	≤ 6.39%	
Inter-batch Accuracy (%RE)	−5.23% to −2.90%	
Precision and Accuracy QCs		
Intra-batch Pooled Precision (%CV)	≤ 5.80%	≤ 4.30%
Inter-batch Precision (%CV)	≤ 9.53%	≤ 6.41%
Mean Bias (%RE)	−3.87% to 0.383%	−2.65% to 0.219%
Total Error	≤ 11.7%	≤ 8.86%
SELECTIVITY		
Normal Serum, 10 Individuals	All but one serum met criteria	All but one serum met criteria
RA Patient Serum, 20 Individuals	All serum met criteria	All serum met criteria
Hemolysis, 2% Final Blood Concentration	No significant effect	No significant effect
HOOK EFFECT		
High concentration QC stock above the upper limit of quantitation, undiluted and a 1.33-fold diluted working solution, were prepared over 2 different points above the range of calibration	No hook effect observed	No hook effect observed
DILUTIONAL LINEARITY		
Samples were prepared from a point above the calibration range and diluted into range using 5-, 25-, and 125-fold dilutions to test dilution linearity	Met acceptance criteria up to a 125-fold dilution	Met acceptance criteria up to a 125-fold dilution
BENCH TOP AND FREEZE-THAW STABILITY IN HUMAN SERUM		
Short-term Bench (Ambient)	44 hours	24 hours
Short-term Bench (4°C)	24 hours	24 hours
Freeze/Thaw (-80°C)	4 cycles	4 cycles
Freeze/Thaw (-20°C)	3 cycles	3 cycles
Long-term (-80°C and -20°C)	760 days	762 days
Intermediate solution (1000 µg/mL) (-80°C)	77 days	79 days
Intermediate solution (100 µg/mL) (-80°C)	77 days	79 days
ANTI-DRUG ANTIBODY INTERFERENCE		
QC samples were prepared at 5 concentration levels (100, 300, 1000, 7450, and 10000 ng/mL) and then each of these levels were spiked with 3 ADA positive control concentrations (100, 5000, and 50000 ng/mL)	No significant effect observed across the assay range in the presence of up to 5000 ng/mL of ADA	No significant effect observed across the assay range in the presence of up to 5000 ng/mL of ADA

Source: Table 6 of Summary of Biopharmaceutic Studies and Associated Analytical Methods

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13.5. Clinical and Statistics Appendices

13.5.1. Tipping Point Analysis Methodology[9]

The goal is to evaluate the potential effect of violations in assumptions about missing data on the reliability of conclusions. Suppose that outcomes Y are independently distributed on the control and test drug arms. The parameter of interest is the difference in means θ. Consider the following parameterization and notation to describe the probabilities of completing the study (non-missingness), the true means in completers and dropouts, and the numbers of completers and total patients on the two treatment arms:

Table 70: Parameters and Notation for Tipping Point Analysis in Presence of Missing Data

Arm	Probability of non-missing	Mean among completers	Mean among dropouts	Number of completers	Sample size per arm
Placebo	π_c	μ_c	$\mu_c + \delta_c$	N_c	n_c
Treated	π_t	μ_t	$\mu_t + \delta_t$	N_t	n_t

Given this parameterization, the target of inference is

$$\theta = [\pi_t\mu_t + (1 - \pi_t)(\mu_t + \delta_t)] - [\pi_c\mu_c + (1 - \pi_c)(\mu_c + \delta_c)]$$
$$\mu_t + (1 - \pi_t)\delta_t - [\mu_c + (1 - \pi_c)\delta_c]$$

An analysis based on completers will provide reliable inference on θ if the missing-at random assumption, i.e., the assumption that $\delta_c = \delta_t = 0$, is valid. We will perform sensitivity analyses that allow for the possibility that outcomes among dropouts are not missing-at-random by performing inference under different assumed values of the parameters δ_c and δ_t.

Denote $M_{j,i}$ to be an indicator that patient i on treatment j is a completer, i.e., his or her outcome is observed where $i = 1, \cdots, n_j$ and $j = c, t$. By assuming fixed values of sensitivity parameters δ_c and δ_t, an estimator of θ can be represented by

$$\hat{\theta} = \hat{\mu}_t + (1 - \hat{\pi}_t)\delta_t - [\hat{\mu}_c + (1 - \hat{\pi}_c)\delta_c]$$

Where $\hat{\mu}_i = \frac{1}{N_j}\sum_{i=1}^{n_j} Y_{j,i}|M_{j,i} = 1$is the sample mean in the completers and $\hat{\pi}_j = \frac{N_j}{n_j}$ $\frac{1}{n_j}\sum_{i=1}^{n_j} M_{j,i}$ is the observed proportion of completers on treatment arm j, with $j = c, t$.

[9] Source: BLA: 125544 Statistical Review

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It can be shown that

$$\frac{\hat{\theta} - \theta}{\sqrt{\frac{S_t^2}{N_t} + \frac{S_c^2}{N_c} + (1 - \hat{\pi}_t)\delta_t^2 \frac{\hat{\pi}_t}{n_t} + (1 - \hat{\pi}_c)\delta_c^2 \frac{\hat{\pi}_c}{n_c}}} \xrightarrow{d} N[0,1]$$

where S_j^2 is the sample variance of the outcomes in completers on treatment j, with $j = c, t$. Thus, we can compute a Wald-type $(1-\alpha) * 100\%$ confidence interval for θ of the form

$$\hat{\theta} \pm z_{\alpha/2} \sqrt{\frac{S_t^2}{N_t} + \frac{S_c^2}{N_c} + (1 - \hat{\pi}_t)\delta_t^2 \frac{\hat{\pi}_t}{n_t} + (1 - \hat{\pi}_c)\delta_c^2 \frac{\hat{\pi}_c}{n_c}}$$

where $z_{\alpha/2}$is the upper $(1-\alpha/2)$ quantile of the standard normal distribution

Table 71:Tipping Point Analysis of the ACR20 Response Rate at Week 24 (Applicant's Analysis)

Shift[1]		Estimated Treatment Difference	90% CI
FKB327	Humira		
0	0	-2.33	(-7.5, 2.9)
0.2	0	-3.1	(-8.3, 2.1)
	0.2	-2.49	(-7.8, 2.9)
0.4	0	-3.75	(-9.2, 1.6)
	0.2	-3.13	(-8.5, 2.3)
	0.4	-2.46	(-7.9, 2.9)
0.6	0	-4.45	(-9.8, 0.9)
	0.2	-3.84	(-9.2, 1.7)
	0.4	-3.17	(-8.5, 2.2)
	0.6	-2.27	(-7.7, 3.1)
0.8	0	-5.04	(-10.4, 0.3)
	0.2	-4.43	(-9.9, 1.0)
	0.4	-3.76	(-9.2, 1.7)
	0.6	-2.86	(-8.6, 2.5)
	0.8	-2.01	(-7.4, 3.4)
1	0	-5.63	(-10.9, -0.3)
	0.2	-5.02	(-10.4, 0.4)
	0.4	-4.35	(-9.8, 1.0)
	0.6	-3.46	(-8.9, 1.9)
	0.8	-2.6	(-8.0, 2.8)
	1	-1.85	(-7.3, 3.6)

Source: Generated from the Clinical Study Report Table 14.2.1.2.2

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/s/

MIYA O PATERNITI
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