

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761343Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 26, 2024

To: Sascha Randolph, BSDH, PHDHP
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Lonice Carter, MS, RN, CNL, NHDP-BC
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Montherson L. Saint Juste, PharmD, MS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Proprietary name AVT04 (ustekinumab-aekn)¹
(nonproprietary name):

Dosage Form and injection, for subcutaneous use
Route:

¹ AVT04 has been developed as a proposed biosimilar to US-licensed STELARA (ustekinumab). The proposed proprietary name, Selarsdi, was found conditionally acceptable on December 16, 2022 and December 29, 2023. The nonproprietary name, ustekinumab-aekn, was found conditionally acceptable on July 27, 2023 and February 16, 2024.

Application Type/Number: BLA 761343

Applicant: Alvotech USA Inc.
PharmaLex US Corporation
c/o AmerisourceBergen

1 INTRODUCTION

On October 16, 2023, Alvotech USA Inc., PharmaLex US Corporation c/o AmerisourceBergen submitted for the Agency’s review a Class 2 Resubmission of Biologics License Application (BLA) 761343 AVT04 (ustekinumab-aekn) injection, for subcutaneous use in response to the Agency’s Complete Response (CR) Letter dated October 11, 2023. As described by the Applicant, “AVT04 (ustekinumab-aekn) is a proposed biosimilar to the licensed drug product STELARA. This BLA seeks approval for the treatment of a subset of the approved indications and presentations of STELARA. These indications are:

- Plaque Psoriasis (PsO)
- Pediatric Plaque Psoriasis in children age 6 years and older
- Psoriatic Arthritis (PsA)
- Pediatric Psoriatic Arthritis in children age 6 years and older”

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on January 24, 2024, for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) and Instructions for Use (IFU) for AVT04 (ustekinumab-aekn) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft AVT04 (ustekinumab-aekn) MG and IFU received on October 16, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 1, 2024.
- Draft AVT04 (ustekinumab-aekn) Prescribing Information (PI) received on October 16, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 1, 2024.
- Approved STELARA (ustekinumab) comparator labeling dated March 6, 2023.
- Approved STELARA (ustekinumab) IFU comparator labeling dated April 6, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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

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/

LONICE J CARTER
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MARCIA B WILLIAMS
03/26/2024 01:46:36 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 19, 2024

TO: Shari Targum, M.D.
Deputy Director
Division of Dermatology and Dentistry (DDD)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI, OSIS

SUBJECT: Review of Clinical Inspections of 1) New Zealand Clinical Research/NZCR, Christchurch, New Zealand; and 2) New Zealand Clinical Research/NZCR, Auckland, New Zealand; and 3) Nucleus Network, Ltd., Brisbane, Australia

1. Inspection Summary

Per the request of OND/DDD, OSIS arranged inspections of clinical portion of **Study AVT04-GL-101** (BLA 761343, Ustekinumab/AVT04) conducted at:

- New Zealand Clinical Research (NZCR), Christchurch, New Zealand
- New Zealand Clinical Research (NZCR), Auckland, New Zealand
- Nucleus Network, Ltd., Brisbane, Australia

For NZCR, Christchurch, New Zealand, objectionable conditions were observed and a one-item Form FDA 483 was issued at the inspection close-out for failure to conduct the study in accordance with the investigational plan and good clinical practices. In addition, three items were verbally discussed with the site's management at the inspection close-out. After reviewing the inspectional findings, exhibits provided in the EIR, and the clinical site's response to Form FDA 483 and Discussion Items, there are no concerns regarding the clinical data reliability. However, I recommend the review division to

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determine the potential impact of the missed safety assessments on subject safety and welfare.

For NZCR, Auckland, New Zealand, objectionable conditions were observed and a one-item Form FDA 483 was issued at the inspection close-out for failure to conduct the study in accordance with the investigational plan and good clinical practices. In addition, four items were verbally discussed with the site's management at the inspection close-out. After reviewing the inspectional findings, exhibits provided in the EIR, and the clinical site's response to Form FDA 483, there are no concerns regarding the clinical data reliability. However, I recommend the review division to determine the potential impact of delayed review of safety assessments on subject safety and welfare.

For Nucleus Network, Ltd., Brisbane, Australia*, objectionable conditions were not observed and no Form FDA 483 was issued at the inspection close-out. No items were verbally discussed with the site's management at the inspection close-out. Based on the inspection findings shared by email by the ORA investigator, there are no concerns regarding the clinical data reliability and human subject protection for inspected Study AVT04-GL-101 for the review division consideration.

**** Please note that the EIR for the inspection of Nucleus Network, Ltd., Brisbane, Australia is still pending at the time of this review. This review will be amended, if necessary, once the EIR becomes available at a later time.***

2. Inspected Study

BLA 761343

Study Number: AVT04-GL-101

Study Title: "A Phase 1, first-in-human, randomized, double-blind, single-dose, parallel-group, 3-arm study comparing the pharmacokinetic, safety, tolerability, and immunogenicity profiles of AVT04, Eu-approved Stelara®, and US-licensed Stelara® in healthy adult subjects"

Dates of study conduct: June 9, 2021 - March 14, 2022

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Clinical Sites:

Site #1. New Zealand Clinical Research (NZCR) (Study Site #101)
(f.k.a. Christchurch Clinical Studies Trust Ltd.)
Level 4, 264 Antigua Street
Christchurch 8011
New Zealand

of Subjects: 107

Site #2. New Zealand Clinical Research (NZCR) (Study Site #201)
(f.k.a. Auckland Clinical Studies Limited)
Ground Floor, 3 Ferncroft Street
ACS House, Grafton
Auckland 1010
New Zealand

of Subjects: 34

Site #3: Nucleus Network, Ltd. (Study Site #301)
Level 5, Clive Berghofer Cancer Research Centre
300C Herston Road, Herston
Brisbane, Queensland 4006
Australia

of Subjects: 155

3. Inspection Findings

3.1 Site #1. NZCR, Christchurch, New Zealand (Study Site #101)

ORA investigator Dawn C. Olenjack conducted an inspection of NZCR, Christchurch, New Zealand from January 15 to 19, 2024.

3.1.1 Previous inspection/RRA

The previous clinical RRA of the site was conducted by OSIS in May 2021. At the RRA closeout, no objectionable conditions were observed. There was no previous FDA inspection history of this site.

3.1.2 Current inspection

The current inspection included auditing the following items: protocol adherence; informed consent; adverse event and protocol deviation reporting; ethics committee oversight; biologic sample collections and processing; facilities and equipment; and receipt, storage, dispensing, and final disposition of the investigational products (IPs).

3.1.3 Inspection findings

At the conclusion of the inspection, Investigator Olenjack observed objectionable conditions and issued a one-item Form FDA 483 (**Attachment 1**). She also discussed three verbal items with the site's management. The FDA-483 observations, the discussion items, my evaluation, and the site's response dated 02/09/2024 (**Attachments 2 and 3**) are presented below.

3.1.3.1 FDA 483 Observations

Observation #1. Failure to conduct this clinical study in accordance with the investigational plan and good clinical practices. Specifically,

- A. The site failed to assure safety assessments including ECGs, physical exams, hematology, chemistry, and coagulation labs, urinalysis, and injection site assessments were completed at the next visit for all ten subjects that missed visits Day 9, 29, or 64. This included serum pregnancy testing at Day 29 for three female subjects of childbearing potential.**
- B. Serum pregnancy tests were not completed on at least three additional female subjects of childbearing potential, at their Day 29 visits.**

OSIS Evaluation: These findings are true in fact. Per study protocol, the safety assessments were scheduled as following:

- Physical exams: Screening, Pre-dose, Day 9, Day 29, Day 64 and Day 92 (EOS/ET)
- ECGs: Screening, Day 2, Day 5, Day 9, Day 64 and Day 92 (EOS/ET)
- Clinical safety laboratory tests: Screening, Day 2, Day 5, Day 9, Day 64 and Day 92 (EOS/ET)
- Injection site reaction assessment: Pre-dose, Day 1 15-min, 30-min, 1-hour, 2-hour, and 8-hour, and then Day 2, Day 3, Day 5, Day 9, Day 29 and Day 64 visits
- Pregnancy test (childbearing women only): serum tests at Screening and Day 29, and urine tests at Screening and EOS/ET

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Investigator Olenjack identified that one or more safety assessments were missed, including pregnancy tests for some subjects on Day 29.

The following Table 1 summarizes the missing safety assessments and if they were reported as protocol deviation and reported AEs for the study.

Table 1. Subjects missed the safety assessments

Subject #	Treatment Group	Visit #	Missing safety Assessment	Reported as protocol deviation?	Reported AEs related to IP
(b) (6)	US-Stelara	D29	PE, injection site, labs, urinalysis	Missed visit reported	Upper respiratory tract infection (Day 22-30); Recovered.
	EU-Stelara	D9	ECG, PE, injection site, urinalysis	Missed visit due to COVID reported	Injection site erythema (Day 1); Resolved.
	EU-Stelara	D64	ECG, PE, labs, urinalysis	Missed visit due to COVID reported	None
	EU-Stelara	D29	PE, injection site, labs including pregnancy test, urinalysis	Missed visit due to AE reported	Nausea (Day 17-20); vomiting (Day 17); upper respiratory tract infection (Day 18-31); Recovered.
	EU-Stelara	D29	PE, injection site, pregnancy test, urinalysis	Missed visit due to COVID reported	None
	US-Stelara	D29	PE, injection site, labs including pregnancy test, urinalysis	Missed visit due to COVID reported	Upper respiratory tract infection (Day 21-34); Recovered.
	EU-Stelara	D9	ECG, PE, injection site, labs, urinalysis	Missed visit due to personal reason reported	Bladder irritation (Day 1); Recovered.
	AVT04	D29	injection site, urinalysis	Missed visit due to COVID reported	Upper respiratory tract infection (Day 3-11); Recovered.

(b) (6)	US-Stelara	D29	serum pregnancy test	Yes	Fatigue (Day 3-12); Recovered.
	AVT04	D29	PE, injection site	Missed visit due to COVID AE reported	Injection site bruising (Day 1-10); Resolved.
	AVT04	D29	serum pregnancy test	No	None
	US-Stelara	D9	ECG, PE, injection site, labs, urinalysis	Missed visit due to COVID reported	Intermittent palpitations (Day 1-4); headache (Day 33); Recovered.
	EU-Stelara	D29	serum pregnancy test	Yes	None

Most of the above missed visits were COVID-related and were reported as protocol deviations except serum pregnancy test for subject (b) (6). However, the associated missed safety assessments were not performed at the subsequent visit(s) for the following:

- Subjects who experienced non-IP related AEs (Subjects # (b) (6) (b) (6))
- Subjects who experienced mild IP-related AEs occurred and recovered prior to the missed visits (Subjects # (b) (6) (b) (6))
- Subjects who experienced mild IP related AEs occurred and recovered around the missed visits (Subjects # (b) (6) (b) (6))
- For the three female subjects whose serum pregnancy tests were missed on Day 29 (Subjects # (b) (6) (b) (6)), the negative pregnancy results were obtained at Day -1, screening, and EOS/ET (Day 92). However, the negative confirmation on pregnancy was missing from Day -1 to Day 92.

Therefore, I recommend the review division to determine the potential impact of the missed safety assessments on safety and welfare of the subjects listed in Table 1 above.

Site's Response: The site acknowledged the findings in the written response (**Attachment 2**). They stated that the study took place while participant attendance for scheduled visits was affected by the COVID-19 pandemic restrictions imposed by the New Zealand Government.

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For **Observation 1A**, they stated that if a visit was cancelled, the site staff maintained contact with the participant by phone and email, and thereby remotely assessed adverse events, and re-scheduled the affected appointments. Further, monitoring of safety was conducted by the protocol-mandated safety tests as described in the Schedule of Assessments. According to the PI's interpretation of protocol, it did not explicitly state to conduct missed safety assessments at the next visit. The PI would refer to additional tests and assessments or visits to be done only if the study participant has health concerns. The missed safety assessments were limited to 10 participants listed in Table 1 above, and their health was checked via phone calls at the time of the missed visit. At the subsequent on-site visit, these participants' health status was reviewed and there were no clinically significant abnormalities noted.

For **Observation 1B**, the site identified one additional subject (# (b) (6)) whose Day 29 serum pregnancy test was not performed. Out of the four subjects, urine pregnancy test was done and confirmed negative for two subjects ((# (b) (6))). There were no reported pregnancies in any participant and end of study (EOS) pregnancy test results were conducted in all 71 participants of child-bearing potential and were negative.

Some of the actions taken by the site to address missed protocol specified visits for observations 1A and 1B were consistent with FDA's guidance on "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency". In the guidance, FDA recognizes that protocol modifications may be required, and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public health control measures.

The proposed and implemented corrective and preventive actions include: updating SOP, re-training staff, updating the Participant Information Sheet and Consent Form and documentation workbooks.

3.1.3.2 Discussion Items

#1. The facility design and procedures do not adequately restrict access to prohibited items while subjects are housed in the wards.

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#2. There was no documentation of identifications of specific centrifuges for sample processing, freezers for sample storage, or refrigerators for IP storage.

#3. Delegation of blinded and unblinded duties must be clearly documented and done in a manner that prevents staff from performing blinded assessments on subjects to which they conducted blinded dosing.

OSIS Evaluation: These findings are true in fact. However, there was no direct evidence to show that these findings would negatively impact the study data reliability or subject safety and welfare. For Item #3, although the delegation of blinded or unblinded duties were not documented, Investigator Olenjack did not find any instances where unblinded assessments on subjects were conducted by staff who conducted blinded dosing.

The discussion items do not have impact on study data reliability.

Site's Response: The site acknowledged the findings in the written response (**Attachment 3**). The site evaluated the impact and also performed and provided root cause analysis results in the written response. The proposed and implemented corrective and preventive actions include updating SOP, training staff, creating new instrument logs.

3.2 Site #2. NZCR, Auckland, New Zealand (Study Site #201)

ORA Investigator Dawn C. Olenjack conducted an inspection of NZCR, Auckland, New Zealand from January 22 to 26, 2024.

3.2.1 Previous inspection/RRA

The previous RRA of the site was conducted by OSIS in May 2021. At the RRA closeout, no objectionable conditions were observed. The previous inspection of the site was conducted by ORA in May 2017. At the inspection closeout, Form FDA 483 was not issued and the final classification was NAI.

3.2.2 Current inspection

The current inspection included auditing the following items: protocol adherence; adverse event and protocol deviation reporting; ethics committee oversight; biologic sample

collections and processing; facilities and equipment; and receipt, storage, dispensing, and final disposition of the IPs.

3.2.3 Inspection findings

At the conclusion of the inspection, Investigator Olenjack observed objectionable conditions and issued a one-item Form FDA 483 (**Attachment 4**). She also discussed four verbal items with the site's management. The summarized FDA-483 observations, the discussion items, my evaluation, and the site's response dated 02/15/2024 (**Attachment 5**) are presented below.

3.2.3.1 FDA 483 Observations

Observation #1. Failure to conduct this clinical study in accordance with the investigational plan and good clinical practices. Specifically,

- A. For 12 subjects reviewed during the inspection, there were data irregularities, changes, and/or additions made to the source case report forms (CRFs) after it was reasonable to recall the data that was missing, by individuals who did not complete the task, and/or without other records to substantiate the late or changed entries. Specifically,**
 - 1. The CRFs of two visits were partially completed for one subject but were noted later that the subject did not come to either visit.**
 - 2. The previously entered times of the 8-hour post-dose Injection Site Assessments (ISAs) were changed to 2 hours later after three months for several subjects.**
 - 3. A Sub-Investigator failed to document the date when the informed consent form (ICF) was signed by one subject.**
- B. Multiple inconsistencies in the recorded PK sample collection time were observed.**
- C. For 28 subjects reviewed during the inspection, one or more safety assessments, including ECG and/or urinalysis results, were reviewed much later or not reviewed at all by an Investigator.**

OSIS Evaluation:

The findings in **Observation #1.A** are true in fact and summarized below. I also included the treatment groups, the reported

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protocol deviations and AEs related to the IPs below for evaluation purpose.

Table 2 Subjects with documentation errors

Subject #	Treatment Group	Visit #	Documentation Issues	Reported as deviation?	Reported AEs related to IP
(b) (6)	US-Stelara	D36 & D43	Partially pre-filled CRFs when subject did not come to visit	Yes (see details below)	None
		D1 8h	Recorded ISA time altered	No	Injection site erythema from 15 min post-dose and lasted for 1.75 hrs.
	US-Stelara	Screening	Late entry of ICF signature of the Sub-Investigator	No	None
		D1 8h	Recorded ISA time altered	No	None
		D3	Late entry of vital signs	No	None
	US-Stelara	D1 15min	Recorded ISA time altered	No	None
		D1 8h	Recorded ISA time altered	No	None
	AVT04	D1 8h	Recorded ISA time altered	No	None
	US-Stelara	D1 8h	Recorded ISA time altered	No	Injection site erythema from 15 min post-dose and lasted for 1.75 hrs.
	EU-Stelara	D1 8h	Recorded ISA time altered	No	Injection site erythema from 15 min post-dose and lasted for 22 hrs.

For **Observation #1.A.1:** the CRF sections for "AE, Med and Restriction Check" of Subject # (b) (6) were partially prefilled for dates (b) (6) (Day 36 visit) and (b) (6) (Day 43 visit). The reported protocol deviations noted that the Subject did not complete Day 36 and Day 43 visits "as they were unable to travel to Auckland due to Covid-19 travel restrictions and difficulty

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using/acquiring a method of transport. Therefore, study assessments including PK was not done. Subject had safety blood tests completed at local lab - (b) (4). However, source document does not indicate any phone call to subject for AE review. It was also reported that the 'source document does not confirm subject was called for AE check.'"

Based on the source documents, Subject # (b) (6) missed the visits of Days 29, 36, 43, 50, 78 and End-of-Study (EOS) due to COVID-related travel restrictions. The reported IP-related AEs of this subject included mild injection site erythema 15-minute post-dose and recovered after 1 hour and 45 minutes on Day 1. Therefore, this finding is unlikely to impact study data reliability. I recommend the review division to determine the impact on subject safety and welfare.

For **Observation #1.A.2:** this study was designed as a single-dose, subcutaneous injection of the drug product. Per the study protocol, the Injection Site Assessments (ISAs) were scheduled at pre-dose, 15 min, 30 min, 1-hour, 2-hour, and 8-hour post-dose on Day 1 visit, and then Day 2, Day 3, Day 5, Day 9, Day 29 and Day 64 visits. For the ISAs scheduled at 8-hour post-dose timepoint, they were actually performed at 6-hour post-dose timepoint for these six subjects listed in Table 2 above (Subjects # (b) (6) on the same day ((b) (6)) and were correctly documented contemporaneously. r, the documentation was altered three months later to the scheduled time of 8-hour post-dose instead of the actual assessment time of 6-hour post-dose.

Although no reasonable justification was given by the site for alteration of the documented ISA times from 6-hour post dose to 8-hour post-dose on Day 1 visit, it appeared to be an isolated incident that only occurred on one day. These five subjects also went through the subsequent multiple ISA assessments according to the study protocol and did not experience any AEs related to injection site reactions. Therefore, this finding is unlikely to impact study data reliability. I recommend the review division to determine the impact on subject safety and welfare.

For **Observation #1.A.3:** per the study protocol, the informed consent process should occur during subject screening phase (2 to 28 days prior to dosing). Additionally, "The medical record must include a statement that written informed consent was

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obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF."

Per the collected exhibits during the inspection, the ICF was signed by Subject # (b) (6) (the participant) on (b) (6) but not by the Investigator (the consentor). Another Sub-Investigator signed the ICF on (b) (6) and backdated the ICF as (b) (6), which was documented in the ICF. The subject then was enrolled into the study, dosed on (b) (6) and withdrew from the study (early termination) on (b) (6) (Visit Day 50 completed) due to relocation. The only AE this subject experienced was non IP-related mild headache around Day 34 and later recovered. Based on the exhibit collected and information provided in the EIR, it is not possible to determine the chronology of events. This is a documentation issue and is unlikely to have an impact on study data reliability. I recommend the review division to determine the impact on subject safety and welfare.

For **Observation #1.B**, the finding is true in fact. According to the study protocol, Section 8.4 *Pharmacokinetics*, 8.4.1 *Collection of Samples* (Version 2.0, 20July2021), "venous blood samples (4 mL per sample) will be collected for measurement of serum concentrations of ustekinumab" at various timepoints. The allowed windows for each affected collection timepoints are as follow:

- Day 5: $\pm$ 2 hours
- Day 29, Day 36, Day 43, Day 57 and Day 64: $\pm$ 48 hours

The study protocol also specified that "the actual date and time (24-hour clock time) of each sample, including the reason for any samples not collected, will be recorded in the eCRF. Instructions for the collection and handling of biological samples, including details for sample collection, labeling, storage, and shipping will be provided in a Laboratory Manual."

The Laboratory Manual was not collected as an exhibit during the inspection, so there is no information available regarding the detailed instructions for the collection and handling of biological samples. Therefore, I cannot confirm if any protocol deviation occurred during sample collection and processing and associated documentation.

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Although documentation of the PK sample collection timepoints showed discrepancies between the CRF/Nurse's notes, the electronic data capture (EDC) system, and the Central Lab Requisition Forms, it appears that all the time differences were within the allowed windows for the respective collection timepoints. Additionally, most of the observed incidents occurred at later visits (Day 36 and beyond), while the half-life ($t_{1/2}$) of ustekinumab is approximately 3 weeks.

Therefore, this finding is unlikely to have impact on PK data reliability.

For **Observation #1.C**, the findings are true in fact. Based on the EIR, the late reviews included at least ten ECG tracings with abnormal findings and there were at least eight instances where out of range vitals were repeated only once, and were still out of range, but the subjects were discharged without a physician assessment. The study protocol does not include instruction for repeating the vitals recording. Late review of safety assessments is summarized in a table in **Attachment 6**.

Therefore, I recommend the review division to determine if the observation impacts subject safety and welfare.

Site's Response: The site acknowledged the findings in the written response (**Attachment 4**) (please note that Attachment 4 also contains 35 additional embedded PDF attachments including training records, CAPAs, updated documentation templates and so on).

They stated that the study was primarily conducted during the most significantly restrictive period of the COVID-19 pandemic in New Zealand. Through that time, their operations and study participants were impacted by stringent isolation requirements; participant unwillingness to visit; the clinical staff were separated into different groups and participant outpatient visit times, and so on.

They also stated that some of the observations had been identified and addressed prior to the FDA inspection through a number of corrective and preventative actions (CAPA), including additional ALCOAC-CEA training for Nursing and Investigators, QC checks scheduled at multiple timepoints, oversight of QC

completion by team lead/shift supervisor and a change in staffing and process for Investigator review of both inpatient and outpatient visits. Further improvements are already underway with respect to accurate source data collection, including electronic source (eSource), which will automate some processes that are currently conducted manually. With the implementation of the CAPAs and the new electronic system, the site expected to improve on the adherence to study protocol-driven procedures and GCP.

3.2.3.2 Discussion Items

#1. The facility design and procedures do not adequately restrict access to prohibited items while subjects are housed in the wards.

#2. There was no documentation of identifications of specific centrifuges for sample processing, freezers for sample storage, or refrigerators for IP storage.

#3. Documentation was not consistent if the subjects were provided with time to read and have questions answered prior to signing the ICF when the process was done electronically.

#4. Data queries from the Clinical Data Coordinators should not suggest or request the addition or change of data without substantiating documents.

OSIS Evaluation: Specific exhibits were not collected for the above discussion items but were implied throughout the entire EIR. It was also indicated in the EIR that the firm had begun revising their procedures to require a bag check at every in-house stay and were considering options for identifying subjects by specific food and water restrictions for better oversight.

There was no direct evidence to show that these findings would negatively impact the study data reliability or subject safety and welfare. However, the clinical site's general documentation practices could use some improvements.

3.3 Site #3. Nucleus Network, Ltd., Brisbane, Australia (Study Site #301)

Page 15 - Review of Clinical Inspections of 1) New Zealand Clinical Research/NZCR, Christchurch, New Zealand; and 2) New Zealand Clinical Research/NZCR, Auckland, New Zealand; and 3) Nucleus Network, Ltd., Brisbane, Australia

ORA investigator Sherri N. Rohlf conducted an inspection of Nucleus Network, Ltd., Brisbane, Australia from February 5 to 9, 2024.

3.3.1 Previous inspection/RRA

There was no previous FDA inspection or RRA history of this site.

3.3.2 Current inspection

The current inspection included auditing the following items: protocol adherence; informed consent; adverse event and protocol deviation reporting; ethics committee oversight; biologic sample collections and processing; facilities and equipment; and receipt, storage, dispensing, and final disposition of the investigational products (IPs).

3.3.3 Inspection findings

At the conclusion of the inspection, Investigator Rohlf did not observe objectionable conditions and did not issue a Form FDA 483 to the site. She did not discuss any verbal item with the site's management.

Yiyue Zhang, Ph.D.
Senior Staff Fellow

Attachments:

- Attachment 1.** Form FDA 483 issued to NZCR, Christchurch, New Zealand
- Attachment 2.** Written response to Form FDA 483 from NZCR, Christchurch, New Zealand
- Attachment 3.** Written response to Discussion Items from NZCR, Christchurch, New Zealand
- Attachment 4.** Form FDA 483 issued to NZCR, Auckland, New Zealand
- Attachment 5.** Written response to Form FDA 483 from NZCR, Auckland, New Zealand
- Attachment 6.** Summary table of late review of safety assessments at NZCR, Auckland, New Zealand

Page 16 - Review of Clinical Inspections of 1) New Zealand Clinical Research/NZCR, Christchurch, New Zealand; and 2) New Zealand Clinical Research/NZCR, Auckland, New Zealand; and 3) Nucleus Network, Ltd., Brisbane, Australia

Draft: YZ 03/08/2024, 03/18/2024; 03/19/2024

Edit: GB 03/14/2024, 03/18/2024, 3/19/2024; AD 03/16/2024, 03/18/2024, 3/19/2024

OSIS File#: BE 10058

eNSpect Assignment ID: 234878

eNSpect Op IDs: 271784 (NZCR, Christchurch, New Zealand)
271785 (NZCR, Auckland, New Zealand)
271786 (Nucleus Network, Ltd., Brisbane, Australia)

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/s/

YIYUE ZHANG
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GOPA BISWAS
03/19/2024 08:00:03 PM

ARINDAM DASGUPTA
03/19/2024 08:03:47 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: 3/12/2024

To: Sascha Randolph, Regulatory Project Manager, DDD
Sangeeta Jian MD, Clinical Reviewer, DDD
Matthew White, Associate Director for Labeling, DDD

From: Montherson L. Saint Juste, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for SELARSDI™ (ustekinumab-aekn)
injection, for subcutaneous use

BLA: 761343

Background:

In response to DDD's consult request dated January 24, 2024, OPDP has 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).

PI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 1, 2024, and we do not have any comments at this time.

OPDP comments on the proposed Medication Guide/IFU will be sent under separate cover, either as a combined OPDP and Division of Medical Policy Programs (DMPP) review or a separate OPDP review.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on March 8, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Montherson L. Saint Juste at 301-796-1200 or Montherson.SaintJuste@fda.hhs.gov.

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/s/

MONTHERSON L SAINT JUSTE
03/12/2024 02:47:52 PM

MEMORANDUM
REVIEW OF REVISED LABELS

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 11, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761343
Product Name, Dosage Form, and Strength:	Selarsdi (ustekinumab-aekn) injection, 45 mg/0.5 mL and 90 mg/mL
Applicant Name:	Alvotech USA Inc.
FDA Received Date:	March 8, 2024
TTT ID #:	2022-2209-4
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Alvotech USA Inc. submitted revised container labels received on March 8, 2024 for Selarsdi. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels for Selarsdi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Alvotech USA Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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^a Bao, A. Label and Labeling Review for Selarsdi (BLA 761343). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAR 04. TTT ID: 2022-2209-3.

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/s/

AMY J BAO
03/11/2024 03:30:44 PM

YEVGENIYA M KOGAN
03/11/2024 05:19:05 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 4, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761343
Product Name, Dosage Form, and Strength:	Selarsdi (ustekinumab-aekn) injection, 45 mg/0.5 mL and 90 mg/mL
Applicant Name:	Alvotech USA Inc. (Alvotech)
FDA Received Date:	March 1, 2024
TTT ID #:	2022-2209-3
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Alvotech USA Inc. submitted revised container labels and carton labeling received on March 1, 2024 for Selarsdi. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Selarsdi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Alvotech USA Inc. implemented our recommendations for the carton labeling. The container labels are unacceptable from a medication error perspective because information such as the storage information, package type term, and manufacturer information have become more unclear after the recent changes to increase the proprietary name and strength.

3 RECOMMENDATIONS FOR ALVOTECH USA INC.

A. Container Labels

1. We note that the proprietary name and strength have been increased in size, the preprinted terms “LOT:” and “EXP:” have been made smaller, the storage information has been reformatted, and the “Discard unused portion” statement has been removed. The original goal of our recommendation was to decrease the size of the variable data in order to allow for the size of “other information” (storage information, package type term, manufacturer information, etc.) to be increased. Given that the variable data cannot be made any smaller than 7 point type and the “other information” now appears more unclear in comparison to the previous versions of the labels, we recommend reverting the changes made, for purposes of increased clarity and adherence to FDA’s *Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (i.e., revert proprietary name and strength to their original size, replace hyphens with “to” in the storage conditions statement, and add back the “Discard unused portion” statement). If the font size and/or spacing of the “other information” has been altered in any way, we request that those changes are reverted as well. The smaller font size used for the preprinted terms “LOT:” and “EXP:” is acceptable and may remain the same.

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^a Bao, A. Label and Labeling Review Memo for Selarsdi (BLA 761343). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 FEB 21. TTT ID: 2022-2209-2.

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/s/

AMY J BAO
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YEVGENIYA M KOGAN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 21, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761343
Product Name, Dosage Form, and Strength:	Selarsdi (ustekinumab-aekn) injection, 45 mg/0.5 mL and 90 mg/mL
Applicant/Sponsor Name:	Alvotech USA Inc. (Alvotech)
TTT ID #:	2022-2209-2
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 14, 2024 for Selarsdi. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Selarsdi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and has made additional changes to the container labels and carton labeling, which we have reviewed. The revised container labels and carton labeling are unacceptable from a medication error perspective. The lot number and expiration date on the revised syringe container labels compete in prominence with other critical information, while the carton labeling has braille that is positioned over the product ingredient information, and the abbreviation used for “serial number” is not one that is recommended by FDA.

^a Bao, A. Label and Labeling Review for Selarsdi (BLA 761343). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 03. TTT ID No.: 2022-2209-1.

3 RECOMMENDATIONS FOR ALVOTECH USA INC.

We recommend the following be implemented prior to approval of this BLA:

A. Container Labels

- a. We note that the lot number and expiration date on the syringe container labels are significantly larger in size than other critical information on the labels, and take up space which could be used to increase the size of other information that may be difficult to read as currently presented. We recommend decreasing the font size of the lot number and expiration date on the syringe container labels and increasing the font size of other critical information on the labels. Consider implementing font size and spacing similar to what was used for the previously submitted syringe container labels.

B. Carton Labeling

- a. The current location of the braille on the back panel of the carton labeling may prevent users from reading the product ingredient information. We recommend moving the braille to a different area of the carton labeling where it will not obscure any product information.
- b. The abbreviation used for “serial number” on the carton labeling is not one of the abbreviations recommended in the FDA Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). We recommend updating the abbreviation “SN” to “S/N” or one of the other FDA-recommended abbreviations for serial number. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*

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/s/

AMY J BAO
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YEVGENIYA M KOGAN
02/22/2024 08:37:15 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 16, 2024

To: Sascha Randolph, BSDH, PHDHP
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Lonice Carter, MS, RN, CNL, NHDP-BC
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Close-out Memo

Proprietary name (nonproprietary name): AVT04 (ustekinumab-aekn)¹

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761343

Applicant: Alvotech USA Inc.
PharmaLex US Corporation

¹ AVT04 has been developed as a proposed biosimilar to US-licensed STELARA (ustekinumab). The proposed proprietary name, Selarsdi, was found conditionally acceptable on December 16, 2022 and December 29, 2023. The nonproprietary name, ustekinumab-aekn, was found conditionally acceptable on July 28, 2023.

c/o AmerisourceBergen

1 INTRODUCTION

On October 16, 2023, Alvotech USA Inc., PharmaLex US Corporation c/o AmerisourceBergen submitted for the Agency's review a Class 2 Resubmission of Biologics License Application (BLA) 761343 AVT04 (ustekinumab-aekn) in response to the Agency's Complete Response (CR) Letter dated October 11, 2023. As described by the Applicant, the purpose of this submission is to propose AVT04 (ustekinumab-aekn) as a biosimilar to US-licensed STELARA, with the following indications:

- Plaque Psoriasis (PsO)
- Pediatric Plaque Psoriasis in children age 6 years and older
- Psoriatic Arthritis (PsA)
- Pediatric Psoriatic Arthritis in children age 6 years and older

The Division of Medical Policy Programs (DMPP) was consulted by the Division of Dermatology and Dentistry (DDD) on October 31, 2023, for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for AVT04 (ustekinumab-aekn) injection, for subcutaneous use.

This memorandum documents DMPP's close-out of the above-referenced consult request for AVT04 (ustekinumab-aekn) injection, for subcutaneous use.

2 CONCLUSIONS

On January 8, 2024, the Patient Labeling Reviewer informed the Project Manager in DDD that DMPP will not be able to complete a review of the MG and IFU by the requested due date because DMPP does not have a Substantially Complete Prescribing Information needed to complete the review.

Please let us know if you have any questions.

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/s/

LONICE J CARTER
01/16/2024 11:30:42 AM

MARCIA B WILLIAMS
01/16/2024 11:44:23 AM

LASHAWN M GRIFFITHS
01/16/2024 11:49:48 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	January 3, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761343
Product Name, Dosage Form, and Strength:	Selarsdi (ustekinumab-aekn) injection, 45 mg/0.5 mL and 90 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Alvotech USA Inc. (Alvotech)
FDA Received Date:	October 16, 2023 and November 7, 2023
TTT ID #:	2022-2209-1
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 REASON FOR REVIEW

As part of the approval process for Selarsdi (ustekinumab-aekn) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Selarsdi prescribing information (PI), medication guide (MG), instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

BLA 761343 is a 351(k) BLA and the listed drug product is Stelara, BLA 125261. It is a Class 2 resubmission in response to the Complete Response Letter (CRL) issued on October 11, 2023. A previous DMEPA Label and Labeling review was conducted on May 16, 2023, but recommendations were not communicated to the applicant before issuance of the CRL. In the previous Label and Labeling review, an Information Request was sent on April 11, 2023 to request a certificate of translation for braille present on the carton labeling, and Alvotech subsequently submitted braille translation reports on June 9, 2023.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed Selarsdi prescribing information (PI), medication guide (MG), and instructions for use (IFU) did not identify areas of vulnerability that may lead to medication errors. However, our review identified areas for improvement for the proposed container labels and carton labeling. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Alvotech USA Inc.

4 RECOMMENDATIONS FOR ALVOTECH USA INC.

Table 2. Identified Issues and Recommendations for Alvotech USA Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The 45 mg/0.5 mL strength is not clearly differentiated due to the overlap with the font color used for the proprietary name.	Lack of adequate differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme.	We recommend revising the color scheme of the 45 mg/mL strength (b) (4) or proprietary name such that the strength and the proprietary name appear in their own unique colors that do not overlap.
2.	The Recommended Dosage statement uses the terminology “(b) (4)” instead of “Prescribing Information”.	To ensure consistency of terminology.	We recommend revising the recommended dosage statements to read, “Dosage: see Prescribing Information.”
Carton Labeling			
1.	The nonproprietary name on the Principal Display Panel for the 45 mg/0.5 mL strength carton is missing a closing parenthesis.	The proper name should be enclosed by parentheses.	Add a closing parenthesis to update the nonproprietary name from “(ustekinumab-aekn” to “(ustekinumab-aekn)”.
2.	We note that there are placeholders for the serial number, lot number, and expiration date, but that the placeholders are not labeled to indicate what the placeholder represents.	As currently presented, the three codes are located in close proximity and their meaning may be unclear if not labeled.	We recommend defining the placeholders with labels (e.g., “S/N:”, “LOT:”, and “EXP:”).
3.	A placeholder name was not updated in the	We reference our December 29, 2023	Replace the placeholder “TRADENAME” with the

Table 2. Identified Issues and Recommendations for Alvotech USA Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	statement “Do not use TRADENAME after the expiration date on the carton or on the prefilled syringe”.	Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Selarsdi, was found conditionally acceptable.	conditionally acceptable proprietary name “Selarsdi”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Selarsdi that Alvotech USA Inc. submitted on October 16, 2023, and Stelara.

Table 3. Relevant Product Information for Listed Drug and Selarsdi		
Product Name	Stelara ^a	Selarsdi
Initial Approval Date	September 25, 2009	N/A
Active Ingredient	ustekinumab	ustekinumab-aekn
Indication	Treatment of: Adult patients with: • moderate to severe plaque psoriasis (Ps) 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 Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA)	Treatment of: Adult patients with: • moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA)
Route of Administration	Subcutaneous, Intravenous	Subcutaneous
Dosage Form	Subcutaneous injection (prefilled syringe and single-dose vial), intravenous infusion (single-dose vial)	Subcutaneous injection (prefilled syringe)
Strength	45 mg/0.5 mL, 90 mg/mL, 130 mg/26 mL	45 mg/0.5 mL, 90 mg/mL

^a Stelara [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. March 2023. [cited 2023 Nov 9]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125261s158lbl.pdf

Dose and Frequency	<u>Psoriasis Adult Subcutaneous Recommended Dosage:</u>	<table><tr><th>Weight Range (kg)</th><th>Dosage Regimen</th></tr><tr><td>less than or equal to 100 kg</td><td>45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks</td></tr><tr><td>greater than 100 kg</td><td>90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks</td></tr></table>	Weight Range (kg)	Dosage Regimen	less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks	greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks	<u>Psoriasis Adult Subcutaneous Recommended Dosage:</u>	<table><tr><th>Weight Range (kg)</th><th>Dosage Regimen</th></tr><tr><td>less than or equal to 100 kg</td><td>45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks</td></tr><tr><td>greater than 100 kg</td><td>90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks</td></tr></table>	Weight Range (kg)	Dosage Regimen	less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks	greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks	
	Weight Range (kg)	Dosage Regimen															
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less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks																
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks																
<u>Psoriasis Pediatric Patients (6 to 17 years old) Subcutaneous Recommended Dosage:</u> Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.	<u>Psoriasis Pediatric Patients (6 to 17 years old) Subcutaneous Recommended Dosage:</u> Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.																
<table><tr><th>Weight Range (kg)</th><th>Dose</th></tr><tr><td>Less than 60 kg</td><td>0.75 mg/kg</td></tr><tr><td>60 kg to 100 kg</td><td>45 mg</td></tr><tr><td>Greater than 100 kg</td><td>90 mg</td></tr></table>	Weight Range (kg)	Dose	Less than 60 kg	0.75 mg/kg	60 kg to 100 kg	45 mg	Greater than 100 kg	90 mg	<table><tr><th>Weight Range (kg)</th><th>Dose</th></tr><tr><td>Less than 60 kg</td><td>-</td></tr><tr><td>60 kg to 100 kg</td><td>45 mg</td></tr><tr><td>Greater than 100 kg</td><td>90 mg</td></tr></table>	Weight Range (kg)	Dose	Less than 60 kg	-	60 kg to 100 kg	45 mg	Greater than 100 kg	90 mg
Weight Range (kg)	Dose																
Less than 60 kg	0.75 mg/kg																
60 kg to 100 kg	45 mg																
Greater than 100 kg	90 mg																
Weight Range (kg)	Dose																
Less than 60 kg	-																
60 kg to 100 kg	45 mg																
Greater than 100 kg	90 mg																
<u>Psoriatic Arthritis Adult Subcutaneous Recommended Dosage:</u>	<u>Psoriatic Arthritis Adult Subcutaneous Recommended Dosage:</u>																
- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks. - For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered	- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks. - For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and																

Table 3. Relevant Product Information for Listed Drug and Selarsdi

Product Name	Stelara ^a	Selarsdi																								
	subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks. <u>Psoriatic Arthritis Pediatric (6 to 17 years old) Subcutaneous Recommended Dosage:</u> Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter. <table><tr><th>Weight Range (kg)</th><th>Dose</th></tr><tr><td>Less than 60 kg</td><td>0.75 mg/kg</td></tr><tr><td>60 kg to 100 kg</td><td>45 mg</td></tr><tr><td>Greater than 100 kg with co-existent moderate-to-severe plaque psoriasis</td><td>90 mg</td></tr></table> <u>Crohn’s Disease and Ulcerative Colitis Initial Adult Intravenous Recommended Dosage:</u> A single intravenous infusion using weight-based dosing: <table><tr><th>Weight Range (kg)</th><th>Recommended Dosage</th></tr><tr><td>Up to 55 kg</td><td>260 mg (2 vials)</td></tr><tr><td>Greater than 55 kg to 85 kg</td><td>390 mg (3 vials)</td></tr><tr><td>Greater than 85 kg</td><td>520 mg (4 vials)</td></tr></table> <u>Crohn’s Disease and Ulcerative Colitis Maintenance Adult Subcutaneous Recommended Dosage:</u> A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.	Weight Range (kg)	Dose	Less than 60 kg	0.75 mg/kg	60 kg to 100 kg	45 mg	Greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg	Weight Range (kg)	Recommended Dosage	Up to 55 kg	260 mg (2 vials)	Greater than 55 kg to 85 kg	390 mg (3 vials)	Greater than 85 kg	520 mg (4 vials)	4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks. <u>Psoriatic Arthritis Pediatric (6 to 17 years old) Subcutaneous Recommended Dosage:</u> Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter. <table><tr><th>Weight Range (kg)</th><th>Dose</th></tr><tr><td>Less than 60 kg</td><td>-</td></tr><tr><td>60 kg to 100 kg</td><td>45 mg</td></tr><tr><td>Greater than 100 kg with co-existent moderate-to-severe plaque psoriasis</td><td>90 mg</td></tr></table>	Weight Range (kg)	Dose	Less than 60 kg	-	60 kg to 100 kg	45 mg	Greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg
Weight Range (kg)	Dose																									
Less than 60 kg	0.75 mg/kg																									
60 kg to 100 kg	45 mg																									
Greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg																									
Weight Range (kg)	Recommended Dosage																									
Up to 55 kg	260 mg (2 vials)																									
Greater than 55 kg to 85 kg	390 mg (3 vials)																									
Greater than 85 kg	520 mg (4 vials)																									
Weight Range (kg)	Dose																									
Less than 60 kg	-																									
60 kg to 100 kg	45 mg																									
Greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg																									

Table 3. Relevant Product Information for Listed Drug and Selarsdi		
Product Name	Stelara ^a	Selarsdi
How Supplied	STELARA[®] (ustekinumab) injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials. Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber	SELARSDI (ustekinumab-aekn) injection for subcutaneous use, is a sterile, preservative-free, colorless to slightly yellow solution and practically free of visible particles. It is supplied as individually packaged, single-dose prefilled syringes. Each prefilled syringe is equipped with a 29 gauge fixed ½ inch needle equipped with a passive safety device and a needle cover. Not made with natural rubber latex.

Table 3. Relevant Product Information for Listed Drug and Selarsdi		
Product Name	Stelara ^a	Selarsdi
Storage	STELARA[®] vials and prefilled syringes must be refrigerated at 2°C to 8°C (36°F to 46°F). Store STELARA[®] vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. If needed, individual prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use STELARA[®] after the expiration date on the carton or on the prefilled syringe.	SELARSDI prefilled syringes must be refrigerated at 2°C to 8°C (36°F to 46°F). Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. If needed, individual prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use SELARSDI after the expiration date on the carton or on the prefilled syringe.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 2, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, “BLA 761343”. Our search identified one previous review^b, and we considered our previous recommendations to see if they are applicable for this current review.

^b Howard, Corwin. Label and Labeling Review for Selarsdi (BLA 761343). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 May 16. TTT ID No.: 2022-2209.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error experiences with similar products, we reviewed the following Selarsdi labels and labeling submitted by Alvotech USA Inc.

- Container labels received on November 7, 2023
- Blister labeling received on November 7, 2023
- Carton labeling received on October 16, 2023
- Instructions for Use received on October 16, 2023, available from <\\CDSESUB1\EVSPROD\bla761343\0034\m1\us\114-labeling\1141-draft-label\1-14-1-3-draft-labeling-text-ifu-clean.pdf>
- Medication Guide received on October 16, 2023, available from <\\CDSESUB1\EVSPROD\bla761343\0034\m1\us\114-labeling\1141-draft-label\1-14-1-3-draft-labeling-med-guide-clean.pdf>
- Prescribing Information received on October 16, 2023, available from <\\CDSESUB1\EVSPROD\bla761343\0034\m1\us\114-labeling\1141-draft-label\1-14-1-3-draft-labeling-package-insert-clean.pdf>

C.2 Label and Labeling Images

Container labels

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: August 28, 2023

To: Sascha Randolph, BSDH, PHDHP
Regulatory Project Manager
Division of Dermatology and Dentistry

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): AVT04 SELARSDI (ustekinumab-xxxx)¹

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761343

Applicant: Alvotech USA Inc.

¹ AVT04 was developed as a proposed biosimilar to US-licensed Stelara (ustekinumab) BLA 125261. The proposed Tradename SELARSDI was found to be conditionally acceptable by the Division of Medication Error Prevention and Analysis I (DMEPA I) on December 14, 2022. The nonproprietary name has not been determined this time and we therefore use the placeholder “-xxxx” for the 4-letter nonproprietary name suffix.

1 INTRODUCTION

On October 11, 2022, Alvotech USA Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761343 for AVT04 SELARSDI (ustekinumab-xxxx) injection, a proposed biosimilar to STELARA (ustekinumab) injection [BLA 125261] for the treatment of the following:

- Plaque Psoriasis (PsO)
- Pediatric Plaque Psoriasis in children 6 years and older
- Psoriatic Arthritis (PsA)
- Pediatric Psoriatic Arthritis in children age 6 year and older

On November 20, 2022, the Division of Dermatology and Dentistry) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for AVT04 SELARSDI (ustekinumab-xxxx).

This memorandum documents the DMPP review deferral of the Applicant's proposed MG and IFU for AVT04 SELARSDI (ustekinumab-xxxx).

2 CONCLUSIONS

On June 20, 2023 the Division of Dermatology and Dentistry (DDD) sent a Deficiencies Preclude Discussion Letter to the Applicant, and intends to issue a Complete Response (CR). Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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SHARON R MILLS
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Clinical Inspection Summary

Date	7/19/2023
From	Stephanie Coquia, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sangeeta Jain, MD, Clinical Reviewer Snezana Trajkovic, MD, Clinical Team Leader Sascha Randolph, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
BLA #	761343
Applicant	Alvotech USA Inc.
Drug	AVT04 (ustekinumab-xxxx)
NME (Yes/No)	Biosimilar
Therapeutic Classification	Human interleukin-12 and -23 antagonist
Proposed Indication	Adult and pediatric patients 6 years and older with: • Moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy • Active psoriatic arthritis
Consultation Request Date	1/6/2023
Summary Goal Date	8/11/2023
Action Goal Date	9/21/2023
PDUFA Date	10/11/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Alvotech USA Inc., submitted clinical data from Study AVT04-GL-301 (NCT04930042) to support a Biologics License Application (BLA 761343) for AVT04 (ustekinumab-xxxx), a biosimilar for Stelara® (ustekinumab). The proposed indication is for use in adult and pediatric patients 6 years and older with moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy and active psoriatic arthritis.

Two clinical investigators (Drs. Wilkowska-Trojniel and Pulka) were selected for clinical inspections. The sponsor of the study, Alvotech Swiss AG, was also inspected in support of this BLA.

The inspections did not find significant concerns regarding the management and oversight of the clinical trial or GCP or regulatory compliance. Based on the results of these inspections, data generated by the inspected clinical investigators and submitted by the sponsor appear acceptable in support of the proposed indication.

II. BACKGROUND

Alvotect USA Inc. seeks approval of a BLA for AVT04 (ustekinumab-xxxx). In support of the BLA, the Applicant submitted clinical data from Study AVT04-GL-301, a phase 3 study. The following is a summary of the study protocol and key study information relevant to the clinical inspections.

Study AVT04-GL-301 was a comparative clinical efficacy and safety study aiming to establish therapeutic equivalence of AVT04 to the European Union-approved Stelara® (EU-Stelara) in the treatment of adults with moderate to severe chronic PsO.

The primary endpoint was the percent improvement in the Psoriasis Area and Severity Index (PASI) from Baseline (BL) to Week 12.

PASI was assessed by scoring PsO lesions on three characteristics – erythema, infiltration, and desquamation – weighted by area of involvement. The lesions were scored for four anatomical regions: head, upper extremities, trunk, and lower extremities (including buttocks). Therefore, 16 individual component scores comprised the total PASI score at each assessed timepoint.

Key eligibility criteria included:

- Adult with diagnosis of moderate to severe chronic PsO for at least six months, with the following at both Screening and BL:
 - Involved body surface area (BSA) $\geq 10\%$
 - PASI ≥ 12
 - Static Physician's Global Assessment (sPGA) ≥ 3 (moderate)
- Stable disease for at least two months
- Candidate for systemic therapy
- Naïve to ustekinumab therapy, approved or investigational
- None of the following:
 - Diagnosis of psoriatic arthritis, erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, other skin conditions (e.g., eczema), or other systemic autoimmune disorder or inflammatory disease at the time of the Screening Visit that would interfere with evaluations of the effect of the study drug on psoriasis.
 - Underlying condition which significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy.
 - Active infection or history of infections.

The study was conducted in Europe (Poland, Ukraine, Georgia, and Estonia). Twenty-nine sites randomized subjects. A total of 581 subjects received treatment.

III. RESULTS

1. Dr. Marta Wilkowska-Trojniel (Site 4810)

ul. Stoleczna 7/200
Bialystok, Podlaskie, 15-879
Poland

Inspection Dates: March 27-31, 2023

This investigator was inspected as a routine BsUFA inspection for Study AVT04-GL-301. This was the first FDA inspection of this investigator.

At this site, 47 subjects were screened, and 39 subjects were randomized (eight screen failures). Signed informed consent forms (ICFs) for all 47 subjects who agreed to enroll in the study were reviewed. Adverse event (AE) and concomitant medication documentation for all 39 subjects randomized were reviewed and compared to data submitted in the BLA. Otherwise, subject records for 17 out of 39 subjects were reviewed for compliance with the protocol. Other subject records reviewed included: study visit sheets designed by the site to comply with the plan as defined by the protocol, eligibility documents, investigational product (IP) accountability records, lab reports, electrocardiograms (ECGs), and protocol-required assessments. In addition to these paper source records, the PASI score source data that were originally entered on a tablet were reviewed from a thumb drive and compared to submitted line listings for all 39 subjects randomized.

Study-related records reviewed included: clinical investigator curriculum vitae, protocol version 3.0, Ethics Committee (EC) submissions and approvals, screening and enrollment log, delegation of authority log, investigator agreements, training log, site initiation visit checklist, central laboratory certification, financial disclosure forms, IP accountability records, monitoring documents, and audit certificate.

There was no evidence of underreporting of adverse events, concomitant medications, or protocol deviations. There were no discrepancies in the PASI score source data values when compared to the submitted line listings.

2. Dr. Grazyna Pulka (Site 4801)

ul. Henryka Sienkiewicza 23, Centrum Medyczne All-Med
Krakow, Malopolskie, 30-033 Poland

Inspection Dates: March 20-24, 2023

This investigator was inspected as a routine BsUFA inspection for Study AVT04-GL-301. This was the second FDA inspection for this investigator. The last inspection for this investigator concluded February 5, 2016, without issues identified.

At this site, 50 subjects were enrolled, randomized, and treated. Signed ICFs for all 50 subjects who agreed to enroll in the study were reviewed. AE documentation for all 50 subjects randomized were reviewed and compared to data submitted in the BLA. Concomitant medications for six subjects were reviewed and compared to data submitted in the BLA. Otherwise, the subject records for 19 out of 50 subjects were reviewed for compliance with the protocol. Other subject records reviewed included: study visit sheets designed by the site to comply with the plan as defined by the protocol, eligibility documents, IP accountability records, lab reports, ECGs, and protocol-required assessments. In addition to these paper source records, the PASI score source data that were originally entered on a tablet were reviewed from a thumb drive and compared to submitted line listings for all 50 subjects randomized.

Study-related records reviewed included: clinical investigator curriculum vitae, IP accountability records, investigator agreements, training certification, EC submission and approval documents, central laboratory certification, screening and enrollment log, financial disclosures, and monitoring documents.

There was no evidence of underreporting of adverse events or protocol deviations. There were no discrepancies in the PASI score source data values when compared to the submitted line listings.

3. Alvotech Swiss AG

Thurgauerstrasse 54
Zurich, Zurich, 8050 Switzerland

Inspection Dates: June 12-22, 2023

The sponsor was inspected as a routine BsUFA inspection for Study AVT04-GL-301. This was the first FDA inspection for the sponsor.

The inspection consisted of review of records and procedures related to the protocol and its amendments, registration of the clinical trial, selection and monitoring of clinical investigators, selection of monitors and their activities, safety reporting, data collection and handling, record retention, and use of electronic records. Review also included curriculum vitae, signed investigator agreements, financial disclosures, temperature logs, subject enrollment logs, delegation logs, training records, monitoring reports, AE reports, EC approvals, and IP accountability for the above-inspected sites as well as for nine additional sites (Sites 3701, 3703, 3804, 3807, 4802, 4809, 4814, 9902, and 9905).

No deficiencies were noted concerning monitoring procedures, blinding procedures, safety reporting, protocol deviations, or data management for Study AVT04-GL-301.

(b) (4)

{See appended electronic signature page}

Stephanie Coquia, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
(Acting) Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division /Division Director/Shari Targum, MD
Review Division /Project Manager/Sascha Randolph
Review Division/Cross Discipline Team Lead/Snezana Trajkovic, MD
OSI/Office Director/David Burrow
OSI/ GCP Program Analysts/Yolanda Patague

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STEPHANIE F COQUIA
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MICHELE B FEDOWITZ
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JENN W SELLERS
07/19/2023 02:37:10 PM

MEMORANDUM
USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 18, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761343
Product Name, Dosage Form, and Strength:	Selarsdi ^a (ustekinumab-xxxx ^b) injection, 45 mg/0.5 mL and 90 mg/mL
Device Constituent:	Prefilled Syringe (PFS)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Alvotech USA Inc. (Alvotech)
FDA Received Date:	October 11, 2022, November 21, 2022; December 2, 2022
OSE TTT #:	2022-2245
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director of Human Factors:	Jason Flint, MBA, PMP

^a The proprietary name for this BLA, Selarsdi, was found conditionally acceptable on December 16, 2022. Selarsdi is used throughout this review. Selarsdi was developed as a proposed biosimilar to US-licensed Stelara.

^b The nonproprietary name suffix for this BLA has not yet been determined. Therefore, the placeholder “ustekinumab-xxxx” is used to refer to the non-proprietary name for this product and is not intended to be included in the final labels and labeling.

1 REASON FOR REVIEW

On August 31, 2022, Alvotech submitted a biologics license application (BLA) under BLA 761343 that included a use-related risk analysis (URRA), threshold analyses (hereafter called comparative analyses (CA)) and justification for not submitting human factors (HF) validation study results to support their marketing application for Selarsdi (ustekinumab-xxx) injection, 45 mg/0.5 mL and 90 mg/mL; a proposed biosimilar to US-licensed Stelara.

2 BACKGROUND

Selarsdi is a single ingredient combination product with a single-dose prefilled syringe (PFS) device constituent part that is intended for the treatment of:

- patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
- patients 6 years or older with active psoriatic arthritis.

Selarsdi injection, for subcutaneous use, is a sterile, preservative-free, colorless to slightly yellow solution and practically free of visible particles. It is supplied as an individually packaged, single-dose prefilled syringe. The PFS is available in the 45 mg/0.5 mL and 90 mg/mL strengths. Each PFS is equipped with a 29- gauge fixed ½ inch needle equipped with a passive safety device and a needle cover that is not made with natural rubber latex.

On April 08, 2021, under IND 148023, Alvotech submitted a URRA, CA and justification for not submitting human factors validation study results to support their future marketing application for Selarsdi (ustekinumab-xxx) injection, 45 mg/0.5 mL and 90 mg/mL; a proposed biosimilar to US-licensed Stelara.

On November 19, 2021, we reviewed the aforementioned URRA , CA and justification and determined Alvotech did not need to submit HF validation study results to support their future marketing application. We also stated that if Alvotech modified the product user interface, additional human factors considerations may apply.^c

On October 11, 2022, Alvotech submitted their marketing application under BLA 761343 for Selarsdi (ustekinumab-xxx) injection, 45 mg/0.5 mL and 90 mg/mL; a proposed biosimilar to US-licensed Stelara. The submission included a URRA, CA and justification for not submitting human factors (HF) validation study results to support their marketing application. However, it was not clear if the product user interface of the proposed Selarsdi PFS evaluated in the URRA, CA and justification submitted on October 11, 2022, under BLA 761343, was identical to the product user interface of the proposed Selarsdi PFS evaluated in the URRA, CA and justification submitted on April 08, 2021. Additionally, Alvotech did not indicate whether the commercial product user interface had been modified since the April 08, 2021, submission. As such, we

^c Lee H. Use-Related Risk Analysis and Comparative Analyses review for Ustekinumab Injection, (IND 148203). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);19 NOV 2021. RCM No.: 2021-754.

issued an information request (IR) on November 20, 2022, asking Alvotech to clarify the following:

- *“if the product user interface of your proposed ustekinumab injection in your April 08, 2022, submission is identical to the product user interface of the sarilumab injection proposed in your October 11, 2022, submission.*
- *if the URRAs, comparative analyses and justification submitted on April 08, 2021, is the same as the URRAs, comparative analyses and justification submitted in your October 11, 2022, submission.”*

Subsequently, on November 21, 2022, Alvotech provided the following response to the IR:

“Alvotech can confirm that the product user interface included April 8, 2021, submission “our Human Factors – General Advice letter dated November 24, 2021” is identical to the product user interface included within October 11, 2022, submission under BLA 761343 (5.3.5.4 - Threshold Analysis AVT04-PFS SD - Appendix B).

“Alvotech can confirm that the URRAs, comparative analyses and justification included April 8, 2021, submission “our Human Factors – General Advice letter dated November 24, 2021” is materially identical to the URRAs, and identical to the comparative analyses and justification included within October 11, 2022, submission under BLA 761343 (5.3.5.4 - Use-related risk assessment for AVT04-PFS SD & Threshold Analysis AVT04-PFS SD - 5 Comparative Task Analysis). Revisions to URRAs content are minor in nature, having no impact upon the product user interface. As a result of the above responses, no update are required to eCTD Section 5.3.5.4 – Other Study reports and related information.”

Based on Alvotech’s November 21, 2022, IR response it was not clear what minor revisions to the URRAs were made. As such, we issued another IR on November 30, 2022, asking Alvotech to clarify the following:

“Please specify what revisions you made to the URRAs in a table that includes the information submitted April 8, 2021, information submitted October 11, 2022, the reason for the change and impact on product user interface.”

Subsequently, on December 02, 2022, Alvotech indicated in their IR response that they made the following changes to the URRAs:

- Changed the severity of harm score from 5 “Catastrophic” to 4 “Critical” for the failure mode of “left in reach of children”; Harm: Injury- child. The rationale for this change is that the size of the needle cover could cause impaired respiration but not completely stop breathing. The needle cover is small enough to fit into the throat of a small child but not large enough to completely block the airway. There were no changes to the risk mitigations and no additional control measures required.

- Changed the severity of harm score from 2 “Minor” to 1 “Negligible” for the failure mode of *“Grasps with finger on plunger; Hazard: Needle slip; Harm: Injury – Patient (Needlestick)”*. The rationale for the change was reflecting an evolution in the understanding of the severity of the potential harm arising from the hazardous situation; a needle stick prior to use of the product is more consistent with “temporary discomfort” rather than “temporary injury or impairment.” Medical input was solicited during development of the revised URRAs.
- Changed the harm from “none” to “discomfort-patient” for the failure mode of *“Pulls back on Plunger; Hazard: Increased syringe air volume”*. The rationale for the change was to clarify the kind of harm the patient may experience. Alvotech, stated that there is no change to severity.
- Changed the severity of harm score from 2 “Minor” to 1 “Negligible” for the failure mode of *“Inserts needle by pressing plunger; Hazard: Needle slip; Harm: Injury – User (Needlestick)”*. The rationale for the change was reflecting an evolution in the understanding of the severity of the potential harm arising from the hazardous situation; a needle stick prior to use of the product is more consistent with “temporary discomfort” rather than “temporary injury or impairment.” Medical input was solicited during development of the revised URRAs.
- Changed the severity of harm score from 2 “Minor” to 1 “Negligible” for the failure mode of *“Moves syringe or needle during injection; Hazard: Needle breakage; Harm: Injury – Patient (Needlestick)”*. The rationale for the change was reflecting an evolution in the understanding of the severity of the potential harm arising from the hazardous situation; a needle stick prior to use of the product is more consistent with “temporary discomfort” rather than “temporary injury or impairment.” Medical input was solicited during development of the revised URRAs.

Additionally, Alvotech stated that none of the changes above impact the product user interface or the risk mitigations/control measures.

Based on the aforementioned information, we agree that these URRAs changes do not impact the risk mitigations/control measures, did not change critical task categorization, and are not new, differing, or unique risks associated with the proposed product as compared to US-licensed Stelara. As such, we maintain that the tasks evaluated appear to be comprehensive and appropriate based on what Alvotech proposes for the design and intended use of this product.

3 CONCLUSION

Based on the aforementioned information, we maintain that Alvotech does not need to submit human factors validation study results with their biologics license application (BLA) under BLA 761343 for Selarsdi (ustekinumab) injection, 45 mg/0.5 mL and 90 mg/mL; a proposed biosimilar to US-licensed Stelara. We have no HF recommendations for this marketing application.

APPENDIX A.

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On November 20, 2022, we issued an information request asking Alvotech to clarify the following:

(b) (4)

On November 30, 2022, we issued an IR asking Alvotech to clarify the following:

"We note in your information request (IR) response submitted on November 21, 2022, you stated, "Revisions to URRR content are minor in nature, having no impact upon the product user interface." However, you did not specify what revisions are made to the URRR. As such, we are

unable to fully review your URRAs. Please specify what revisions you made to the URRAs in a table that includes the information submitted April 8, 2021, information submitted October 11, 2022, the reason for the change and impact on product user interface.”

Alvotek provided an acceptable response on December 02, 2022, that can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761343\0005\m1\us\111-info-amend\1-11-4-response-fda-ir.pdf>

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/

OLUWAMUREWA OGUNTIMEIN
05/18/2023 01:36:33 PM

JASON A FLINT
05/18/2023 01:58:40 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 16, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761343
Product Name, Dosage Form, and Strength:	Selarsdi (ustekinumab-xxxx) ^a injection, 45 mg/0.5 ml and 90 mg/1.0 ml
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Alvotect USA Inc.
FDA Received Date:	October 11, 2022, and January 6, 2023
TTT ID #:	2022-2209
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

^aThe non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder ustekinumab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 REASON FOR REVIEW

As part of the approval process for Selarsdi (ustekinumab-xxxx) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Selarsdi Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Alvotech USA Inc..

4 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

Table 2. Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, the proprietary name is denoted by the placeholder “TRADENAME”.	The proposed proprietary name, “Selarsdi”, was found conditionally acceptable under OSE RCM# 2022-1044724798 on December 16, 2022.	We recommend replacing all presentations of the placeholder “ TRADENAME” with the conditionally acceptable proprietary name “Selarsdi”.
2.	The nonproprietary name suffix is denoted by the placeholder ‘-xxxx’.	An undefined nonproprietary name suffix placeholder may lead to identification medication errors.	Replace ‘-xxxx’ with the conditionally acceptable nonproprietary name suffix when it is determined.

5 RECOMMENDATIONS FOR ALVOTECH USA INC.

Table 3. Identified Issues and Recommendations for Alvotech USA Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently presented, the proprietary name is denoted by the placeholder “Trade name”.	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	We reference our December 16, 2022, Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Selarsdi, was found conditionally acceptable. We recommend replacing the placeholder “Tradenam” with the conditionally acceptable proprietary name, Selarsdi, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2.	The 45 mg/0.5 mL strength is not clearly differentiated due to the overlap with the font color used for the proprietary name.	Lack of adequate differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme	We recommend revising the color scheme of the 90 mg/mL strength and the proprietary name appear in their own unique colors that do not overlap.
3.	The terminology within the Recommended Dosage statement (b) (4) inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the recommended dosage statement to read, “Dosage: see Prescribing Information.”
Carton Labeling			

Table 3. Identified Issues and Recommendations for Alvotech USA Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	It appears you intend to include braille on the carton labeling.	It is unclear what information you intend to include in braille.	Without the translation certification, we cannot assess the information presented in braille from a medication safety perspective. Submit the translation certificate for braille.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Selarsdi that Alvotech USA Inc. submitted on January 6, 2023, and Stelara.

Table 4. Relevant Product Information for Listed Drug and Selarsdi		
Product Name	Stelara	Selarsdi
Initial Approval Date	September 25, 2009	N/A
Active Ingredient	ustekinumab	(ustekinumab-xxxx)
Indication	Treatment of: Adult patients with: • <i>moderate to severe plaque psoriasis (Ps)</i> who are candidates for phototherapy or systemic therapy. • <i>active psoriatic arthritis (PsA).</i> • <i>moderately to severely active Crohn's disease (CD).</i> • <i>moderately to severely active ulcerative colitis.</i> Pediatric patients 6 years and older with:	Treatment of: Adult patients with: • moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA). Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA).

	• <i>moderate to severe plaque psoriasis</i>, who are candidates for phototherapy or systemic therapy.							
Route of Administration	Subcutaneous, Intravenous	Subcutaneous						
Dosage Form	Injection	Injection						
Strength	45 mg/0.5 mL, 90 mg/mL, 130 mg/26 mL	45 mg/0.5 mL, 90 mg/mL						
Dose and Frequency	<u>Psoriasis Adult Subcutaneous Recommended Dosage:</u> <table><tr><th>Weight Range (kilograms)</th><th>Dosage Regimen</th></tr><tr><td>less than or equal to 100 kg</td><td>45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks</td></tr><tr><td>greater than 100 kg</td><td>90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks</td></tr></table> <u>Psoriasis Pediatric Patients (6 to 17 years old) Subcutaneous Recommended Dosage:</u> Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.	Weight Range (kilograms)	Dosage Regimen	less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks	greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks	<u>Psoriasis Subcutaneous Adult Dosage Regimen</u> • For patients weighing 100 kg or less, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. • For patients weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks. In subjects weighing more than 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these subjects. <u>Subcutaneous Pediatric Dosage Regimen</u> Administer TRADENAME subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter. The recommended dose of TRADENAME for pediatric patients (6 to 17 years old) based on body weight is shown below (Table 1). Table 1: Recommended Dose of TRADENAME for Subcutaneous Injection in Pediatric Patients (6 to 17 years old) with Psoriasis
Weight Range (kilograms)	Dosage Regimen							
less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks							
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks							

	<table><tr><th>Weight Range (kilograms)</th><th>Dose Regimen</th></tr><tr><td>less than 60 kg</td><td>0.75 mg/kg</td></tr><tr><td>60 kg to 100 kg</td><td>45 mg</td></tr><tr><td>greater than 100 kg</td><td>90 mg</td></tr></table>	Weight Range (kilograms)	Dose Regimen	less than 60 kg	0.75 mg/kg	60 kg to 100 kg	45 mg	greater than 100 kg	90 mg	<table><tr><th>Body Weight of Patient at the Time of Dosing</th><th>Recommended Dose</th></tr><tr><td>less than 60 kg</td><td>-</td></tr><tr><td>60 kg to 100 kg</td><td>45 mg</td></tr><tr><td>more than 100 kg</td><td>90 mg</td></tr></table> There is no dosage form for TRADENAME that allows weight-based dosing for pediatric patients below 60 kg.	Body Weight of Patient at the Time of Dosing	Recommended Dose	less than 60 kg	-	60 kg to 100 kg	45 mg	more than 100 kg	90 mg
Weight Range (kilograms)	Dose Regimen																	
less than 60 kg	0.75 mg/kg																	
60 kg to 100 kg	45 mg																	
greater than 100 kg	90 mg																	
Body Weight of Patient at the Time of Dosing	Recommended Dose																	
less than 60 kg	-																	
60 kg to 100 kg	45 mg																	
more than 100 kg	90 mg																	
	<u>Psoriatic Arthritis Adult Subcutaneous Recommended Dosage:</u> • The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks. • For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.	Psoriatic Arthritis <u>Subcutaneous Adult Dosage Regimen</u> • The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. • For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks. <u>Subcutaneous Pediatric Dosage Regimen</u> Administer TRADENAME subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter. The recommended dose of TRADENAME for pediatric patients (6 -17 years old) with psoriatic arthritis, based on body weight, is shown below (Table 2).																
	<u>Psoriatic Arthritis Pediatric (6 to 17 years old) Subcutaneous Recommended Dosage:</u> Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.	Table 2: Recommended Dose of TRADENAME for Subcutaneous Injection in Pediatric Patients (6 to 17 years old) with Psoriatic Arthritis																

	Weight Range (kilograms)	Dosage Regimen	Body Weight of Patient at the Time of Dosing	Recommended Dose								
	less than 60 kg	0.75 mg/kg	less than 60 kg	-								
	60 kg or more	45 mg	60 kg or more	45 mg								
	greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg	greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg								
			There is no dosage form for TRADENAME that allows weight-based dosing for pediatric patients below 60 kg.									
<u>Crohn's Disease and Ulcerative Colitis Initial Adult Intravenous Recommended Dosage:</u> A single intravenous infusion using weight-based dosing: <table><tr><td>Weight Range (kilograms)</td><td>Recommended Dosage</td></tr><tr><td>up to 55 kg</td><td>260 mg (2 vials)</td></tr><tr><td>greater than 55 kg to 85 kg</td><td>390 mg (3 vials)</td></tr><tr><td>greater than 85 kg</td><td>520 mg (4 vials)</td></tr></table>					Weight Range (kilograms)	Recommended Dosage	up to 55 kg	260 mg (2 vials)	greater than 55 kg to 85 kg	390 mg (3 vials)	greater than 85 kg	520 mg (4 vials)
Weight Range (kilograms)	Recommended Dosage											
up to 55 kg	260 mg (2 vials)											
greater than 55 kg to 85 kg	390 mg (3 vials)											
greater than 85 kg	520 mg (4 vials)											
<u>Crohn's Disease and Ulcerative Colitis Maintenance Adult Subcutaneous Recommended Dosage:</u> A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.												
How Supplied	STELARA® (ustekinumab) injection is a sterile, preservative-free, colorless to		TRADENAME (ustekinumab-xxxx) injection, for subcutaneous use, is a sterile, preservative-free, colorless									

	light yellow solution and may contain a few small translucent or white particles. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials. <u>For Subcutaneous Use</u> <i>Prefilled Syringes</i> • 45 mg/0.5 mL (NDC 57894-060-03) • 90 mg/mL (NDC 57894-061-03) Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber. <i>Single-dose Vial</i> • 45 mg/0.5 mL (NDC 57894-060-02) <u>For Intravenous Infusion</u> <i>Single-dose Vial</i> • 130 mg/26 mL (5 mg/mL) (NDC 57894-054-27)	to slightly yellow solution and practically free of visible particles. It is supplied as individually packaged, single-dose prefilled syringes. <i>Prefilled Syringes</i> • 45 mg/0.5 mL (NDC XXXXX-XXX-XX) • 90 mg/mL (NDC XXXXX-XXX-XX)
Storage	STELARA® vials and prefilled syringes must be refrigerated at 2°C to 8°C (36°F to 46°F). Store STELARA® vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. If needed, individual prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the	TRADENAME prefilled syringes must be refrigerated at 2°C to 8°C (36°F to 46°F). Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. If needed, individual prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first

	original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use STELARA® after the expiration date on the carton or on the prefilled syringe.	removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use TRADENAME after the expiration date on the carton or on the prefilled syringe.
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APPENDIX B. PREVIOUS DMEPA REVIEWS – N/A

APPEARS THIS WAY ON ORIGINAL

APPENDIX E. INFORMATION REQUEST

E.1 Information Request (Issued April 11, 2023):

Please refer to your biologics license application (BLA) dated October 11, 2023, received October 11, 2023, submitted under section 351(k) of the Public Health Service Act for AVT04.

We also refer to carton labeling, containing braille.

- We note the inclusion of braille on the carton labeling. We recommend that you submit a certificate of translation to verify the information represented in braille on the labeling.

We request that you provide your response to the BLA by April 18, 2023.

<https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af806c2725>

E.2 Response (Received via mail April 17, 2023, and eCTD via April 18, 2023):

As agreed with Dr Randolph via email on April 17, 2023.

To verify the information in braille included on the carton labels once a tradename is approved, Alvotech intends to provide translation reports generated with the Global Vision Esko Braille Inspection tool software with the updated labels.

The translation reports will confirm that the braille included on the AVT04 carton labels translates to the approved tradename and that the spacing of the included braille complies with the Marburg Medium Braille specifications and the IADD and BANA Standards for Braille on Folding Cartons (Feb 2012, Rev 1).

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APPENDIX F. LABELS AND LABELING

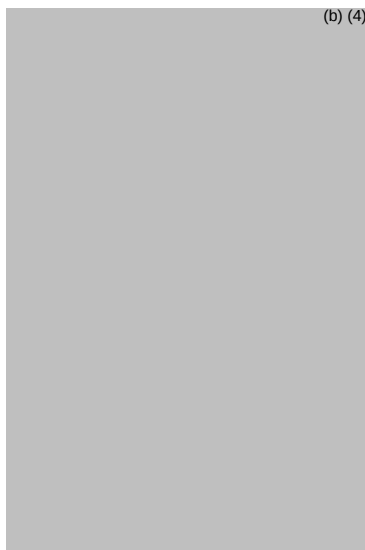
F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Selarsdi labels and labeling submitted by Alvotech USA Inc..

- Container label(s) received on October 11, 2022
- Carton labeling received on October 11, 2022
- Instructions for Use received on October 11, 2022, available from <\\CDSESUB1\EVSPROD\bla761343\0001\m1\us\114-labeling\1141-draft-label\1-14-1-3-draft-labeling-text-ifu.pdf>
- Medication Guide received on October 11, 2022, available from <\\CDSESUB1\EVSPROD\bla761343\0001\m1\us\114-labeling\1141-draft-label\1-14-1-3-draft-labeling-med-guide-clean.pdf>
- Prescribing Information (Image not shown) received on January 6, 2023, available from <\\CDSESUB1\EVSPROD\bla761343\0010\m1\us\114-labeling\1141-draft-label\1-14-1-3-draft-labeling-package-insert.pdf>

F.2 Label and Labeling Images

Container label(s)



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CORWIN D HOWARD
05/16/2023 03:03:33 PM

MADHURI R PATEL
05/16/2023 03:06:12 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: May 8, 2023

To: Sascha Randolph, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)
Sangeeta Jain, Clinical Reviewer, DDD

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (ustekinumab-xxxx) injection, for subcutaneous use

BLA: 761343

Background:

In response to DDD's consult request dated November 30, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original BLA submission for TRADENAME.

PI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 2, 2023, and our comments are provided below.

OPDP comments on the proposed Medication Guide/IFU will be sent under separate cover, either as a combined OPDP and Division of Medical Policy Programs (DMPP) review or a separate OPDP review.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on May 2, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
05/08/2023 05:12:11 PM