

Cross-Discipline Team Leader Review

Date	See Electronic Stamp Date
From	
Subject	Cross-Discipline Team Leader Review
BLA # and Supplement#	761343/s-005
Applicant	Alvotech USA Inc.
Date of Submission	04/19/2024
PDUFA Goal Date	10/19/2024
Proprietary Name	Selarsdi
Established or Proper Name	ustekinumab-aekn
Strength(s)	45mg/0.5mL vial
Applicant Proposed Indication(s)/Population(s)	<ul style="list-style-type: none"> • Moderately to severely active Crohn’s disease • Moderately to severely active ulcerative colitis <div style="background-color: #cccccc; height: 20px; width: 100%; text-align: right; font-size: 8px;">(b) (4)</div>
Recommendation on Regulatory Action	<i>Complete Response</i>
Recommended Indication(s)/Population(s) (if applicable)	<p>Adult patients with:</p> <ul style="list-style-type: none"> • 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). <p>Pediatric patients 6 years and older with:</p> <ul style="list-style-type: none"> • moderate to severe plaque psoriasis (PsO), who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA).

1. Background

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) 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 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 U.S.-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 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 18, 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, 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 is being administratively split. The current memo, for Supplement 005, is for AVT04 45 mg/0.5 mL in a vial. The AVT04 130 mg/26 mL in a vial will be reviewed separately under supplement 002. This is the review summary of this supplemental BLA application.

1. Product Quality

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

Insufficient information was provided on extractables and leachables for AVT04 DP Vial 45 mg in its container closure system (CCS) to determine the safety of the AVT04 drug product administered to patients. Specifically, an extractables study was performed on the AVT04 DP Vial 45 CCS, which identified extractables with potential safety risk to patients. No data were provided from a leachables study performed at accelerated and/or stressed storage conditions or at the long-term storage condition of 2-8°C to demonstrate that the identified extractables are not a safety risk to patients. The stressed leachables screening study at 40°C performed on the AVT04 DP Vial 130 mg CCS could not be used to justify that the extractables identified in the AVT04 DP Vial 45 mg CCS are not of safety concern (b) (4)

These data lead to uncertainty on the safety of the drug product administered from AVT04 DP Vial 45 mg CCS to patient safety.

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 inadequate to support approval. OPQ recommends Complete Response of the proposed AVT04 45mg/0.5mL in a vial. The CDTL and the Division Signatory agree with this assessment and recommendations. See the OPQ review in DARRTS dated 10/08/2024.

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 45mg/0.5mL vial was deemed insufficient, the PMR cannot be considered fulfilled at this time and the review will be deferred until the next review cycle.

9. Other Relevant Regulatory Issues

Not applicable.

10. Labeling

In view of the recommendation for a Complete Response, the labeling review was deferred until the next review cycle.

11. Postmarketing Recommendations

None.

12. Recommended Regulatory Action

Data submitted in this application is insufficient to support a conclusion that to assure safety of the AVT04 vial 45mg/0.5 mL drug product in its container closure system. This reviewer recommends Complete Response 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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