Clinical, Cross-Discipline Team Leader, and Division Director Summary Review of BLA 761154/S-005

Date	See Electronic Stamp Date
From	Wiley A. Chambers, MD
Subject	Clinical, Cross-Discipline Team Leader, and Division Director Summary Review
BLA # and Supplement#	761154/S-005
Applicant	Mylan Pharmaceuticals Inc.
Date of Submission	March 2, 2023
BSUFA Goal Date	September 2, 2023
Proprietary Name	Hulio (adalimumab-fkjp)
Reference Product Proprietary Name (Proper Name)	US-Humira (adalimumab)
Dosage Form(s)	Injection
Applicant Proposed Indication	Expansion of existing indications to include: Uveitis (UV): treatment of non-infectious intermediate, posterior and panuveitis in adult patients
Applicant Proposed Dosing Regimen	Same as US-Humira dosing for the respective indications
Recommendation on Regulatory Action	Approval
Recommended Indication	Uveitis: Treatment of non-infectious intermediate, posterior and panuveitis in adult patients
Recommended Dosing Regimen(s)	Same as reference product dosing regimen

1. Introduction

The Applicant at the time, Mylan Pharmaceuticals, submitted a supplemental biologics license application for BLA 761154 (sBLA-005) to expand the indication for Hulio (adalimumab-fkjp) to include the treatment of non-infectious intermediate, posterior and panuveitis in adults (UV). US-Humira's orphan-drug exclusivity for this indication expired on June 30, 2023. Subsequent to the approval of the UV indication in adult patients, US-Humira was approved to treat pediatric patients 2 years of age and older with UV. The term of orphan-drug exclusivity for US-Humira for "the treatment of non-infectious intermediate, posterior and panuveitis in pediatric patients 2 years of age and older" expires on September 28, 2025. The Applicant cross-references the original application submission under BLA 761154 and the supporting justification of extrapolation for UV in adult patients and pediatric patients 2 to 17 years of age. Only UV in adult patients, however, is currently being sought for licensure.

2. Background

Hulio (adalimumab-fkjp) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against tumor necrosis factor (TNF) alpha, produced by recombinant DNA technology in a mammalian cell expression system. Hulio (adalimumab-fkjp) was approved as a biosimilar to US-licensed Humira (US-Humira) on July 6, 2020, under section 351(k) of the Public Health Service Act (BLA 761154). Hulio is currently approved for the treatment of:

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 2 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 PsA.

4. Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.

5. Crohn's Disease (CD): Treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

6. Ulcerative Colitis (UC): Treatment of moderately to severely active ulcerative coltis in adult patients.

7. Plaque Psoriasis (Ps): 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.

8. Hidradenitis Suppurativa (HS): treatment of moderate to severe hidradenitis suppurativa in adult patients.

Timeline for Hulio (adalimumab-fkjb) original approval and subsequent supplements related to expansion of indications:

Under the original BLA submission, Hulio (adalimumab-fkjp) was approved as a biosimilar to US-Humira on July 6, 2020 in patients with RA, JIA in patients 4 years of age and older, AS, adult CD, adult UC, PsA and Ps. The approval was based on the following:

The original application included the following:

- A comprehensive comparative analytical assessment of adalimumab-fkjp, US-Humira, and EU-approved Humira (EU-Humira). These included comparative characterization of physicochemical attributes and comparative functional assessments.

- A pharmacokinetic (PK) similarity study (FKB327-001) in healthy subjects following a single subcutaneous (SC) 40 mg dose of adalimumab-fkjp, EU-Humira, or US-Humira.

- A comparability study (FKB327-005) of adalimumab-fkjp in healthy subjects following a single SC dose of adalimumab-fkjp by vial, pre-filled syringe, or autoinjector.

- A comparative clinical study (FKB327-002) evaluating comparative efficacy, safety, and immunogenicity of adalimumab-fkjp and US-Humira in combination with methotrexate in patients with moderately to severely active RA.

- An open-label extension study (FKB327-003) comparing efficacy and safety between adalimumab-fkjp and US-Humira in RA.

- An adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) for extrapolation of data and information submitted in the application to support licensure of adalimumab-fkjp for each of the additional indications for which licensure was sought and for which US-Humira had been previously licensed.

In considering the totality of the evidence in the original BLA submission, review of the data submitted by the Applicant showed that Hulio (adalimumab-fkjp) is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between adalimumab-fkjp 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 adalimumab-fkjp for the non-studied indications sought for approval.

Review of the information submitted by the Applicant demonstrated that adalimumab-fkjp is biosimilar to US-Humira for each of the following indications for which US-Humira has been previously approved and the Applicant was seeking licensure for adalimumab-fkjp: RA, pJIA in patients 4 years of age and older, PsA, AS,

PS in adults, CD in adults, HS in adults and UC in adults. See Biosimilar Multi-Disciplinary Evaluation and Review (BMER), dated July 2, 2020.

Under supplement 002, the approved indications were expanded to include the following: treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 to less than 4 years of age and treatment of moderately to severely active Crohn's disease in pediatric patients ages 6 years to 17 years of age. Refer to Cross-Discipline Team Leader review dated July 12, 2022, for additional details.

Under supplement 004, the approved indications were expanded to include the treatment of of moderate to severe hidradenitis suppurativa in adult patients.

Hulio is approved in the following presentations:
- 40 mg/0.8 mL single-dose prefilled pen
- 40 mg/0.8 mL single-dose prefilled syringe
- 20 mg/0.4 mL single-dose prefilled syringe

3. CMC/Product Quality

For sBLA-005, no new product quality information was submitted nor required. There are no CMC or product quality issues that would preclude approval of the indication sought for licensure.

In accordance with 21 CFR Part 25, the Applicant claimed a categorical exclusion from the preparation of an environmental assessment (EA) for Hulio for the additional indication being sought. The basis for the claim for categorical exclusion under 21 CFR 25.31(c) for the addition of the new indication is considered appropriate and acceptable.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA-011. There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indication sought for licensure.

5. Clinical Pharmacology

No new clinical pharmacology information was submitted nor required for this sBLA. There are no clinical pharmacology issues that would preclude approval of the indication sought for licensure.

6. Clinical/Statistical-Efficacy

Adalimumab-fkjp was previously studied in subjects with RA in the comparative clinical study (FKB327-002 and open-label extension FKB327-003). The data were previously reviewed and summarized in the BMER dated July 2, 2020, for the original application. No new clinical/statistical efficacy information was submitted nor required for this sBLA. There are no clinical/statistical efficacy issues that would preclude approval of the indications sought for licensure.

7. Safety

There are no clinical safety issues that would preclude approval of the indication sought for licensure.

8. Considerations for Extrapolation of Biosimilarity in Other Conditions of Use

Hulio (adalimumab-fkjp) is an approved biosimilar for the treatment of RA, PsA, AS, CD in patients 6 years of age and older, UC, pJIA in patients 2 years of age and older, Ps and HS. In the original BLA submission, the Applicant provided data and support for biosimilarity, including extensive analytical characterization that demonstrated that adalimumab-fkjp is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, as well as clinical data that demonstrated that there were no clinically meaningful differences between adalimumab-fkjp and US-Humira in terms of safety, purity, and potency based on similar clinical PK, and similar efficacy, safety, and immunogenicity in subjects with RA.

<u>Justification for Extrapolation to Non-studied Indications in Original BLA</u>
Additional points considered in the justification for extrapolation of data and information to support licensure of adalimumab-fkjp as a biosimilar for each non-studied indication for which licensure was sought and for which US-Humira was previously approved included:

- PK similarity was demonstrated between adalimumab-fkjp and US-Humira. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between adalimumab-fkjp and US-Humira in the indications sought for licensure. A similar PK profile would be expected between adalimumab-fkjp and US-Humira in patients with JIA, PsA, AS, adult CD, UC, Ps, HS and UV.

- 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 assay used (per labeling for US-Humira). Similar immunogenicity was

observed between adalimumab-fkjp and US-Humira in patients with RA, and in healthy subjects. Therefore, similar immunogenicity would be expected between adalimumab-fkjp and US-Humira in patients with JIA, PsA, AS, adult CD, UC, Ps, HS and UV.

- There were no clinically meaningful differences between adalimumab-fkjp and US-Humira in patients with RA, nor in healthy subjects. Coupled with the demonstration of analytical and PK similarity between adalimumab-fkjp and US-Humira, a similar safety profile would be expected in patients with JIA, PsA, AS, adult CD, UC, Ps, HS and UV.

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

Justification for Extrapolation to UV Indication

In this sBLA, the Applicant has cross-referenced the previously submitted justification for extrapolation of the data and information in support of licensure of adalimumab-fkjp for this indication. The scientific justification for extrapolation to non-studied indications which was submitted with the original BLA is also applicable to UV and supports licensure of adalimumab-fkjp for the treatment of adult patients with non-infectious intermediate, posterior and panuveitis.

9. Pediatrics

To address the Pediatric Research Equity Act (PREA), the Applicant confirmed on August 10, 2023, that they have submitted a pediatric assessment of the use of adalimumab-fkjp for the treatment of non-infectious intermediate, posterior and panuveitis in pediatric subjects age 2 years and above . A term of orphan-drug exclusivity for US-Humira for “the treatment of non-infectious intermediate, posterior and panuveitis in pediatric subjects age 2 years and above” expires on September 28, 2025. The Applicant proposed to fulfill PREA requirements for pediatric patients 2 years and above for this indication by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-Humira to Hulio; however, FDA cannot license Hulio for this indication in this age group until US-Humira’s orphan drug exclusivity for it expires on September 28, 2025. The labeling for US-Humira does not contain adequate pediatric information for UV patients younger than 2 years of age, and no pediatric assessment will be required of the Applicant under PREA for UV patients younger than 2 years of age. The Applicant refers to the following guidance for industry: “Questions

and Answers on Biosimilar Development and the BPCI Act." The Pediatric Review Committee (PeRC) reviewed the information and considered the product to be assessed. On May 2, 2023, the Pediatric Review Committee (PeRC) reviewed the assessment and agreed with the assessment.

10. Other Relevant Regulatory Issues

None.

11. Labeling

Prescribing Information

Labeling for Hulio was updated to include the indication of treatment of non-infectious intermediate, posterior and panuveitis in adult patients. The submitted package insert, and Medication Guide have been reviewed and found to be acceptable. The final label will be included in the approval letter.

Mylan Specialty L.P.
Morgantown, WV 26505 U.S.A.
U.S. License No. 2210
Product of Japan

PCI:ADAL:RX14

12. Postmarketing Recommendations

There are no new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement or commitment.

13. Risk Evaluation and Mitigation Strategies

The review team did not identify a need for Risk Evaluation and Mitigation Strategies (REMS) to ensure the safe use of adalimumab-fkjp.

14. Recommended Regulatory Action

Approval.

Authors:

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Division Director	Clinical Team Leader	Deputy Division Director

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/s/

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