CDER Clinical, CDTL, and Division Summary Memo

Date	March 29, 2023
From	K. Dev Verma, MD
Subject	Clinical, Cross-Discipline Team Leader, and Division Summary Review
BLA # and Supplement#	761216/S-003
Applicant	Coherus BioSciences, Inc.
Date of Submission	October 3, 2022
BSUFA Goal Date	April 3, 2023
Proprietary Name	YUSIMRY (adalimumab-aqvh)
Reference Product Proprietary 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: • 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, Coherus BioSciences, Inc., submitted a supplemental biologics license application for BLA 761216 (sBLA-003) to expand the indication for YUSIMRY (adalimumab-aqvh) to include the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS). The HS indication was not included in the initial approval dated December 17, 2021 because this indication was protected under orphan drug exclusivity which expired September 9, 2022. No new clinical information is included nor 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

YUSIMRY (adalimumab-aqvh) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against tumor necrosis factor (TNF) alpha. Adalimumab-aqvh was approved as a biosimilar to US-licensed HUMIRA (US-HUMIRA) on December 17, 2021 under section 351(k) of the Public Health Service Act (BLA 761216), 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. Limitations of Use: 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 for adalimumab-aqvh included the following:

- A comprehensive comparative analytical assessment of adalimumab-aqvh and US-licensed HUMIRA (US-HUMIRA). This assessment included a comparative characterization of physicochemical attributes and comparative functional assessments.

- Nonclinical studies including a one-month, repeat-dose general toxicology and toxicokinetic study in cynomolgus monkeys to compare the effects of adalimumab-aqvh to those of US-HUMIRA.

- A pharmacokinetic (PK) similarity study (CHS-1420-03) in healthy adult subjects following a single SC 40 mg dose of adalimumab-aqvh or US-HUMIRA.

- A comparative clinical study (CHS-1420-02) evaluating comparative efficacy, safety, and immunogenicity of adalimumab-aqvh and US-HUMIRA in patients with chronic PsO.

  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-aqvh for each of the additional indications for which Coherus BioSciences, Inc. was seeking licensure and for 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-aqvh is highly similar to US-HUMIRA, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between adalimumab-aqvh 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-aqvh for the non-studied indications sought for approval.

Review of the information submitted by the Applicant demonstrated that adalimumab-aqvh 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-aqvh: RA, pJIA in patients 2 years of age and older, PsA, AS, PsO, CD in patients 6 years of age and older, and adult UC. Refer to the Biosimliar Multidisciplinary Evaluation and Review (dated December 17, 2021) from Division of Rheumatology and Transplant Medicine (DRTM), Division of Dermatology and Dentistry (DDD), and Division of Gastroenterology (DG) for additional details.

YUSIMRY is approved in the following presentations:

- 40 mg/0.8 mL single-dose prefilled glass syringe
- 40 mg/0.8 mL single-dose prefilled pen

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 YUSIMRY for the additional indication being sought (SDN 50). In the sBLA submission, the Applicant provided information to support their claim.

In a review dated February 15, 2023, Anshu Rastogi, Ph.D. from the Office of Biotechnology Products/ Division of Biotechnology Review & Research I (OBP/DBRR I), provided the following comments from the CMC assessment team:

> "The applicant requested a categorical exclusion from the requirements to prepare an EA under 21 CFR 25.31(c), and provided justifications thereof, in Section 1.12.14 of their response to an information request (sent 12/16/2022, received 01/18/2023). Assessor Comment: The claim of categorial exclusion from an EA is acceptable."

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

Adalimumab-aqvh was previously evaluated in a comparative clinical study in subjects with PsO (20120263). The data were previously reviewed and summarized in the clinical and statistical reviews of the original BLA by DDD and DRTM, dated December 17, 2021. 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

Adalimumab-aqvh was previously evaluated in a comparative clinical study in subjects with PsO (CH-1420-02), and in healthy subjects in a PK similarity study (CHS-1420-03). The data were previously reviewed and summarized in the clinical review dated December 17, 2021 of the original BLA by DDD and DRTM. No new safety data were submitted nor 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-aqvh is an approved biosimilar for the treatment of RA, pJIA in patients 2 years of age and older, PsA, AS, CD in patients 6 years of age and older, UC, and PsO. In the original BLA submission, the Applicant provided data and support for biosimilarity, including extensive analytical characterization that demonstrated that adalimumab-aqvh 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-aqvh 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 PsO.

Justification for Extrapolation to Non-studied Indications in Original BLA

Points considered in the justification for extrapolation of data and information to support licensure of adalimumab-aqvh 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-aqvh and US-HUMIRA. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between adalimumab-aqvh and US-HUMIRA in the indications sought for licensure. A similar PK profile would be expected between adalimumab-aqvh and US-HUMIRA in the rheumatology indications 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 assay used (per labeling for US-HUMIRA). There were sufficient data to support similar immunogenicity between CHS-1420 and US-HUMIRA with repeat dosing in patients with PsO, and between CHS-1420 and US-HUMIRA, after a single dose in healthy subjects. Accordingly, similar immunogenicity would

be expected between CHS-1420 and US-HUMIRA in patients with RA, JIA, PsA, and AS.

- There were no clinically meaningful differences between adalimumab-aqvh and US-HUMIRA in patients with PsO nor in healthy subjects. Coupled with the demonstration of analytical and PK similarity between adalimumab-aqvh and US-HUMIRA, a similar safety profile would be expected in patients with RA, JIA, PsA, 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-aqvh 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 submitted justification for extrapolation of the data and information in support of licensure of adalimumab-aqvh 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-aqvh for the treatment of adult patients with moderate to severe HS.

9. Pediatrics

On December 17, 2021, adalimumab-aqvh was approved as a biosimilar to US-HUMIRA. Adalimumab-aqvh was considered to be 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 Study Plan (agreed to by the Agency on November 23, 2020) to IND 119540. The HS indication was not addressed in this PSP since the adult indication was protected under orphan drug exclusivity which expired September 9, 2022

In the October 3, 2022 sBLA, the Applicant submitted an amended Pediatric Study Plan (PSP). This PSP included the approach to address the entire pediatric age range using biosimilar extrapolation for the 12 to 18 year age group and to refer to the biosimilar Q&A guidance for patients younger than 12 years of age. The Applicant noted that the reference product is not approved for patients younger than 12 years old and the labeling does not include information for those patients. (b) (4)

(b) (4)

On February 28, 2023, the Pediatric Review Committee (PeRC) reviewed the amended PSP and agreed with the proposed assessments for the HS indication.

10. Other Relevant Regulatory Issues

None.

11. Labeling

Prescribing Information

Labeling for YUSIMRY 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. A new presentation, 40 mg/0.8 mL prefilled autoinjector (AI) pen, was approved through BLA 761216-S001 on 2/27/2023 before the BSUFA goal date for this application. Therefore, this dosage form was also added to labeling.

Table 1: Summary of Significant Labeling Changes

Section	Labeling Changes and Discussion
Highlights of Prescribing Information	• HS was added under Indications and Usage (1.8). • The dosing regimen for HS was added under Dosage and Administration (2.6). • The newly approved single-dose prefilled pen was added under Dosage Forms and Strengths (3).
Section 1 Indications and Usage	• The indication for treatment of moderate to severe HS in adult patients was added (1.8).
Section 2 Dosage and Administration	• The dosing regimen for HS in adults was added (2.6).
Section 3 Dosage Forms and Strengths	• The new dosage form (single-dose prefilled pen) approved through S-001 on 2/27/23 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.
Section 6.2 Immunogenicity	• Immunogenicity data from clinical trials evaluating adalimumab for the treatment of HS was added to Table 2 for alignment with the reference product labeling.
Section 7.2 Biological Products	• HS was added as an indication for the statement "There is insufficient information regarding the concomitant use of YUSIMRY and other biologic products for the treatment of …," 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-aqvh.

14. Recommended Regulatory Action

Approval.

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/

KAPIL D VERMA
03/29/2023 03:05:09 PM

MELINDA L MCCORD
03/29/2023 03:28:26 PM