CDER Clinical, CDTL, and Division Summary Memo

Date	June 20, 2023
From	Shera Schreiber, MD
Subject	Clinical, Cross-Discipline Team Leader, and Division Summary Review
BLA # and Supplement#	761059/S-006
Applicant	Samsung Bioepis Co., Ltd.
Date of Submission	February 25, 2022
BSUFA Goal Date	January 10, 2023
Proprietary Name	Hadlima (adalimumab-bwwd)
Reference Product Proprietary Name	US-Humira
Dosage Form(s)	No new proposed dosage forms
Applicant Proposed Indication(s)/Population(s)	Expansion of existing indications to include the following: • Treatment of moderate to severe hidradenitis suppurativa in adult patients
Applicant Proposed Dosing Regimen(s)	Proposed dosing regimen is consistent with the reference product dosing regimen: • Initial dose of 160 mg (given in one day or split over two consecutive days), followed by 80 mg two weeks later (Day 15). Begin 40 mg weekly or 80 mg every other week dosing two weeks later (Day 29).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	For the treatment of moderate to severe hidradenitis suppurativa in adult patients
Recommended Dosing Regimen(s)	Same as reference product dosing regimen

1. Introduction

The Applicant, Samsung Bioepis Co., Ltd., submitted a supplemental biologics license application for BLA 761059 (sBLA-006) to expand the indication for Hadlima (adalimumab-bwwd) to include the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS). This indication was not included in the initial approval of BLA 761059 because at the time of that approval, US-Humira (adalimumab) was eligible for orphan-drug exclusivity for "the treatment of moderate to severe hidradenitis suppurativa." US-Humira's orphan-drug exclusivity for this indication expired on September 9, 2022.

No new clinical information is included nor required for the Applicant's 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. A term of orphan-drug exclusivity for US-Humira for "the treatment of moderate to severe hidradenitis suppurativa (HS) in adolescent patients 12 years of age and older" expires on October 16, 2025.

2. Background

HADLIMA (adalimumab-bwwd) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against tumor necrosis factor (TNF) alpha. Adalimumab-bwwd was approved as a biosimilar to US-licensed Humira (US-Humira) on July 23, 2019 under section 351(k) of the Public Health Service Act (BLA 761059), 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 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 PsA.

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

5. Adult Crohn's Disease (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 UC who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine. The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers.

7. Plaque Psoriasis (PsO): 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.

The original BLA included the following:

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

- Nonclinical studies including a 7-week pharmacology study in Tg197 mice and a 4-week repeat-dose toxicology study in monkeys to compare the effects of adalimumab-bwwd to those of EU-Humira.

- A PK similarity study (SB5-G11-NHV) in healthy subjects following a single SC 40 mg dose of adalimumab-bwwd, EU-Humira, or US-Humira.

- A comparative clinical study (SB5-G31-RA) evaluating comparative efficacy, safety, and immunogenicity of adalimumab-bwwd and EU-Humira in combination with methotrexate in patients with moderately to severely active RA who have had an inadequate response to methotrexate.

- 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-bwwd for each of the additional indications for which Samsung was seeking licensure and for which US-Humira had been previously licensed.

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

Review of the information submitted by the Applicant demonstrated that adalimumab-bwwd 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-bwwd: RA, pJIA in patients 4 years of age and older, PsA, AS, PsO, adult CD, and adult UC. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review (dated July 23, 2019).

Under supplement 4, 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 June 16, 2022 for additional details.

Hadlima is approved in the following strengths and presentations:

- 40 mg/0.8 mL in a single-dose prefilled autoinjector (HADLIMA PushTouch)
- 40 mg/0.8 mL in a single-dose prefilled glass syringe
- 40 mg/0.4 mL prefilled syringe
- 40 mg/0.4 mL autoinjector

3. CMC/Product Quality

For sBLA-006, 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. Of note, at the time of sBLA-006 submission, the Agency was undergoing review of two previously submitted supplements: 761059/S-004 (40 mg/0.8 mL glass vial addition and indication extension) and 761059/S-005 (Hadlima 40 mg/0.4 mL strength addition).

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor 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 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

Hadlima was previously studied in patients with RA in the comparative clinical study (SB5-G31-RA). The data were previously reviewed and summarized in the Biosimilar Multi-Disciplinary Evaluation and Review dated July 23, 2019 for the original application.

There are no clinical/statistical efficacy issues that would preclude approval of this sBLA.

7. Safety

Hadlima was previously studied in patients with RA in the comparative clinical study (SB5-G31-RA) and in healthy subjects in the comparative PK study (SB5-G11-NHV). The data were previously reviewed and summarized in the Biosimilar Multi-Disciplinary Evaluation and Review dated July 23, 2019 for the original application. There are no clinical safety issues that would preclude approval of this sBLA.

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

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

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-bwwd 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-bwwd (Hadlima) and US-Humira. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between adalimumab-bwwd and US-Humira in the indications sought for licensure. A similar PK profile would be expected between adalimumab-bwwd and US-Humira in patients with JIA, PsA, AS, adult CD, and UC.

- 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-bwwd (Hadlima) and US-Humira in patients with

RA and adalimumab-bwwd, US-Humira, and EU-Humira in healthy subjects. Therefore, similar immunogenicity would be expected between adalimumab-bwwd and US-Humira in patients with JIA, PsA, AS, adult CD, and UC.

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

- The Applicant addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that adalimumab-bwwd (Hadlima) 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 Moderate to Severe HS Indication

In the original BLA submission, the Applicant did not seek licensure for the indication of moderate to severe HS in adult patients because of remaining orphan-drug exclusivity for US-Humira for the HS 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-bwwd (Hadlima) for this indication. The scientific justification for extrapolation to non-studied indications which was submitted with the original BLA is also applicable to HS, and supports licensure of adalimumab-bwwd for the treatment of adult patients with moderate to severe HS.

9. Pediatrics

On July 23, 2019, Hadlima (adalimumab-bwwd) was approved as a biosimilar to US-Humira. Adalimumab-bwwd was considered a new active ingredient. As such, it triggered the Pediatric Research Equity Act (PREA). At the time of initial licensure, no PREA postmarketing requirement was issued for the HS indication. In order to fulfill PREA requirements, the Applicant submitted a pediatric plan (dated June 22, 2022) as an addendum to this sBLA submission.

A term of orphan-drug exclusivity for US-Humira for “the treatment of moderate to severe hidradenitis suppurativa (HS) in adolescent patients 12 years of age and older” expires on October 16, 2025. The Applicant proposes to fulfill PREA requirements for adolescents aged 12 years to 17 years for this indication by (b) (4)
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FDA cannot license Hadlima for this indication in this age group until US-Humira's orphan-drug exclusivity for it expires on October 16, 2025. The Applicant also noted that the labeling for US-Humira does not contain adequate pediatric information for pediatric patients less than 12 years of age. PREA requirements were partially waived for US-Humira for the HS indication in pediatric patients less than 12 years of age due to the extremely low prevalence of HS in this age group. The Applicant refers to the following guidance for industry: "Questions and Answers on Biosimilar Development and the BPCI Act."

The pediatric plan was discussed at the Pediatric Review Committee (PeRC) on November 22, 2022, and the PeRC was again consulted on June 20, 2023. (b) (4)

10. Other Relevant Regulatory Issues

Not applicable.

11. Labeling

Prescribing Information

Labeling for HADLIMA was updated to include the indication of moderate to severe HS in adult patients. The table below presents a high level summary of the labeling proposal and subsequent interaction between the Applicant and the Agency. Revisions made by the Agency are presented in *italics* in the table below.

Table 1: Summary of Significant Labeling Changes

Section	Labeling Changes and Discussion
Highlights of Prescribing Information Recent Major Changes	• Indications and Usage (1.8), Dosage and Administration (2.6), and Warnings and Precautions, Malignancies (5.2) were added to this section.
Highlights of Prescribing Information	• HS was added under Indications and Usage (1.8). • The dosing regimen for HS was added under Dosing and Administration (2.6).
Section 1 Indications and Usage	• The indication for treatment of moderate to severe HS *in adult patients* was added.
Section 2 Dosage and Administration	• The dosing regimen for HS *in adults* was added.

Section 5 Warnings and Precautions	• 5.2 Malignancies: HS was added to list of conditions studied in clinical trials for adalimumab.
Section 6.1 Clinical Trials Experience	• Information regarding liver enzyme elevations in clinical trials evaluating adalimumab for the treatment of HS was added for alignment with the reference product labeling. • Safety information from clinical trials evaluating adalimumab for the treatment of HS was added for alignment with the reference product labeling. • Immunogenicity data from clinical trial evaluating adalimumab for the treatment of HS was added for alignment with the reference product labeling
Section 12.2 Pharmacodynamics	• Information regarding HS was added for alignment with the reference product labeling.
Section 12.3 Pharmacokinetics	• PK data relevant to the indication of HS was added for alignment with the reference product labeling.
Section 14.9 Adult Hidradenitis Suppurativa	• Information regarding clinical trials which evaluated adalimumab for the treatment of moderate to severe HS in adults was added for alignment with the reference product labeling.

Source: Reviewer's Table

Other Labeling/Medication Guide

The Medication Guide was updated to include the HS indication, consistent with the Medication Guide for the reference product.

Labeling consultants, including Office of Biotechnology Products (OBP)-labeling, Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP), and the Division of Medical Policy Programs (DMPP) have reviewed the submitted labeling and found the proposed revisions acceptable. All labeling changes were agreed upon with the Applicant.

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-bwwd.

14. Recommended Regulatory Action

Approval.

15. DDD Designated Signatory Comments

To be added.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERA C SCHREIBER
06/26/2023 04:09:01 PM

DAVID L KETTL
06/27/2023 09:05:34 AM

SHARI L TARGUM
06/27/2023 02:33:02 PM