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APPLICATION NUMBER:

761379Orig2s000

SUMMARY REVIEW

Office of Therapeutic Biologics and Biosimilars
Clinical, Cross-Discipline Team Leader, and Division Memo

Date	See Electronic Stamp Date
From	Juwaria Waheed, MD (Clinical Reviewer, OTBB) Thomas Herndon, MD (CTL, CDTL, OTBB) Tatiana Oussova, MD (Division Signatory, DDD, OII)
Subject	Request for Approval for Interchangeability - Cross-Discipline Review of the amendments to BLA 761379/Original 2, and sBLA 761379/S-004, BsUFA Category F
Application Type	351(k) BLA, and 351(k) BLA Prior Approval Supplement
BLA/Supplement Number	BLA 761379/Original 2 and sBLA 761379/S-004
Received Date	October 30, 2024 and April 11, 2025
Target Action Date	April 30, 2025
Division/Office	Division of Dermatology and Dentistry (DDD)
Proprietary Name	Otulfi
Proper Name	ustekinumab-aauz
Product Code	FYB202
Reference Product	US-licensed Stelara (ustekinumab)
Pharmacologic Class	Human interleukin-12 and -23 antagonist
Applicant	Fresenius Kabi USA, LLC
Approved Indication(s)	Adult 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) • moderately to severely active ulcerative colitis (UC) Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA)
Purpose of the Submission	Approval of Otulfi (ustekinumab-aauz) injection as interchangeable with US-Stelara (ustekinumab) as follows per the provisional determination letters for BLA 761379/Original 2 dated September 27, 2024 and for sBLA 761379-004 dated March 21, 2025: • Otulfi injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use

	• Otulfi injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use • Otulfi injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use as interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use • Otulfi injection 45 mg/0.5 mL single-dose vial for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5mL single-dose vial for subcutaneous use
Recommendation on Regulatory Action	Approval of the following as interchangeable products: • Approval of Otulfi (ustekinumab-aauz) injection 45 mg/0.5 mL and 90 mg/mL prefilled syringe (PFS) for subcutaneous use • Approval of Otulfi (ustekinumab-aauz) injection 45 mg/0.5 mL single-dose vial for subcutaneous use • Approval of Otulfi (ustekinumab-aauz) injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

1. Introduction

The subjects of this review are the October 30, 2024 amendment to BLA 761379/Original 2, and the April 11, 2025 amendment to sBLA 761379/S-004 to seek approval for interchangeability for all products under each application or supplement, respectively, that previously received a provisional determination of interchangeability.

On September 28, 2023, Fresenius Kabi USA, LLC (hereafter referred to as "the Applicant"[1]) submitted Biologics License Application (BLA) 761379 under section 351(k) of the Public Health Service (PHS) Act seeking licensure of Otulfi (proper name: ustekinumab-aauz; product code: FYB202) as an interchangeable biosimilar product as follows:

- Otulfi injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as biosimilar to and interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
- Otulfi injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as biosimilar to and interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
- Otulfi injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use as biosimilar to and interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

On November 22, 2024, the Applicant submitted a supplemental BLA 761379/S-002 under section 351(k) of the PHS Act seeking licensure of Otulfi (ustekinumab-aauz; product code: FYB202) as an interchangeable biosimilar product as follows:

- Otulfi injection 45 mg/0.5 mL single-dose vial for subcutaneous use as biosimilar to and interchangeable with US-Stelara injection 45 mg/0.5mL single-dose vial for subcutaneous use

The data and information in the original BLA and in Supplement 2 (S-002) supported licensure of Otulfi as a biosimilar product. The Applicant included a scientific justification that Otulfi will produce the same clinical result in any given patient for each condition of use for which licensure is sought and for which US-Stelara has been approved, a scientific justification for extrapolating data and information to support licensure of Otulfi as an interchangeable for each indication for which licensure is sought and for which US-Stelara has been previously approved, and use-related risk analyses and

[1] At the time of the original submission, Formycon AG owned BLA 761379. During the review cycle, Formycon AG informed the FDA that they transferred ownership of BLA 761379 to Fresenius Kabi USA, LLC on April 23, 2024. FDA acknowledged the change in ownership prior to licensure (of BLA 761379 Original 1) via an acknowledgement letter to the new applicant. For the purposes of this review, Fresenius Kabi USA, LLC will be referred to as "the Applicant".

comparative analyses for the PFS platforms. The data and information in the BLA demonstrated that Otulfi can be expected to produce the same clinical result as US-Stelara in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Otulfi and US-Stelara is not greater than the use of US-Stelara without such alternation or switch.

After reviewing the original BLA 761379 and sBLA 761379/S-002, FDA did not identify any deficiencies that would justify a complete response action. FDA considered whether any unexpired first interchangeable exclusivity precluded approval of any products in the original application and supplemental application as interchangeable. The Otulfi (ustekinumab-aauz) injection 45 mg/0.5 mL and 90 mg/mL prefilled syringe (PFS) for subcutaneous use, 45 mg/0.5 mL single-dose vial for subcutaneous use and 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use could not be approved as interchangeable due to unexpired first interchangeable exclusivity for Wezlana (ustekinumab-auub) injection 45 mg/0.5 mL and 90 mg/mL for subcutaneous use, and 130 mg/26 mL (5 mg/mL) for intravenous use.
Refer to the Purple Book at https://purplebooksearch.fda.gov for more information about unexpired first interchangeable exclusivity.

BLA 761379 was administratively split to facilitate the following:

- An approval action for BLA 761379/Original 1
    - Otulfi injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as biosimilar to US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
    - Otulfi injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as biosimilar to US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
    - Otulfi injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use as biosimilar to US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

- A provisional determination for BLA 761379/Original 2
    - Otulfi injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use would be interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
    - Otulfi injection 90 mg/mL single-dose prefilled syringe for subcutaneous use would be interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
    - Otulfi injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use would be interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

BLA 761379 Supplement 002 (S-002) was administratively split into S-002 and S-004 to facilitate the following:

- An approval action for S-002:
  - Otulfi injection 45 mg/0.5 mL single-dose vial for subcutaneous use as biosimilar to US-Stelara injection 45 mg/0.5mL single-dose vial for subcutaneous use

- A provisional determination for S-004:
  - Otulfi injection 45 mg/0.5 mL single-dose vial for subcutaneous use would be interchangeable with US-Stelara injection 45 mg/0.5mL single-dose vial for subcutaneous use

The "Biosimilar Multidisciplinary Evaluation and Review" (BMER) documenting the Agency's review of the original application dated September 26, 2024 and the CDTL memo documenting the Agency's review of supplement 002 dated March 20, 2025, are incorporated herein by reference. Refer to them for additional information.

The Original 1 application received an approval letter dated September 27, 2024, and the Original 2 application received a provisional determination letter dated September 27, 2024.

Supplement 002 received an approval letter dated March 21, 2025, and supplement 004 received a provisional determination letter dated March 21, 2025.

The provisional determination letters instructed the Applicant to submit an amendment no more than six months prior to the date it believed that the application or the supplemental application would be eligible for approval.

To obtain approval of Otulfi (ustekinumab-aauz) injection 45 mg/0.5 mL and 90 mg/mL prefilled syringes for subcutaneous use, and Otulfi (ustekinumab-aauz) injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use as interchangeable products, the Applicant submitted an amendment, "Request for Approval" on October 30, 2024, which is the subject of this review.

To obtain approval of Otulfi (ustekinumab-aauz) injection 45 mg/0.5 mL single-dose vial for subcutaneous use as an interchangeable product, the Applicant submitted an amendment, "Request for Approval" on April 11, 2025, which is also the subject of this review.

2. Background

Otulfi (proper name: ustekinumab-aauz; product code: FYB202) was approved as a biosimilar to US-Stelara (ustekinumab) on September 27, 2024. Refer to the BMER dated September 26, 2024, and the CDTL memo dated March 20, 2025, for background information, including a summary of key regulatory interactions.

3. Product Quality

No new product quality information was submitted nor required for these amendments. There are no product quality issues that would preclude approval. Refer to the BMER dated September 26, 2024 and the CDTL memo dated March 20, 2024. All facilities remain compliant to support approval.

The review team considered and determined that there are no new product quality information or updates since the provisional determination letters were issued (September 27, 2024, and March 21, 2025, respectively) that would impact the provisional determination of interchangeability. The Applicant also confirmed the same in its April 16, 2025 response an information request (IR).

4. Clinical and Statistical Evaluation and Recommendations

No new clinical efficacy and safety or statistical information was submitted nor required for these amendments. There are no clinical efficacy and safety or statistical issues that would preclude approval. Refer to the BMER dated September 26, 2024 and the CDTL memo dated March 20, 2024.

The review team considered and determined that there are no new safety information or updates since the provisional determination letters were issued (September 27, 2024, and March 21, 2025, respectively) that would impact the provisional determination of interchangeability. The Applicant also confirmed the same in response to the information request (IR) dated April 16, 2025.

5. Labeling

Labeling for the original application and S-004 was reviewed and agreed upon with the Applicant during FDA's reviews of the original application and S-004, respectively. No changes to the labeling are necessary for the approval of this amendment. The final labeling will be attached to the approval letter.

The review team determined that there are no new labeling updates since the provisional determination letters were issued (September 27, 2024, and March 21, 2025, respectively) that would impact the provisional determination of interchangeability. The Applicant also confirmed the same in its April 16, 2025 response to an IR.

6. Summary Assessment

The PD letters issued September 27, 2024 and March 21, 2025 state that "In addition to a safety update, the amendment should also identify changes, if any, in the application,

i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS)."

An IR was sent to the Applicant on April 9, 2025 to confirm if any changes have occurred to BLA 761379 and sBLA 761379/S-004 from the date of FDA's issuance of the PD letter that could impact the provisional determination of interchangeability, specifically addressing the following: safety, labeling changes, chemistry, manufacturing, and controls (CMC) data, and interim supplement approvals or expected supplement approvals.

The Division has approved supplements in the interim since the Original 2 application and supplement 004 received provisional determination letters. The review team has considered if there are any changes approved in these intervening supplements that could impact our finding, at the time we issued the PD letters, that this application/supplement met relevant statutory standards for approval. We have determined that they do not. The Applicant also confirmed the same in its April 16, 2025 response to an IR.

The review team also determined that there are no changes or updates to the application and/or supplements including safety, labeling, CMC data, and expected supplement approvals (when applicable) since the issuance of the PD letters (September 27, 2024 and March 21, 2025, respectively) and until the expiration of the FIE on April 30, 2025 that would impact the provisional determination of interchangeability. The Applicant confirmed the same in its April 16, 2025 response to an IR.

7. Pediatrics

No pediatric studies would be required under PREA for this BLA and S-004.

Refer to the BMER dated September 26, 2024 and CDTL memo dated March 21, 2025, for more information.

8. REMS and Postmarketing Requirements and Commitments

There are no REMS, PMRs, or PMCs associated with these amendments to BLA 761379/Original 2 and to sBLA 761379/S-004.

All previously issued PMC(s) that have not been fulfilled remain in place. Refer to BLA 761379/Original 1 approval letter, dated September 27, 2024.

Refer to the BMER dated September 26, 2024 for more information.

9. Other Regulatory Issues

None.

10. Recommended Regulatory Action

The data and information in BLA 761379 and sBLA 761379/S-004, including the information submitted by the Applicant with these amendments, are sufficient to maintain FDA's determination that Otulfi can be expected to produce the same clinical result as US-Stelara in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Otulfi and US-Stelara is not greater than the use of US-Stelara without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that:

- Otulfi injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use meets the statutory standards to be interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
- Otulfi injection 90 mg/mL single-dose prefilled syringe for subcutaneous use meets the statutory standards to be interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
- Otulfi injection 45 mg/0.5 mL single-dose vial for subcutaneous use meets the statutory standards to be interchangeable with US-Stelara injection 45 mg/0.5mL single-dose vial for subcutaneous use
- Otulfi injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use meets the statutory standards to be interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

These Otulfi (ustekinumab-aauz) products have met the statutory interchangeability requirements for the following indications for which US-Stelara has been previously approved:

Adult 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)
- moderately to severely active ulcerative colitis (UC)

Pediatric patients 6 years and older with:

- moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis (PsA)

As noted in the Purple Book (https://purplebooksearch.fda.gov), the first interchangeable exclusivity expiration date is as follows:

- April 30, 2025 – Wezlana (ustekinumab-auub) injection 45 mg/0.5 mL and 90 mg/mL for subcutaneous use and 130 mg/26 mL (5 mg/mL) for intravenous use.

The recommended regulatory action is approval of the following:

- BLA 761379 Original 2
  - Otulfi injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use is interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
  - Otulfi injection 90 mg/mL single-dose prefilled syringe for subcutaneous use is interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
  - Otulfi injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use is interchangeable with US-Stelara injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

- sBLA 761379/S-004:
  - Otulfi injection 45 mg/0.5 mL single-dose vial for subcutaneous use is interchangeable with US-Stelara injection 45 mg/0.5mL single-dose vial for subcutaneous use

11. Recommended Comments to the Applicant

None.

12. Division Director or Designated Signatory Comments

I concur with the review team's assessment of the data and information submitted in this amendment and support the regulatory action.

13. Appendices

None.

14. References

None.

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/

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