Cross-Discipline Team Leader and Division Summary Review

Date	See Electronic Stamp Date
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Subject	Cross-Discipline Team Leader Review Division Summary Review
NDA/BLA # and Supplement#	BLA 761299/016 (b) (4)
Applicant	Alvotech, USA
Date of Submission	October 15, 2024
BsUFA Goal Date	February 15, 2025
Proprietary Name	Simlandi
Proper Name/Code Name	Adalimumab-ryvk/AVT02
Dosage Form(s)	Injection
Purpose of the Submission	Seeking licensure as (b) (4) biosimilar for Simlandi 80 mg/0.8 mL Autoinjector
Applicant Proposed Indication(s)	No new indications are proposed with this supplement
Recommendation on Regulatory Action	Approval of Simlandi (adalimumab-ryvk) injection 80 mg/0.8 mL in an autoinjector (AI) for subcutaneous use as biosimilar to US-Humira (adalimumab) injection 80 mg/0.8 mL in an AI for subcutaneous use. (b) (4)

1. Introduction

Alvotech USA Inc. (hereafter referred to as the "Applicant") submitted a supplemental biologics license application (BLA 761299/S-16) under section 351(k) of the Public Health Service (PHS) Act to propose a new single dose autoinjector (AI) for 80 mg/0.8 mL Simlandi. In this supplement, the Applicant is seeking licensure of 80 mg/0.8 mL Simlandi injection in an AI for subcutaneous use as (b) (4) biosimilar with US-Humira (adalimumab) 80 mg/0.8 mL injection in a prefilled pen (pen) for subcutaneous use.

Simlandi is currently approved in a

- 40 mg/0.4 mL AI as interchangeable with US-Humira 40 mg/0.4 mL in a pen
- 40 mg/0.4 mL in a prefilled syringe (PFS) as interchangeable with US-Humira 40 mg/0.4 mL in a PFS
- 20 mg/0.2 mL in a PFS as biosimilar to US-Humira 20 mg/0.2 mL in a PFS
- 80 mg/0.8 mL in a PFS as biosimilar to US-Humira 80 mg/0.8 mL in a PFS

This memorandum provides an overview of the supplement with a focus on the data relevant to whether the supplement is approvable under section 351(k) of the Public Health Service Act.

2. Background and Regulatory History

Simlandi (adalimumab-ryvk, AVT02) is a recombinant human immunoglobulin (Ig) G1 monoclonal antibody (mAb) against tumor necrosis factor (TNF)-alpha. Simlandi (adalimumab-ryvk) injection 40 mg/0.4 mL in a single dose autoinjector for subcutaneous use was approved on February 23, 2024, under BLA 761299, as interchangeable with US-Humira (adalimumab) injection 40 mg/0.4 mL in a pen for subcutaneous use, for the treatment of rheumatoid arthritis (RA) in adults, juvenile idiopathic arthritis (JIA) in patients 2 years of age and older, psoriatic arthritis (PsA) in adults, ankylosing spondylitis (AS) in adults, Crohn's disease (CD) in patients 6 years of age and older, ulcerative colitis (UC) in adults, plaque psoriasis (Ps) in adults, hidradenitis suppurativa (HS) in adults, and uveitis (UV) in adults.

On June 26, 2024, under supplement 7, 40 mg/0.4 mL Simlandi in a PFS was approved as interchangeable with US-Humira 40 mg/0.4 mL in a PFS and 20 mg/0.2 mL and 80 mg/0.8 mL Simlandi in a PFS were approved as biosimilar to 20 mg/0.2 mL and 80 mg/0.8 mL US-Humira in a PFS, respectively. (b) (4)

On July 22, 2024, the Applicant received a Complete Response for prior approval supplement (PAS) BLA 761299/S- (b) (4) (b) (4) Therefore, due to the deficiencies identified by the product quality review team (b) (4) (b) (4) the Agency recommended Complete Response action for supplement (b) (4) The Applicant, subsequently, withdrew PAS S- (b) (4) on October 7, 2024.

On October 22, 2024, the Applicant submitted the current supplement (S-016).

3. Product Quality

3.1 Product Quality

The Office of Product Quality Assessment (OPQA) III review team recommends approval of this supplement from a product quality perspective.

The Applicant submitted Supplement 16 (eCTD #0113, SDN-159) as a PAS for the assembly of the 80 mg/0.8 mL AVT02 (b) (4) in an AI (AVT02- (b) (4)) presentation at the (b) (4) (FEI: (b) (4)) site. Under this supplement, the AVT02- (b) (4) will be assembled, packaged, and labeled at the (b) (4) site and this site was previously approved for the same functions for the AVT02- (b) (4) with the original BLA submission.

In support of this proposal the Applicant has provided the following:

1. Pre- and post-assembly physicochemical data of the AVT02- (b) (4) presentation from three AI batches manufactured (b) (4) (b) (4)
2. Description of and results from the manufacturing process development and validation of the AVT02- (b) (4) manufacturing process in comparison to the AVT02- (b) (4) assembly process.
3. Relevant transport validation studies for the AVT02- (b) (4) presentation manufactured at the (b) (4) site.
4. Stability results from the AVT02- (b) (4) batch in the physicochemical stability study and a comparison to physicochemical stability testing for AVT02- (b) (4)

The AVT02- (b) (4) assembled, packaged, and labeled at (b) (4) did not show any difference in physicochemical quality attributes between the pre- and post-assembly presentation. The device manufacturing process has minor differences between AVT02- (b) (4) and AVT02- (b) (4) and this assessment is deferred to CDRH reviewers. Transport validation for AVT02- (b) (4) has been submitted previously and the shipping process has been found suitable without affecting product quality and stability. The Applicant provided a physicochemical comparison of three months of stability data for the newly manufactured AVT02- (b) (4) to the AVT02- (b) (4) upon information request. The critical quality attributes and physicochemical stability profile for the AVT02- (b) (4) and AVT02- (b) (4) are comparable.

The Applicant provided sufficient information and data to support the proposed addition of the AVT02- (b) (4) presentation assembled at the (b) (4) site and therefore approval of this supplement is recommended.

The CDRH team recommended approval of the medical device with a post-approval inspection of the (b) (4) (FEI: (b) (4)) under the applicable Medical

Device Regulation. The CDRH assessment for approval was based on data from process development, process validation, shipping qualification as well as release and stability testing.

For additional details, refer to OPQA III review in Panorama dated February 02, 2025.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) reviewed the application from a sterility assurance and a manufacturing facility perspective and did not identify any issues that would preclude approval. Refer to OPMA review in Panorama dated January 30, 2025.

3.2. Devices

3.2.1. Center for Devices and Radiological Health (CDRH)

The proposed presentation includes assembling of the already approved prefilled syringe into an autoinjector. The CDRH team determined that the device constituent parts of the combination product are approvable. Refer to CDRH review in DARRTS dated January 17, 2025.

From the facilities perspective, CDRH recommends a post-approval inspection for the following two facilities:

a. Alvotech hf.
b. (b) (4)

Refer to CDRH review in DARRTS dated January 17, 2025, ICCR Quality System Review Memo.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

The DMEPA 1 review team has concluded that based on the use-related risk analysis, comparative analyses and justifications provided by the Applicant, a comparative use human factors study is not needed to support approval of Simlandi 80 mg/0.8 mL in an AI. Refer to DMEPA 1 review in DARRTS dated January 23, 2025.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA. There are no nonclinical pharmacology/toxicology issues that would preclude approval.

5. Clinical Pharmacology

No new clinical pharmacology information was submitted nor required for this sBLA. There are no clinical pharmacology issues that would preclude approval.

6. Clinical

No new clinical information was submitted nor required for this sBLA. There are no clinical issues that would preclude approval.

7. Advisory Committee Meeting

An Advisory Committee meeting was not held for this supplement, as it was determined that there were no issues where the Agency needed input from the Committee.

8. Pediatrics

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act states that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA.

Because Simlandi injection, 80 mg/0.8 mL for subcutaneous use in an AI will be approved as a biosimilar, this product will be considered to have a new active ingredient for purposes of PREA. Alvotech has completed the pediatric assessment for all the indications for which Simlandi is approved. However, as currently proposed, there is no available presentation to allow for the direct administration of doses of Simlandi lower than 20 mg. This impacts patients who weigh less than 15 kg for the Juvenile Idiopathic Arthritis indication.

Supplement 16 was discussed at the PeRC meeting on February 4, 2025. PeRC recommended issuing a PREA-PMR to the Applicant requiring them to develop a presentation to dose pediatric patients weighing less than 15 kg. Of note, a PMR with the same requirements was issued with the approval of S-007 (BLA 761299/S-007) on June 26, 2024.

The following PREA PMR will be issued:

> 4803-1 Develop a presentation that can be used to accurately administer Simlandi (adalimumab-ryvk) to pediatric patients who weigh less than 15 kg
>
> Final Report Submission: 06/2026

The Applicant was notified that both PMRs (requiring the development of an age-appropriate presentation to dose pediatric patients weighing less than 15 kg) can be fulfilled at the same time. The Applicant agreed.

9. Other Relevant Regulatory Issues

Not applicable.

10. Labeling

Alvotech submitted Branded and Unbranded biological product labeling in this sBLA, and the proposed labeling is acceptable as submitted.

11. Postmarketing Recommendations

Postmarketing Requirements (PMRs)

PMR 4803-1: Develop a presentation that can be used to accurately administer Simlandi (adalimumab-ryvk) to pediatric patients who weigh less than 15 kg.

Final Report Submission: 06/2026

12. Recommended Comments to the Applicant

None.

13. Recommended Regulatory Action

The Applicant provided adequate CMC, human factors, and device data and 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 Simlandi 80 mg/0.8 mL in an AI is highly similar to US-Humira 80 mg/0.8 mL in a pen, 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 Simlandi 80 mg/0.8 mL in an AI and US-Humira 80 mg/0.8 mL in a pen. The conditions of use for Simlandi 80 mg/0.8 mL in an AI have been previously approved for US-Humira, and the strengths, dosage form, and route of administration of Simlandi 80 mg/0.8 mL in an AI are the same as those of US-Humira 80 mg/0.8 mL in a pen. The Applicant has provided adequate data and information to support a

demonstration that Simlandi 80 mg/0.8 mL in an AI can be expected to produce the same clinical result as that of US-Humira 80 mg/0.8 mL in a pen in any given patient. The risk in terms of safety or diminished efficacy of alternating or switching between use of the Simlandi 80 mg/0.8 mL in an AI and US-Humira 80 mg/0.8 mL in a pen is not greater than the risk of using US-Humira 80 mg/0.8 mL in a pen without such alternation or switch.

The FDA review team recommends Approval of the sBLA 761299-016 supplement for Simlandi injection 80 mg/0.8 mL in an AI for subcutaneous use as biosimilar to US-Humira injection 80 mg/0.8 mL in a pen for subcutaneous use.

(b) (4)

Therefore, the FDA review team recommended that sBLA 761299-016 be administratively split to facilitate an approval action for Simlandi injection 80 mg/0.8 mL in an AI for subcutaneous use as a biosimilar product (sBLA 761299-016) (b) (4)

(b) (4)

14. Division Director/Designated Signatory Comments

I concur with the review team's assessment of the data and information submitted in this supplemental BLA and support the regulatory action, as described in Section 13.

[1] https://purplebooksearch.fda.gov/

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