Cross-Discipline Team Leader Review

Date	See Electronic Stamp Date
From	Division of Dermatology and Dentistry
Subject	Cross-Discipline Team Leader Review
BLA # and Supplement#	761343/s-005
Applicant	Alvotech USA Inc.
Date of Submission	11/18/2024
BsUFA Goal Date	02/19/2025
Proprietary Name	Selarsdi
Established or Proper Name	ustekinumab-aekn
Strength(s)	45 mg/0.5 mL vial
Applicant Proposed Indication(s)/Population(s)	• Moderately to severely active Crohn's disease • Moderately to severely active ulcerative colitis (b) (4)
Recommendation on Regulatory Action	*Approval*

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1. Background

The subject of this summary review is the resubmission of supplement 005 to support licensure of AVT04 45 mg/0.5 mL in a vial and to fulfill PMR 4623-1, which required the Applicant to develop a presentation that can be used to accurately administer Selarsdi (ustekinumab-aekn) to pediatric patients who weigh less than 60 kg.

Alvotech (also referred to as "Applicant" in this review) submitted an original biologics license application (BLA 761343) under section 351(k) of the Public Health Service Act (PHS Act) for AVT04 (Selarsdi; ustekinumab-aekn) 45 mg/0.5 mL and 90 mg/mL in a prefilled syringe as a proposed biosimilar to US-licensed Stelara (US-Stelara, ustekinumab), on October 11, 2022. The totality of the evidence submitted by the Applicant supported the conclusion that AVT04 was highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components, and that there were no clinically meaningful differences between AVT04 and US-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 US-licensed Stelara for each of the requested indications for which US-licensed Stelara was 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 (BMER) filed in DARRTS on October 11, 2023.

On October 16, 2023, the Applicant resubmitted their biologics 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 which received an approval on April 16, 2024. Refer to the Cross-Disciplinary Team Leader (CDTL) memo filed in DARRTS on April 16, 2024.

The Applicant submitted a supplemental BLA (BLA (b) (4) /S-002) for Selarsdi on April 19, 2024 as an application to support licensure of AVT04 45 mg/0.5 mL in a vial and 130 mg/26 mL in a vial as a biosimilar to US licensed Stelara, under section 351(k) of the PHS Act, to add the indications of treatment of adult patients with moderately to severely active Crohn's disease (CD) and moderately to severely active ulcerative colitis (UC), and to fulfill postmarketing requirement (PMR) 4623-1, which required the Applicant to develop a presentation that can be used to accurately administer Selarsdi (ustekinumab-aekn) to pediatric patients who weigh less than 60 kg. The application was administratively split. The AVT04 130 mg/26 mL in a vial and the proposed indications were reviewed separately under supplement 002 and

received an approval on October 18, 2024. Supplement 005 was reviewed to support licensure of AVT04 45 mg/0.5 mL in a vial and to fulfill postmarketing requirement (PMR) 4623-1. However, data submitted in this application was insufficient to assure safety of the AVT04 vial 45mg/0.5 mL drug product in its container closure system. Therefore, the FDA review team issued a Complete Response for the application on October 18, 2024. The Complete Response Letter outlined the deficiencies, and the information and data required to address the deficiencies. Refer to the Cross-Discipline Team Leader Review Memo dated October 17, 2024, for more information about FDA's review of the proposed AVT04 45 mg/0.5 mL vial at that time.

OnOctober 31, 2024, the Applicant resubmitted supplement 005 to support licensure of AVT04 45 mg/0.5 mL in a vial and to fulfill PMR 4623-1, the subject of this review.

1. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761343/005 for AVT04 45mg/0.5mL in a vial manufactured by Alvotech hf, Reykjavik, Iceland.

Sufficient information was provided on extractables and leachables for AVT04 DP Vial 45 mg in its container closure system (CCS) to address the CR issues and to determine the safety of the AVT04 drug product administered to patients using the 45 mg/0.5 mL vial.

The OPQ team determined that the data submitted for the proposed presentation in this application is adequate to support approval. OPQ recommends approval of the proposed AVT04 45mg/0.5mL in a vial with Post-Marketing Commitments (PMC)s. Refer to Section 11 for details of the PMCs. The CDTL and the Division Signatory agree with this assessment and recommendations. See the OPQ reviews in Panorama.

2. 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.

3. Clinical Pharmacology

No new clinical pharmacology information is included in this resubmission. There are no new clinical pharmacology issues that would preclude approval. Refer to the

Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on October 11, 2023.

4. Clinical Microbiology

Not applicable.

5. Clinical/Statistical- Efficacy

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

7. Advisory Committee Meeting

Not applicable.

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 weighing at least 60 kg. With the approval of the BLA for Selarsdi (ustekinumab-aekn), and with recommendations from the Pediatric Review Committee (PeRC) meeting on February 20, 2024, a post marketing requirement (PMR) was 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.

> PMR-4623-1: Develop a presentation that can be used to directly and accurately administer Selarsdi (ustekinumab-aekn) to pediatric patients who weigh less than 60 kg.

Given that the review of the new information supporting licensure of 45mg/0.5mL vial was deemed sufficient, with the recommendations from PeRC on January 21, 2025, the PMR can be considered fulfilled at this time.

9. Other Relevant Regulatory Issues

FDA received a Citizen Petition[1] requesting that "FDA refuse to license any biosimilar version of Ustekinumab as interchangeable with the brand-name reference product that is manufactured using a Chinese hamster ovary ("CHO") cell-line system—and in particular Ustekinumab-ttwe—unless and until the Agency has evaluated and concluded that the differences in sialyation between the proposed interchangeable biosimilar and the reference product, Stelara (ustekinumab), do not have the potential to adversely affect half-life and clinical effectiveness—particularly with respect to therapeutic response durability."[2] The product proposed in this supplement is not manufactured using a CHO cell-line system, and this supplement seeks licensure of the proposed product as biosimilar to Stelara but does not seek licensure of the proposed product as interchangeable with Stelara; therefore, this supplement is not implicated by the Citizen Petition.

10. Labeling

This supplement provides for 45 mg/0.5 mL vial presentation that can be used to directly and accurately administer Selarsdi (ustekinumab-aekn) to pediatric patients who weigh less than 60 kg therefore, the statement "There is no dosage form for SELARSDI that allows weight-based dosing for pediatric patients below 60kg" will be removed from Section 2 of labeling.

11. Postmarketing Recommendations

The OPQ team has issued the following PMCs:

[1] See Docket FDA-2024-P-4538 available at https://www.regulations.gov/docket/FDA-2024-P-4538.
[2] See Citizen Petition from Alvotech USA Inc. dated September 24, 2024 available at https://www.regulations.gov/document/FDA-2024-P-4538-0001

PMC 4801-01 To implement [redacted] the control strategy for PS-80 in the drug product (DP) manufacturing process of AVT04-DP Vial 45. Update Sections 3.2.P.3.3 Description of Manufacturing Process and Process Controls and 3.2.P.3.4 Control of Critical Steps and Intermediate with the appropriate information on DP manufacturing process step [redacted] Provide justification(s) for the selected process [redacted] in ensuring consistent [redacted] concentrations during DP manufacturing process and in the final drug product, AVT04-DP Vial 45.
Final Report Submission Date: 03/2025

PMC 4801-02 To implement a method for drug product (DP) gross content per vial with upper and lower limits in the DP release specification for AVT04-DP Vial 45. Submit the final study report that will include the description of the analytical method, method verification/validation to support that the method is suitable to test the DP gross content per vial, and data and information to support the specification.
Final Report Submission Date: 10/25

PMC 4801-03 Update the acceptance criteria for extractable volume from single to two decimal points for release and shelf-life test results for AVT04-DP Vial 45 to ensure that for each released DP lot the labeled dose of 0.5 mL can be withdrawn and administered to the patients throughout the shelf-life of the product.
Final Report Submission Date: 03/2025

PMC 4801-04 To provide results from the real-world shipping study for AVT04-DP Vial 45 [redacted] to ensure that the quality of the drug product and integrity of the container closure system are maintained until it reaches the end-user. Submit the final study report, including data for the product quality attributes and shipping container temperatures (internal, external), from the drug product shipping studies performed per the real time temperature monitoring study protocol for AVT04-[redacted] vial presentation, [redacted] to qualify the commercial shipping process.
Final Report Submission Date: 06/2025

PMC 4801-05 To validate [redacted] in a new bacterial retention study [redacted] will be controlled within the [redacted] limit. [redacted]
Final Report Submission Date: 10/31/2025

12. Recommended Regulatory Action

The Applicant provided adequate information to support approval of this supplement. FDA has determined that the Applicant has provided adequate data and information in the BLA, including this supplement, to support a demonstration that AVT04 45 mg/0.5 mL in a vial is highly similar to US-Stelara 45 mg/0.5 mL in a vial, notwithstanding minor differences in clinically inactive components. FDA has further determined that the data and information provided by the Applicant in the BLA and this supplement—including the data submitted from the clinical development program and the analytical similarity and comparability data—support a demonstration of no clinically meaningful differences between AVT04 45 mg/0.5 mL in a vial and US-Stelara 45 mg/0.5 mL in a vial. The conditions of use for AVT04 45 mg/0.5 mL in a vial have been previously approved for US-Stelara 45 mg/0.5 mL in a vial, and the strength, dosage form, and route of administration of AVT04 45 mg/0.5 mL in a vial are the same as those of US-Stelara 45 mg/0.5 mL in a vial.

The totality of data and information provided in the BLA, including in this supplement, support licensure of AVT04 vial 45 mg/0.5 mL in a vial as biosimilar to Stelara 45 mg/0.5 mL in a vial. This reviewer recommends approval of the AVT04 injection 45 mg/0.5 mL vial for subcutaneous use as biosimilar to US-Stelara (ustekinumab) injection 45 mg/0.5 mL vial for subcutaneous use. With approval of the AVT04 vial 45mg/0.5 mL, PMR-4623-1 is considered fulfilled.

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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