Cross-Discipline Team Leader Review

Date	*March 20, 2025*
From	Mary Kim, MD (CDTL, DDD)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	BLA 761379, Supplements 2 (b) (4)
Applicant	Fresenius Kabi USA, LLC
Date of Submission	November 22, 2024
BsUFA Goal Date	March 22, 2025
Division/Office	Division of Dermatology and Dentistry (DDD) Office of Immunology and Inflammation (OII)
Product Code Name	FYB202
Proprietary Name	Otulfi
Non-Proprietary Name	Ustekinumab-aauz
Applicant Proposed Indication(s)/Population(s)	• moderate to severe plaque psoriasis (PsO) in adults and pediatric patients (6 years or older) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) in adults and pediatric patients (6 years or older) • moderately to severely active Crohn's disease (CD) in adults • moderately to severely active ulcerative colitis (UC) in adults
Recommended Indication(s)/Population(s) (if applicable)	• moderate to severe plaque psoriasis (PsO) in adults and pediatric patients (6 years or older) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) in adults and pediatric patients (6 years or older) • moderately to severely active Crohn's disease (CD) in adults • moderately to severely active ulcerative colitis (UC) in adults
Recommendation on Regulatory Action	Approval of FYB202 injection 45 mg/0.5 mL in a single dose-vial for subcutaneous use as biosimilar to U.S.-Stelara (ustekinumab) 45 mg/0.5 mL in a single-dose vial for subcutaneous use to fulfill the PMR requirement that the Applicant develop a presentation that can be used to accurately administer FYB202 to pediatric patients who weigh less than 60 kg. (b) (4)

	(b) (4)

1. Background

Stelara (ustekinumab) is a human interleukin-12 and -23 antagonist indicated for the treatment of adults patients with moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy, active psoriatic arthritis (PsA), moderately to severely active Crohn's disease (CD), and moderately to severely active ulcerative colitis, and pediatric patients 6 years and older with moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy and active psoriatic arthritis (PsA). The approved dosage form, strengths, routes of administration, and presentations of Stelara (ustekinumab) include a 45 mg/0.5 mL injection in a single-dose prefilled syringe for subcutaneous use, a 90 mg/mL injection in a single-dose prefilled syringe for subcutaneous use, a 45 mg/0.5 mL injection in a single-dose vial for subcutaneous use (for weight-based dosing of pediatric patients with a body weight of less than 60 kg), and a 130 mg/26 mL (5 mg/mL) injection in a single-dose vial for intravenous use.

On September 27, 2024, Otulfi (ustekinumab-aauz) (FYB202) was approved as biosimilar to Stelara (ustekinumab) for the treatment of adults patients with moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy, active psoriatic arthritis (PsA), moderately to severely active Crohn's disease (CD), and moderately to severely active ulcerative colitis, and pediatric patients 6 years and older with moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy and active psoriatic arthritis (PsA). The approved dosage form, strengths, routes of administration, and presentations of Otulfi (ustekinumab-aauz) include a 45 mg/0.5 mL injection in a single-dose prefilled syringe for subcutaneous use, a 90 mg/mL injection in a single-dose prefilled syringe for subcutaneous use, and 130 mg/26 mL (5 mg/mL) injection in a single-dose vial for intravenous use.

At the time, (b) (4) , as described above. Refer to the Biosimilar

[1] Refer to the Purple Book at https://purplebooksearch.fda.gov/.

Multidisciplinary Evaluation and Review (BMER) for BLA 761379 dated September 26, 2024.

The Applicant did not seek licensure of Otulfi (ustekinumab-aauz) in a 45 mg/0.5 mL single-dose vial for subcutaneous use for weight-based dosing of pediatric patients with a body weight of less than 60 kg under BLA 761379. With the approval of BLA 761379 on September 27, 2024, the following Pediatric Research Equity Act (PREA) Post-Marketing Requirement (PMR) was issued: 4707-1 Develop a presentation that can be used to accurately administer Otulfi (ustekinumab-aauz) to pediatric patients who weigh less than 60 kg.

On November 22, 2024, Fresenius Kabi USA, LLC (also referred to as “Applicant” in this review) submitted a post-approval supplemental (PAS) biologic license application (BLA) 761379, Supplement 2, under section 351(k) of the Public Health Service Act (PHS Act) for a proposed FYB202 45 mg/0.5 mL single-dose vial as biosimilar to (b) (4) US-licensed Stelara (US-Stelara, ustekinumab) 45 mg/0.5 mL single-dose vial to fulfill the PREA PMR requirement to develop a presentation that can be used to accurately administer FYB202 to pediatric patients who weigh less than 60 kg.

2. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval of BLA 761379, Supplement 2 from the product quality perspective. The Applicant has provided additional comparative analytical assessment (CAA) data between the FYB202 45mg/0.5 mL vial and US-Stelara 45mg/0.5mL vial presentations, manufacturing data including process development and validation, comparability assessments. OPQ has concluded that the proposed 45 mg/0.5 mL vial drug product (DP) is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components and the manufacturing data supports that the 45 mg/0.5 mL vial DP manufacturing process can consistently manufacture DP that meets all of its product quality attributes. Therefore, approval of this supplement for the 45 mg/0.5 mL vial DP pediatric presentation of FYB202 and fulfillment of PMR 4707-1 is recommended from the product quality perspective. Refer to the OPQ review by Dr. Eric Hales dated March 03, 2025.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) reviewed BLA 761379, Supplement 2 from a sterility assurance perspective and BLA 761379, Supplement 2 is recommended for approval. Additionally, the manufacturing facility assessment recommendation is for approval. Refer to the OPMA review dated February 28, 2025.

3. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology information is included in this submission. There are no nonclinical pharmacology/ toxicology issues that would preclude approval. Refer to the Biosimilar Multidisciplinary Evaluation and Review (BMER) for BLA 761379 dated September 26, 2024.

4. Clinical Pharmacology

No new clinical pharmacology information was included in this submission. There are no clinical pharmacology issues that would preclude approval. Refer to the BMER for BLA 761379 filed in DARRTS on September 26, 2024.

5. Clinical/Statistical- Efficacy

No new clinical statistical-efficacy information was included in this supplement. There are no clinical/statistical efficacy issues that would preclude approval. Refer to the Biosimilar Multidisciplinary Evaluation and Review (BMER) for BLA 761379 dated September 26, 2024.

6. Safety

No new clinical safety information was included in this supplement. There are no clinical safety issues that would preclude approval. Refer to the Biosimilar Multidisciplinary Evaluation and Review (BMER) for BLA 761379 dated September 26, 2024.

7. Advisory Committee Meeting

Not applicable

8. Pediatrics

The Applicant submitted an Initial Pediatric Study Plan (iPSP) on July 30, 2021. After receiving comments from the Agency on September 16, 2021, the Applicant submitted an Agreed Initial Pediatric Study Plan (iPSP) on December 14, 2021. In July 2022, an additional pediatric indication was approved for Stelara, pediatric psoriatic arthritis (pPsA) in children aged 6 years and older. Additional FDA comments to this submission recommending an update to the pediatric assessment for PsA in the pediatric study plan were conveyed in Jun 2023. The Applicant submitted a revised Agreed iPSP on July 27, 2023, which included a proposed assessment via extrapolation for pediatric patients ages 6-17 years with plaque

psoriasis and psoriatic arthritis. After a Pediatric Review Committee (PeRC) review on September 19, 2023, the FDA sent a letter of agreement for the revised Agreed iPSP on November 24, 2023.

In the original BLA submission, there was no presentation for FYB202 that allowed for accurate weight-based dosing for pediatric patients weighing less than 60 kg. Per the Agreed iPSP, the Applicant committed to also develop an age-appropriate formulation (presentation) for weight-based dosing of FYB202, i.e., a single-dose vial of 45 mg/0.5 mL injection for subcutaneous use that will "contain the same composition as the reference product".

This Application was discussed at the PeRC meeting on September 17, 2024. PeRC recommended that a Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) be issued for the development of an age-appropriate presentation for weight-based dosing of the product for patients with plaque psoriasis and/or psoriatic arthritis as young as 6 years of age and weighing less than 60 kg.

The following PREA PMR (4707-1) was issued:

- Develop a presentation that can be used to accurately administer Otulfi (ustekinumab-aauz) to pediatric patients who weigh less than 60 kg.

Given that the recommended regulatory action for this supplement includes approval of the 45 mg/0.5 mL vial as a biosimilar product, along with the recommendations from PeRC on March 11, 2025, recommend PMR 4707-1 be considered fulfilled.

There are no additional PREA requirements for this supplemental BLA.

9. Other Relevant Regulatory Issues

None.

10. Labeling

This supplement provides for Otulfi (ustekinumab-aauz) 45 mg/0.5 mL vial presentation for subcutaneous use for pediatric patients weighing less than 60 kg which will be reflected in the appropriate sections in labeling. The statement "There is no dosage form for OTULFI that allows weight-based dosing for pediatric patients below 60kg" will be removed from Section 2 of current labeling for Otulfi (ustekinumab-aauz).

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed container labels and carton labeling and recommended approval. Refer to DMEPA reviews dated on 2/19/2025 and 3/14/2025 in DARRTS.

It has been determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

11. Postmarketing Recommendations/Commitments

The Applicant has fulfilled the following PMR issued on September 27, 2024:

4707-1 Develop a presentation that can be used to accurately administer Otulfi (ustekinumab-aauz) to pediatric patients who weigh less than 60 kg.

There are no additional postmarketing recommendations/commitments associated with the approval of this supplement.

12. Recommendation of Regulatory Action

OPQ has concluded that the proposed 45 mg/0.5 mL vial drug product (DP) is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components and the manufacturing data supports that the 45 mg/0.5 mL vial DP manufacturing process can consistently manufacture DP that meets all of its product quality attributes and recommends approval of BLA 761379 Supplement 2 from the product quality perspective. OPMA recommends approval of BLA 761379 Supplement 2 from the sterility assurance perspective. Additionally, the manufacturing facility assessment recommendation is for approval.

FDA has further determined that the data and information provided by the applicant in the BLA and this supplement support a demonstration of no clinically meaningful differences between the Otulfi (ustekinumab-aauz) (FYB202) 45 mg/0.5 mL single-dose vial and US-Stelara 45 mg/0.5 mL single-dose vial. The conditions of use for Otulfi (ustekinumab-aauz) (FYB202) 45 mg/0.5 mL single-dose vial have been previously approved for US-Stelara 45 mg/0.5 mL single-dose vial, and the strength, dosage form, and route of administration of Otulfi (ustekinumab-aauz) (FYB202) 45 mg/0.5 mL single-dose vial are the same as those of US-Stelara 45 mg/0.5 mL single-dose vial. The Applicant has provided adequate data and information to support a demonstration that Otulfi (ustekinumab-aauz) (FYB202) 45 mg/0.5 mL single-dose vial can be expected to produce the same clinical result as the US-Stelara 45 mg/0.5 mL single-dose vial in any given patient. (b) (4)

The FDA review team recommends approval of the Otulfi (ustekinumab-aauz) (FYB202) 45 mg/0.5 mL single-dose vial for subcutaneous use as biosimilar to US-

Stelara (ustekinumab) 45 mg/0.5 mL single-dose vial for subcutaneous use. With approval of the FYB202 45mg/0.5 mL single-dose vial, the review team recommends PMR 4707-1 be considered fulfilled.

(b) (4)

Therefore, the FDA review team recommends that sBLA 761379-002 be administratively split to facilitate an approval action for Otulfi (ustekinumab-aauz) (FYB202) 45 mg/0.5 mL single-dose vial for subcutaneous use as biosimilar to US-Stelara (ustekinumab) 45 mg/0.5 mL single-dose vial for subcutaneous use in sBLA 761379-002, (b) (4)

[2] https://purplebooksearch.fda.gov/

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/s/

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