Cross-Discipline Team Leader Review

Date	*Electronic Stamp Date*
From	Snezana Trajkovic, MD (CDTL, DDD)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	BLA 761343
Applicant	Alvotech USA, Inc.
Date of Submission	October 16, 2023
BsUFA Goal Date	April 16, 2024
Product Code Name	AVT04
Proposed Proprietary Name[1]	Selarsdi
Proposed Non-Proprietary Name[1]	Ustekinumab-aekn
Applicant Proposed Indication(s)/Population(s)	• Patients 6 years and older with plaque psoriasis (PsO) • Patients 6 years and older with psoriatic arthritis (PsA)
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA). Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis (PsO), who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA).
Recommendation on Regulatory Action	Approval

[1] The proposed proprietary and non-proprietary names are conditionally accepted until such time that the application is approved.

APPEARS THIS WAY ON ORIGINAL

1. Background

Alvotech (also referred to as “Applicant” in this review) submitted an original biologic license application (BLA 761343) under section 351(k) of the Public Health Service Act (PHS Act) for AVT04 45 mg/0.5 mL and 90 mg/mL in a prefilled syringe as a proposed biosimilar to US-licensed Stelara (US-Stelara, ustekinumab) 45 mg/0.5 mL and 90 mg/mL, on October 11, 2022. The totality of the evidence submitted by the Applicant supported the conclusion that AVT04 was highly similar to U.S.-licensed Stelara, notwithstanding minor differences in clinically inactive components, and that there were no clinically meaningful differences between AVT04 and U.S.-licensed Stelara 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 AVT04 for PsA in patients 6 years and older and for PsO in patients 6 years and older. The Applicant sufficiently demonstrated that AVT04 is biosimilar to U.S.-licensed Stelara for each of the requested indications for which U.S.-licensed Stelara is currently licensed.

However, data submitted in the application was not sufficient to support a conclusion that the manufacture of AVT04 was well-controlled and would lead to a product that is pure and potent for the duration of the shelf-life. Therefore, the FDA review team recommended a Complete Response for the application on October 11, 2023. The Complete Response Letter outlined the deficiencies and the information and data required to address the deficiencies. Also, refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on October 11, 2023.

On October 16, 2023, the Applicant resubmitted their biologic license application (BLA 761343) under section 351(k) of the Public Health Service Act (PHS Act) for AVT04 as a proposed biosimilar to US-Stelara. This is the review summary of the current application.

2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761343 for AVT04 (45 mg/0.5 mL, 90 mg/mL) manufactured by Alvotech hf, Reykjavik, Iceland. The data submitted in this resubmission are adequate to support a conclusion that the manufacture of AVT04 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. OPQ recommends approval of the proposed AVT04 (45 mg/0.5 mL, 90 mg/mL) prefilled syringe presentation. Refer to the integrated quality assessment and related primary reviews for detailed information. The

OPQ team determined that the data submitted for these proposed presentations in this application are adequate to support the following conclusions:

- The manufacture of AVT04 (45 mg/0.5 mL, 90 mg/mL) is well-controlled and leads to a product that is pure, potent, and safe.
- AVT04 (45 mg/0.5 mL, 90 mg/mL) is highly similar to US-Stelara (45 mg/0.5 mL, 90 mg/mL) notwithstanding minor differences in clinically inactive components.
- The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies using EU-Stelara as the comparator for the assessment of biosimilarity.
- The strength of AVT04 (45 mg/0.5 mL, 90 mg/mL) in a pre-filled syringe is the same as that of US-Stelara (45 mg/0.5 mL, 90 mg/mL).
- AVT04 (45 mg/0.5 mL, 90 mg/mL) also has the same dosage form and route of administration as that of US-Stelara (45 mg/0.5 mL, 90 mg/mL).

The CDTL and the Division Signatory agree with this assessment and recommendations. See the OPQ review dated February 15, 2024.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information is included in this resubmission. There are no nonclinical pharmacology/toxicology issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on October 11, 2023.

4. Clinical Pharmacology

No new clinical pharmacology information is included in this resubmission. There are no clinical pharmacology issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on October 11, 2023.

5. Clinical/Statistical- Efficacy

No new clinical/statistical efficacy information is included in this resubmission. There are no clinical/statistical efficacy issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on October 11, 2023

6. Safety

No new clinical safety information is included in this resubmission. There are no clinical safety issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on October 11, 2023.

7. Advisory Committee Meeting

No advisory committee was held for this biosimilar application as it was determined that there were no issues where the Agency needed input from the committee.

8. Pediatrics

The Applicant submitted an Initial Pediatric Study Plan (iPSP) on November 10, 2021. After receiving comments from the Agency on February 28, 2022, the Applicant submitted an Agreed Initial Pediatric Study Plan on July 18, 2022. In July 2022, an additional pediatric indication was approved for Stelara, pediatric psoriatic arthritis (pPsA) in children aged 6 years and older. A BPD type 4 meeting was held on 15 August 2022 to discuss a revision for inclusion of pPsA patients 6 years and older in the agreed iPSP for AVT04 due to inclusion of this pediatric population in the Stelara labeling from July 2022. Meeting minutes from the BPD type 4 meeting were sent to the Applicant on September 14, 2022 which recommended an update to the pediatric assessment for PsA in the pediatric study plan should be submitted in the initial BLA application. In the BLA application dated October 11, 2022, an amendment to the agreed iPSP was included which

included an assessment via extrapolation for pediatric patients ages 6-17 years with plaque psoriasis and psoriatic arthritis (b) (4)

(b) (4)

This resubmission was discussed at the Pediatric Review Committee (PeRC) meeting on February 20, 2024. PeRC recommended that a post marketing requirement (PMR) be issued for the development of an age-appropriate presentation for weight-based dosing of the product for patients as young as 6 years of age weighing less than 60 kg.

The following PMR has been issued:

- Develop a presentation that can be used to directly and accurately administer Selarsdi (ustekinumab-aekn) to pediatric patients who weigh less than 60 kg.

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9. Other Relevant Regulatory Issues

None

10. Labeling

Nonproprietary Name

The Applicant's proposed nonproprietary name, ustekinumab-aekn, was found to be conditionally accepted by the Agency. See Division of Medication Error and Prevention (DMEPA) reviews dated February 16, 2024 for full details.

Proprietary Name

The proposed proprietary name for AVT02 is conditionally approved as Selarsdi. This name has been reviewed by the DMEPA, who concluded the name was acceptable. See DMEPA reviews dated December 29, 2023, for full details.

Other Labeling Recommendations

FDA 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.

The proposed prescribing information has incorporated relevant data and information from the U.S.-Stelara prescribing information with appropriate modifications relevant to the indications.

Alvotech USA Inc. submitted revised container labels received on March 8, 2024, for Selarsdi. The revisions were made in response to recommendations that were made during a previous label and labeling review recommended by the Division of Medication Error Prevention and Analysis 1 (DMEPA 1). Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on October 11, 2023, and the labeling reviews filed in DARRTS on February 22, 2024, and March 11, 2024.

The Office of Prescription Drug Promotion (OPDP) also reviewed the proposed Prescribing Information (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original BLA submission for SELARSDI(ustekinumab-aekn). See the OPDP review filed in DARRTS on March 12, 2024.

11. Postmarketing Recommendations

The following PREA postmarketing requirement (PMR) is issued:

- Develop a presentation that can be used to directly and accurately administer Selarsdi (ustekinumab-aekn) to pediatric patients who weigh less than 60 kg.

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12. Recommendation of Regulatory Action

Data submitted in this application is sufficient to support a conclusion that the manufacture of AVT04 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. In addition, the data and information included in the application, including this resubmission, are sufficient to support licensure of Selarsdi (ustekinumab-aekn) injection 45 mg/0.5 mL prefilled syringe and 90 mg/mL prefilled syringe for subcutaneous use as a biosimilar to US-licensed Stelara (ustekinumab) injection, 45 mg/0.5 mL and 90 mg/mL for subcutaneous use, respectively. This reviewer recommends Approval of this application.

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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