CDER Clinical, CDTL, and Division Summary Review

Date	October 31, 2023
From	Rhea Lloyd, MD, William Boyd, MD, and Wiley A. Chambers, MD
Subject	Clinical, Cross-Discipline Team Leader, and Division Summary Review
BLA # and Supplement#	761255/S-003
Applicant	Fresenius Kabi USA, LLC
Date of Submission	May 12, 2023
BSUFA Goal Date	November 12, 2023
Name	IDACIO (adalimumab-aacf)
Reference Product Name	US-HUMIRA (adalimumab)
Dosage Form(s)	No new proposed dosage forms
Applicant Proposed Indication(s)/Population(s)	Expansion of existing indications to include the following: • Uveitis (UV): Treatment of non-infectious intermediate, posterior, and panuveitis in adult patients
Applicant Proposed Dosing Regimen	Proposed dosing regimen is consistent with the reference product dosing regimen: • 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)	Uveitis: For the 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, Fresenius Kabi USA, LLC, submitted a supplemental biologics license application for BLA 761255 (sBLA-003) to expand the indication for IDACIO (adalimumab-aacf) to include the treatment of adult patients with non-infectious intermediate, posterior, and panuveitis (UV). Orphan drug exclusivity for the adult HS indication expired June 30, 2023. The UV indication was not included in the initial biosimilar approval for IDACIO dated December 13, 2022. The Applicant is now seeking licensure of adalimumab-aacf for the treatment of UV in adults.

No new clinical information is included or required for this submission. The Applicant has provided a scientific justification for extrapolation for the population currently being sought for licensure. The current submission provides for updated labeling to include the new indication.

2. Background

IDACIO (adalimumab-aacf) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against tumor necrosis factor (TNF) alpha. Adalimumab-aacf was approved as a biosimilar to US-licensed HUMIRA (US-HUMIRA) on December 13, 2022, under section 351(k) of the Public Health Service Act (BLA 761255), 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 active 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 colitis in adult patients.

7. Plaque Psoriasis (Ps): 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.

On October 11, 2023, a supplemental application adding an indication for treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients (sBLA-002) was approved.

The original BLA for adalimumab-aacf included the following:

- A comprehensive comparative analytical assessment of adalimumab-aacf and US-HUMIRA. This assessment included a comparative characterization of physicochemical attributes and comparative functional assessments.
- Pharmacokinetic (PK) similarity studies (FKS022-002 and EMR200588-001) in healthy adult subjects. Study FKS022-022 adequately demonstrated the PK similarity among the to-be-marketed formulation of adalimumab-aacf, US-HUMIRA and a citrate formulation, supporting the PK component of the bridge to use the citrate formulation in the comparative clinical study (EMR200588-002).

- A comparative clinical study (EMR200588-002) evaluating comparative efficacy, safety, and immunogenicity of adalimumab-aacf and EU-approved HUMIRA (EU-Humira) in subjects with Ps.

- A 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-aacf for each of the additional indications for which Fresenius Kabi USA, LLC was seeking licensure and for which US-HUMIRA had been previously licensed.

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

Review of the information submitted by the Applicant demonstrated that adalimumab-aacf 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-aacf: RA, JIA in patients 2 years of age and older, PsA, AS, Ps, CD in patients 6 years of age and older, and adult UC. Refer to the Biosimilar Multidisciplinary Evaluation and Review (dated December 13, 2022) from Division of Rheumatology and Transplant Medicine (DRTM), Division of Dermatology and Dentistry (DDD), and Division of Gastroenterology (DG) for additional details. On October 11, 2023, under supplement 002, the approved indications were expanded to include treatment of moderate to severe HS in adult patients. Refer to CDER Clinical, CDTL, and Division Summary Memo dated October 3, 2023.

IDACIO is approved in the following presentations:

- 40 mg/0.8 mL single-dose prefilled pen (IDACIO Pen)
- 40 mg/0.8 mL single-dose prefilled glass syringe

3. CMC/Product Quality

For sBLA-003, 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 IDACIO for the additional indication being sought (SDN 74). In the sBLA-003 submission, the Applicant provided information to support their claim.

On October 4, 2023, the applicant provided a claim for categorical exclusion from environmental assessment requirements in compliance with the categorical exclusion criteria 21 CFR Part 25.31. The Applicant states that the estimated concentration of the substance(s) at the point of entry into the aquatic environment will be below 1 part per billion (ppb) and there are no extraordinary circumstances as described in 21 CFR 25.15(d). Idacio is a recombinant human IgG1 monoclonal antibody, which can be metabolized to amino acids in the body and are eliminated by either excretion or catabolism. Therefore, the current claim of categorical exclusion from environmental assessment requirements of preparing an environmental assessment for the involved clinical site(s) is acceptable.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted or required for this sBLA. 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 or 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-aacf was previously evaluated in a comparative clinical study in subjects with Ps (EMR200588-002). The data were previously reviewed and summarized in the clinical and statistical reviews of the original BLA by DDD and DRTM, dated December 13, 2022. No new clinical/statistical efficacy information was submitted or required for this sBLA. There are no clinical/statistical efficacy issues that would preclude approval of the indication sought for licensure.

7. Safety

Adalimumab-aacf was previously evaluated in a comparative clinical study in subjects with Ps (EMR200588-002), and in healthy subjects in single-dose clinical pharmacology studies FKS022-022 and EMR200588-001. The data were previously reviewed and summarized in the clinical review dated December 13, 2022, of the original BLA by DDD and DRTM. No new safety data were submitted or required for this sBLA. 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

Adalimumab-aacf is an approved biosimilar for the treatment of RA, JIA in patients 2 years of age and older, PsA, AS, CD in patients 6 years of age and older, adult UC,

adult HS and Ps. In the original BLA submission, the Applicant provided data and support for biosimilarity between adalimumab-aacf and US-Humira, including extensive analytical characterization that demonstrated that adalimumab-aacf 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-aacf and US-HUMIRA in terms of safety, purity, and potency.

Justification for Extrapolation to UV Indication

Consistent with the principles of the FDA Guidance - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015), the Division of Ophthalmology has concluded that the Applicant provided sufficient scientific justification to support extrapolation of data and information submitted in the application to support licensure of adalimumab-aacf as a biosimilar, under section 351(k) of the PHS Act, for the ophthalmic non-studied indication of non-infectious intermediate, posterior, and panuveitis in adults. The scientific justification based on the mechanism of action, PK, immunogenicity and safety supporting this conclusion are summarized in the original Biosimilar Multidisciplinary Evaluation and Review (dated December 13, 2022). This conclusion remains unchanged: The Applicant's scientific justification for extrapolation supports licensure of adalimumab-aacf for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients and pediatric patients 2 to 17 years of age. The scientific considerations are outlined below:

- PK similarity was demonstrated between adalimumab-aacf and US-HUMIRA. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between adalimumab-aacf and US-HUMIRA in the indications sought for licensure. A similar PK profile would be expected between adalimumab-aacf and US-HUMIRA in patients with UV in adults and pediatric patients 2 to 17 years of age.

- 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). There were sufficient data to support similar immunogenicity between adalimumab-aacf and US-HUMIRA with repeat dosing in patients with Ps, and between adalimumab-aacf and US-HUMIRA, after a single dose in healthy subjects. Accordingly, similar immunogenicity would be expected between adalimumab-aacf and US-HUMIRA in patients with RA, JIA, PsA, HS, UV and AS.

- There were no clinically meaningful differences between adalimumab-aacf and US-HUMIRA in patients with Ps or in healthy subjects. Coupled with the demonstration of analytical and PK similarity between adalimumab-aacf and US-HUMIRA, a similar safety profile would be expected in patients with RA, JIA, PsA, HS, UV and AS.

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

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.

In conclusion, the totality of evidence and scientific justification discussed above is adequate to justify extrapolating the data and information submitted to support licensure of adalimumab-aacf for the indication of treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 to 17 years of age. Currently, however, only licensure for "treatment of non-infectious intermediate, posterior and panuveitis in adult patients" is being sought, and approved for this sBLA. See more information in Section 9 "Pediatrics."

9. Pediatrics

On December 13, 2022, adalimumab-aacf was approved as a biosimilar to US-HUMIRA. Adalimumab-aacf was considered to be a new active ingredient. As such, it triggered the Pediatric Research Equity Act (PREA).

In order to fulfill PREA requirements for the Uveitis indication, the Applicant submitted an assessment for the UV indication. A term of orphan-drug exclusivity for US-Humira for "the treatment of non-infectious intermediate, posterior and panuveitis in pediatric subjects aged 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 IDACIO; however, FDA cannot license IDACIO 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 Pediatric Review Committee (PeRC) reviewed the information and considered the product to be assessed. On August 15, 2023, the Pediatric Review Committee (PeRC) reviewed the assessment and agreed with the assessment.

10. Other Relevant Regulatory Issues

None.

11. Labeling

Labeling for IDACIO was updated to include the indication for the treatment of non-infectious intermediate, posterior and panuveitis in in adult patients. The submitted package insert, and Medication Guide have been reviewed and found acceptable. 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 conveys the essential scientific information needed for safe and effective use of the product. The final label will be included in the approval letter and at the end of this review.

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-aacf.

14. Recommended Regulatory Action

Approval.

55 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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