CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761379Orig2s000

OTHER ACTION LETTERS

BLA 761379/Original 2

PROVISIONAL DETERMINATION

Fresenius Kabi USA, LLC
Attention: Navayath Shobana, PhD
Senior Director, Regulatory Affairs Lead
Three Corporate Drive
Lake Zurich, IL 60047

Dear Dr. Shobana:

Please refer to your biologics license application (BLA) dated and received September 28, 2023, and your amendments, submitted under section 351(k) of the Public Health Service (PHS) Act for Otulfi (ustekinumab-aauz) injection.

BLA 761379 seeks licensure of:

- Otulfi (ustekinumab-aauz) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as interchangeable with Stelara (ustekinumab) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use,

- Otulfi (ustekinumab-aauz) injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as interchangeable with Stelara (ustekinumab) injection 90 mg/mL single-dose prefilled syringe for subcutaneous use, and

- Otulfi (ustekinumab-aauz) injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable with Stelara (ustekinumab) injection 130 mg/26 mL single-dose vial for intravenous use.

This BLA proposes the use of Otulfi (ustekinumab-aauz) injection for adult and pediatric patients 6 years and older with moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy, adult and pediatric patients 6 years and older with active psoriatic arthritis (PsA), adult patients with moderately to severely active Crohn's disease (CD), and adult patients with moderately to severely active ulcerative colitis.

For administrative purposes, we have split BLA 761379 as follows:

- BLA 761379/Original 1 – biosimilarity
- BLA 761379/Original 2 – interchangeability

The subject of this correspondence is BLA 761379/Original 2. A separate correspondence was issued for BLA 761379/Original 1.

All future submissions to these BLAs should specify the BLA number and the Original number to which each submission pertains.

We have completed a provisional review of this application, as amended. A final determination under sections 351(i) and 351(k) of the PHS Act that:

- Otulfi (ustekinumab-aauz) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use would be interchangeable with Stelara (ustekinumab) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use

- Otulfi (ustekinumab-aauz) injection 90 mg/mL single-dose prefilled syringe for subcutaneous use would be interchangeable with Stelara (ustekinumab) injection 90 mg/mL single-dose prefilled syringe for subcutaneous use

- Otulfi (ustekinumab-aauz) injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use would be interchangeable with Stelara (ustekinumab) injection 130 mg/26 mL (5 mg/mL) single-dose vial for intravenous use

is currently subject to unexpired exclusivity for the first interchangeable biosimilar biological products, and thus may not be made before the exclusivity has expired. See section 351(k)(6) of the PHS Act. We have not identified any deficiencies that would justify a complete response action at this time; however, we also cannot approve your application because of the unexpired first interchangeable exclusivity. We have therefore provisionally determined that your 351(k) application meets the interchangeability criteria under section 351(k) of the PHS Act.

This provisional determination is based upon information available to the Agency at this time (i.e., information in your application and that the manufacturing of the biological product complies with the standards established in the BLA as well as the requirements in applicable regulations). This determination is subject to change on the basis of any new information that may come to our attention.

To obtain approval of this application, submit an amendment no more than six months prior to the date you believe that your application will be eligible for approval. In your cover letter, clearly identify your amendment as **"REQUEST FOR APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for approval and should include a copy of any relevant supporting documentation, as appropriate. 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). If there are no changes, clearly state so in your cover letter. Any changes require our review before approval, and the goal date for our review will be set accordingly.

BLA 761379/Original 2 is not approved and Otulfi (ustekinumab-aauz) cannot be legally marketed as an interchangeable biosimilar product unless and until you have been

notified in writing that BLA 761379/Original 2 is approved after any necessary additional review. Enclosed are the currently agreed upon labeling (text for the Prescribing Information, Medication Guide, Instructions for Use, Carton and Container labeling). If you believe that there are grounds for issuing the approval letter before the expiration of the exclusivity period, you should amend your application accordingly.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Refer to the BLA Approval letter for BLA 761379/Original 1 for required pediatric assessments.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4707-2	Perform a real-world commercial shipping validation study to confirm the suitability of shipping container and transportation method with respect to maintaining intended product temperature, package integrity, and product quality of the Otulfi drug product, stored in a vial (5 mg/mL) and pre-filled syringe (90 mg/mL), based on the worst case scenario.

The timetable you submitted on September 4, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2025

4707-3 Perform an additional study(ies) to support the control limits for (b) (4) FYB202 90 mg/mL pre-filled syringe drug product batch. The study should be designed to support worst-case (b) (4) FYB202 DS batches (b) (4) Submit the results in a final study report to the BLA.

The timetable you submitted on August 26, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2025

4707-4 Implement pressure monitoring during sterilizing filtration of FYB202 5 mg/mL vial drug product (DP) and update Sections 3.2.P.3.3 and 3.2.P.3.4 of the BLA (b) (4)

The timetable you submitted on May 10, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2025

4707-5 Validate and implement a container closure integrity test (CCIT) method (b) (4)

The timetable you submitted on June 12, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

4707-6 Conduct a minimum load sterilization validation study with three runs (b) (4)

The timetable you submitted on June 12, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

4707-7 Validate and implement an alternative quantitative bacterial endotoxin method not subject to low endotoxin recovery to replace the USP <151> pyrogen test for FYB 202 5 mg/mL vial DP release.

The timetable you submitted on May 10, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2025

4707-8 Revalidate the blue dye ingress CCIT method to demonstrate the CCIT method is reliable for use (i.e., all positive controls show positive results) for FYB202 drug product pre-filled syringe (PFS) 45 mg in 0.5 mL and FYB202 DP PFS 90 mg in 1.0 mL.

The timetable you submitted on May 10, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

Submit clinical protocols to your IND 141478 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

If you have any questions, contact Kimberle Searcy, Regulatory Project Manager, at 240-402-4454.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling

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

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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/

TATIANA OUSSOVA
09/27/2024 01:45:58 PM