Clinical, CrossDiscipline Team Leader, and Division Director Summary Review of BLA 761118/S-011

Date	See Electronic Stamp Date
From	Wiley A. Chambers, MD
Subject	Clinical, Cross-Discipline Team Leader, and Division Director Summary Review
BLA # and Supplement#	761118/S-011
Applicant	Pfizer, Inc.
Date of Submission	February 28, 2023
BSUFA Goal Date	August 28, 2023
Proprietary Name	Abrilada (adalimumab-afzb)
Product Code Name	PF-06410293
Reference Product Proprietary Name (Proper Name)	US-Humira (adalimumab)
Dosage Form(s)	Injection
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(s)	Same as US-Humira dosing for the respective indications
Recommendation on Regulatory Action	Approval
Recommended Indication(s)	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, Pfizer, Inc., submitted a supplemental biologics license application for BLA 761118 (sBLA-011) to expand the indication for Abrilada (adalimumab-afzb) to include the treatment of non-infectious intermediate, posterior and panuveitis in adult patients (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 761118 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

Abrilada (adalimumab-afzb) 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. Abrilada is supplied at 10 mg/0.2 mL (single-dose prefilled syringe), 20 mg/0.4 mL (single-dose prefilled syringe), and 40 mg/0.8 mL (single-dose prefilled syringe, single-dose prefilled pen, and single-dose glass vial for institutional use). Abrilada is administered by subcutaneous injection. Abrilada (adalimumab-afzb) was approved as a biosimilar to US-licensed Humira (US-Humira) on November 15, 2019 under section 351(k) of the Public Health Service Act. Abrilada 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): 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.

PF-06410293 (adalimumab-afzb) was approved as a biosimilar to U.S.-Humira on 15 November 2019, in patients with RA, JIA in patients 4 years of age and older, AS, adult CD, adult UC, PsA, Ps. The approval was based on the following:

- PF-06410293 is highly similar to U.S.-Humira, notwithstanding minor differences in clinically inactive components. The proposed strengths of PF-06410293 in prefilled syringes (40 mg/0.8 mL, 20 mg/0.4 mL, 10 mg/0.2 mL), in prefilled pen (40 mg/0.8 mL) and in a single-dose glass vial for institutional use only (40 mg/0.8 mL) are the same as those of U.S.-Humira. The dosage form and route of administration are also the same as those of U.S.-Humira.
- There are no clinically meaningful differences between PF-06410293 and U.S.-Humira based on PK, immunogenicity, safety and efficacy assessment from the PK similarity study (Study B5381007) in healthy subjects and the comparative clinical study in patients with moderately to severely active RA on stable background methotrexate (MTX) (Study B5381002).
- The PK portion of the scientific bridge was established based on results of a 3-way PK similarity study (Study B5381007) comparing PF-06410293 (40 mg/0.8 mL PFS), E.U.-Humira (40 mg/0.8mL), or U.S.-Humira (40 mg/0.8mL) to support the relevance of the data generated using E.U.-Humira as the comparator in the comparative clinical study (Study B5381002).
- An adequate scientific justification for extrapolation of data and information to support licensure as a biosimilar for each of the additional indications for which the Applicant was seeking licensure and for which U.S.-Humira has been previously approved.

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

Review of the information submitted by the Applicant demonstrated that adalimumab-afzb 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-afzb: RA, pJIA in patients 4 years of age and older, PsA, AS, adult PS, CD in adults, HS in adults and adult UC. See Biosimilar Multi-Disciplinary Evaluation and Review (BMER), dated November 15, 2019.

On July 29, 2022, under supplement 6, PF-06410293 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 (CDTL) review dated July 21, 2022 for additional details.

On June 14, 2023, under supplement 9, the approved indications were expanded to include treatment of moderate to severe HS in adult patients. Refer to DDD Clinical, CDTL, and Division Summary Review dated June 12, 2023.

Abrilada is approved in the following presentations:

- 40 mg/0.8 mL in a single-dose prefilled pen (Abrilada pen)
- 40 mg/0.8 mL in a single-dose prefilled glass syringe
- 20 mg/0.4 mL in a single-dose prefilled glass syringe
- 10 mg/0.2 mL in a single-dose prefilled glass syringe
- 40 mg/0.8 mL in a single-dose glass vial for institutional use only

3. CMC/Product Quality

For sBLA-011, 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 Abrilada for the additional indication being sought. In the August 9, 2023, sBLA amendment, the Applicant provided information to support their claim. The basis for the claim for categorical exclusion under 21 CFR 25.31(c) has not changed with the addition of the new indication and 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-afzb was previously evaluated in comparative clinical studies. The data were previously reviewed and summarized above and in the clinical and statistical reviews of the original BLA (refer to the BMER dated November 15, 2019) and sBLA S-006 by DPARP (refer to Dr. Juwaria Waheed Clinical review dated July 21, 2022). 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 indication 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

Abrilada (adalimumab-afzb) 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, HS and Ps. In the original BLA submission, the Applicant provided data and support for biosimilarity, including extensive analytical characterization that demonstrated that adalimumab-afzb 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-afzb and US-Humira in terms of safety, purity, and potency based on similar clinical PK in healthy subjects and similar efficacy, safety, and immunogenicity.

Justification for Extrapolation to Non-studied Indications in Original BLA

Additional points considered in the justification for extrapolation of data and information to support licensure of adalimumab-afzb 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-afzb and US-Humira. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between adalimumab-afzb and US-Humira in the indications sought for licensure. A similar PK profile would be expected between adalimumab-afzb and US-Humira in patients with JIA, PsA, AS, adult CD, UC, 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-afzb and US-Humira in patients with RA (See summary of evidence for switching study). Therefore, similar immunogenicity would be expected between adalimumab-afzb and US-Humira in patients with JIA, PsA, AS, adult CD, UC, HS and UV.

- There were no clinically meaningful differences between adalimumab-afzb and US-Humira in patients with RA nor in healthy subjects. Coupled with the demonstration of analytical and PK similarity between adalimumab-afzb, US-Humira, and EU-Humira, a similar safety profile would be expected in patients with JIA, PsA, AS, adult CD, UC, 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-afzb 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-afzb 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-afzb for the treatment of adult patients with non-infectious intermediate, posterior and panuveitis.

9. Pediatrics

The Applicant submitted an assessment which addressed pediatric subjects aged 2 years and above 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 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 Abrilada; however, FDA cannot license Abrilada 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.”

On May 5, 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 Abrilada was updated to include the indication of treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

The submitted package insert, Medication Guide, Instructions for Use, Carton and Container have been reviewed and found to be acceptable. The final label will be included in the approval letter.

81 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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-afzb.

14. Recommended Regulatory Action

Approval.

Authors:

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Division Director	Clinical Team Leader	Deputy Division Director

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