

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761379Orig1s000

OTHER REVIEW(S)

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)

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

Date of This Review:	September 25, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761379
Product Name, Dosage Form, and Strength:	Otulfu (ustekinumab-aauz) injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringe and 130 mg/26 mL (5 mg/mL) vial
Applicant Name:	Fresenius Kabi USA, LLC
FDA Received Date:	September 23, 2024
TTT ID #:	2023-6565-2
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Fresenius Kabi USA, LLC submitted revised container labels and carton labeling received on September 23, 2024 for Otulfi. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Otulfi (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

Fresenius Kabi USA, LLC implemented all of our recommendations and we have no additional recommendations at this time.

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

^a Patel, M. Label and Labeling Review Memo for Otulfi (BLA 761379). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 SEP 18. TTT ID: 2023-6565-1.

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/s/

MADHURI R PATEL
09/25/2024 08:47:16 AM

YEVGENIYA M KOGAN
09/25/2024 10:16:40 AM

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:	September 18, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761379
Product Name, Dosage Form, and Strength:	Otulfu (ustekinumab-aauz) injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringe and 130 mg/26 mL (5 mg/mL) vial
Applicant Name:	Fresenius Kabi USA, LLC
FDA Received Date:	September 3, 2024 and September 17, 2024
TTT ID #:	2023-6565-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Fresenius Kabi USA, LLC submitted revised container labels and carton labeling received on September 3, 2024 and September 17, 2024 for Otulfi. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Otulfi (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 container labels and carton labeling are unacceptable from a medication error perspective. We note the addition of duplicative net quantity statements and storage information and the use of coloring/highlighting that competes in prominence with important information. We provide recommendations in Section 3 for Fresenius Kabi USA, LLC.

3 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

A. General Comments (Container Label(s) and Carton Labeling)

1. Consider revising the (b) (4) color font used for the proprietary name and nonproprietary name to enhance the coloring and increase prominence of the names.

B. Carton Labeling

1. Remove the colored background from the net quantity statements “1 Single-dose prefilled syringe” and “1 Single-dose Vial” as it competes in prominence with the product strength.
2. For the prefilled syringe carton labeling, revise the net quantity statement from “1 Single-dose prefilled syringe (b) (4)” to “1 Single-dose prefilled syringe. Discard unused portion.”
3. For the vial carton labeling, remove the duplicative “1 Single-dose Vial (b) (4)” and revise the (b) (4) to read “1 Single-dose vial. Discard unused portion”.
4. On the principal display panel (PDP), remove the following statements to decrease clutter: (b) (4)
“. On the side panels, under the “Carton contains:” statement, remove “- (b) (4)”

^a Patel, M. Label and Labeling Review for Otulfi (BLA 761379). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 APR 12. TTT ID: 2023-6565.

5. We recommend removing the statement “ (b) (4) ” on the PDP of the prefilled syringe carton labeling and the side panel of the vial carton labeling as the intent of this statement is unclear and duplicative with the storage information.

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

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/s/

MADHURI R PATEL
09/18/2024 11:55:59 AM

YEVGENIYA M KOGAN
09/18/2024 01:25:09 PM

MEMORANDUM

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

DATE: September 6, 2024

TO: Jill Lindstrom, M.D.
Director
Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)
Office of New Drugs (OND)

FROM: Makini Cobourne-Duval, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspections of CRS Clinical
Research Services Berlin GmbH, Berlin, Germany and CRS
Clinical Research Services Mannheim GmbH, Mannheim,
Germany

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged clinical inspections of study FYB202-01-02 (BLA 761379) conducted at CRS Clinical Research Services Berlin GmbH, Berlin, Germany and CRS Clinical Research Services Mannheim GmbH, Mannheim, Germany.

Form FDA 483 was not issued at the inspection close-out at either site. However, one discussion item was addressed at the inspection close-out at CRS Clinical Research Services Berlin GmbH, Berlin, Germany. Two discussion items were addressed at the inspection close-out at CRS Clinical Research Services Mannheim GmbH, Mannheim, Germany. After reviewing the inspection findings, exhibits provided in the EIRs, and the firm's response per the EIRs, there are no concerns for either site regarding reliability of the data or human subject protection for inspected study FYB202-01-02 for the review division consideration.

2. Inspected Studies:

BLA 761379

Study Number: FYB202-01-02

Study Title: "A randomised, double-blind, single-dose, 3-arm, parallel-group phase 1 study to demonstrate pharmacokinetic equivalence of FYB202 and Stelara(ustekinumab) administered as a single subcutaneous injection to healthy volunteers - RUSTIC"

Dates of study conduct: 06/20/2022 - 02/22/2023

Clinical site: CRS Clinical Research Services Berlin GmbH
Sellerstrasse 31, Gebäude P300
13353 Berlin, Germany
**Site moved after end of trial to:*
Siemensdamm 65 (via Nikolaus-Groß-Weg)
13627 Berlin, Germany

Clinical site: CRS Clinical Research Services Mannheim GmbH
Grenadierstrasse 1
68167 Mannheim, Germany

3. Inspectional Findings

CRS Clinical Research Services Berlin GmbH, Berlin, Germany

ORA investigator Lakecha N. Lewis inspected CRS Clinical Research Services Berlin GmbH, Siemensdamm 65 (via Nikolaus-Groß-Weg), Berlin, Germany from July 1-5, 2024.

3.1 Previous Inspection

This was the first OSIS inspection of CRS Clinical Research Services Berlin GmbH under the BA/BE program. This was also the first OSIS inspection of Mares-Elaine Strempler, M.D., Ph.D. under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing the following items:

- Case report forms (CRFs) and subject source records
- Informed consent documents
- Screening and enrollment logs
- Protocol adherence
- Standard operating procedures (SOPs)
- Ethics committee correspondence
- Investigational product (IP) accountability and storage
- Randomization records
- Adverse events
- Concomitant medications
- Delegation Logs

3.3 Inspection finding(s)

At the conclusion of the inspection, investigator Lakecha N. Lewis did not issue Form FDA 483 to the clinical site. One discussion item was addressed at the inspection close-out. The discussion item, the firm's response per the EIR, and my evaluation are presented below.

3.3.2. Discussion Item

Discussion item 1:

Several discrepancies in the administered IP were identified when comparing the on-site unblinded IP preparation log to Listing 16.1.7 - "Randomisation scheme and codes (subject identification and treatment assigned)".

Screening	Randomization	IP Kit Allocated	Source Record (Ex. 12, pages 1-3)	Sponsor Listings (Att. 2, page 54)
(b) (6)			Reference 1	Test
			Test	Reference 2
			Reference 2	Reference 1
				Test
			Reference 1	Reference 2
				Test

Additionally, during the ORA investigator's review of the eCRF, it was noted that the IP administration record documents treatment allocation with a "Yes" which was signed/dated by an unblinded staff member. However, there was no reference to the subject's randomization number, or the associated IP kit administered to the subject in the eCRF. Therefore, the ORA

investigator could not confirm that this cohort received their intended IP.

OSIS Evaluation:

In my review and comparison of the provided on-site unblinded IP preparation log source document to Listing 16.1.7 - "Randomisation scheme and codes (subject identification and treatment assigned)" provided to the Agency, the discrepancies identified in the discussion item were confirmed. However, I also reviewed Listing 16.1.6 - "Subjects receiving test drug(s)/ investigational product(s) from specific batches" and compared it to the unblinded IP preparation log source document, and found no discrepancies. Namely, the IP type (Test, Reference 1, Reference 2), IP administration date, and Kit No. all matched each subject number as documented in the unblinded IP preparation log source document. I confirmed that the site/sponsor accurately reported the IP administration to each subject from this site. Therefore, I conclude that this discussion item does not impact the data integrity of this study.

Firm's Response:

The site's management explained that the CRO's eCRF system (SocraMetrics) automatically conducts the randomization and blinding once identified subjects pass the screening phase. The site remained blinded to each subject's randomization number and kit number(s) during the study, both of which were not immediately visible in the eCRF. Per the site's pharmacist, the SocraMetrics eCRF system can generate an extracted report for comparison against subject records. A member of the SocraTech R&D (CRO) management staff, who was present during the inspection, provided a copy of the extracted report on all randomized subjects from the SocraMetrics eCRF system.

OSIS Evaluation of the response:

The protocol states that, "All members of the study team will remain blinded to each subject's assigned study intervention throughout the course of the study." It also states that, "Unblinding due to an emergency will be performed via eCRF, where the information about the administered treatment is available," indicating that unblinding may be performed, if necessary, through the eCRF. Review of the extracted report on all randomized subjects from the eCRF provided by SocraTech R&D revealed that the IP type (Test, Reference 1, Reference 2), IP administration date, and Kit No. for each subject number all matched as documented in the unblinded IP preparation log source document as well as what was reported in Listing 16.1.6 - "Subjects receiving test drug(s)/ investigational product(s)

from specific batches" to the Agency. This additional, supportive document further confirms that the sponsor accurately reported the IP administration to each subject from this site. Hence, my evaluation remains unchanged.

CRS Clinical Research Services Mannheim GmbH, Mannheim, Germany

ORA investigator Yuanyuan Li inspected CRS Clinical Research Services Mannheim GmbH, Grenadierstr 1, Mannheim, Germany from June 10-14, 2024.

3.1 Previous Inspection

The previous OSIS inspection of CRS Clinical Research Services Mannheim GmbH was conducted from May 12-23, 2014. At the conclusion of the inspection, Form FDA 483 was not issued. There were four discussion items addressed at the inspection close-out for: 1) the precarious handling and maintenance of informed consent documents, 2) inappropriate delegation of study tasks, 3) ensuring that the firm maintains a reserve sample if required by the study, 4) the discontinuation of a subject from the study following an elevated serum creatinine concentration measurement although it was deemed not clinically significant. The final classification was NAI.

ORA investigator Li confirmed that CRS Mannheim made corrections in response to the discussion items from the previous BA/BE inspection.

3.2 Current Inspection

The current inspection included auditing the following items:

- Case report forms (CRFs) & study source documents
- Informed consent process
- Protocol adherence
- Dosing records
- Monitoring records
- Site responsibility & training logs
- Institutional review board approvals
- Test article accountability and storage
- Randomization
- Adverse event reporting
- Clinical site facilities & critical equipment maintenance

3.3 Inspection finding(s)

At the conclusion of the inspection, investigator Yuanyuan Li did not issue Form FDA 483 to the clinical site. Two discussion items were addressed at the inspection close-out. The discussion items, the firm's response per the EIR, and my evaluation are presented below.

3.3.1. Discussion Items

Discussion item 1:

Two data entry errors were observed from the manual entry of source data into the electronic data capturing (EDC) system, which led to discrepancies between the source data and the data submitted to the Agency:

- Per the source document, Subject (b) (6) experienced an AE of Tooth Ache on (b) (6). In the EDC system, the AE start date was entered as (b) (6) by mistake.
- Per the source documents, Subject (b) (6) experienced an AE of elevation of Creatine Kinase (CK) above 1000 U/L. In the EDC system, the AE event was entered as elevation of CK over 1600 U/L.

OSIS Evaluation:

Good clinical practice requires that a clinical site reports accurate adverse event details. The firm did not meet this standard as seen with the discrepant dates of AE onset for Subject (b) (6) and creatine kinase level for Subject (b) (6) when comparing the source documents to the EDC system entries at this site. However, per the EIR, besides these two adverse events, all the other adverse events were appropriately reported, and adequately described. Therefore, I conclude that while these incidents were isolated and are unlikely to impact subject safety or data reliability, the review division may consider these discrepancies as deemed appropriate.

Firm's Response:

The Sr. Clinical PI agreed with the discussion item and promised corrections for the future.

Discussion item 2:

The ORA investigator emphasized and reminded the firm of the importance of following the study protocol requirements after reviewing the reported protocol deviations from this site.

OSIS Evaluation:

No specific or further details nor exhibits were provided in the EIR regarding this discussion item. Since no new, undisclosed information was provided in this discussion item, I conclude that this discussion item has no impact on data integrity or subject safety.

Firm's Response:

No specific response was provided per the EIR to this discussion item beyond promised corrections for future clinical studies.

Makini Cobourne-Duval, Ph.D.
Pharmacologist

Draft: MCD 08/29/2024, 08/30/2024, 09/04/2024, 09/05/2024
Edit: MO 09/05/2024; JC 09/05/2024

OSIS File #: BE 10089

eNSpect Assignment ID: 238109

eNSpect OpID:

276619 (CRS Clinical Research Services Mannheim GmbH)

276618 (CRS Clinical Research Services Berlin GmbH)

Dr. Kimberly Benson signed on behalf of Dr. Seongeun (Julia) Cho

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/s/

MAKINI COBOURNE-DUVAL
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09/06/2024 11:32:41 AM

KIMBERLY A BENSON
09/06/2024 01:06:48 PM

**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: August 28, 2024

To: Kimberle Searcy, MPH
Regulatory Health 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)

From: Laurie Buonaccorsi, PharmD
Senior 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)

Drug Name [FYB202] OTULFI (ustekinumab-aaaz)¹ injection, for
(nonproprietary name); subcutaneous or intravenous use
Dosage Form and • subcutaneous injection, 45 mg/0.5 mL or 90 mg/mL in a
Route: • intravenous infusion, 130 mg/26 mL (5 mg/mL) in a
single-dose vial

Application Type/Number: BLA 761379

Applicant: Fresenius Kabi USA, LLC

1 INTRODUCTION

On September 28, 2023, Fresenius Kabi USA, LLC submitted for the Agency's review an original Biologics License Application (BLA) 761379 for [FYB202]

¹ FYB202 was developed as a proposed interchangeable biosimilar to US-licensed Stelara (ustekinumab) BLA 125261 and BLA 761044. The proposed proprietary name OTULFI and nonproprietary name -aaaz were found to be conditionally acceptable by the Division of Medication Error Prevention and Analysis I (DMEPA 1) on January 12, 2024, and July 25, 2024, respectively.

OTULFI (ustekinumab-aauz) injection, a proposed interchangeable biosimilar to US-licensed STELARA (ustekinumab) injection (BLA 125261 and BLA 761044) for the treatment of the following:

- patients 6 years or older and weighing 60 kg or more with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
- patients 6 years or older and weighing 60 kg or more with active psoriatic arthritis
- adults with moderately to severely active Crohn's Disease
- adults with moderately to severely active ulcerative colitis

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 December 20, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for [FYB202] OTULFI (ustekinumab-aauz) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft [FYB202] OTULFI (ustekinumab-aauz) injection MG received on September 28, 2023, revised throughout the review cycle, and received by DMPP and OPDP on August 7, 2024.
- Draft [FYB202] OTULFI (ustekinumab-aauz) injection single-dose prefilled syringe IFU, received on September 28, 2023, revised throughout the review cycle, and received by DMPP and OPDP on August 7, 2024.
- Draft [FYB202] OTULFI (ustekinumab-aauz) injection Prescribing Information (PI) received on September 28, 2023, revised throughout the review cycle, and received by DMPP and OPDP on August 7, 2024.
- Approved US-licensed STELARA (ustekinumab) injection PI and MG dated March 18, 2024, and IFU 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. In our review of the IFU, the target reading level is at or below an 8th grade 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.

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 they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- evaluated the MG and IFU per the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- evaluated the IFU per 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 labeling for US-licensed STELARA (ustekinumab) injection 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.

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/s/

LAURIE J BUONACCORSI
08/28/2024 02:59:14 PM

MONTHERSON L SAINT JUSTE
08/28/2024 04:05:00 PM

LASHAWN M GRIFFITHS
08/28/2024 05:02:29 PM

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

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

Memorandum

Date: August 20, 2024

To: Kim Searcy, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Felisa (Sally) Lewis, 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 OTULFI (ustekinumab-aauz) injection, for subcutaneous or intravenous use

BLA: 761379

Background:

In response to DDD's consult request dated December 20, 2023, OPDP has reviewed the proposed Prescribing Information (PI), and Medication Guide, and Instructions for Use (IFU) for the original BLA submission for OTULFI (ustekinumab- aauz).

PI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 7, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide/IFU, and comments will be sent under separate cover.

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
08/20/2024 01:06:01 PM

MEMORANDUM

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

DATE: 8/2/2024

TO: Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761379

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not possible for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) informed OSIS on April 29, 2024, that an inspection of the site below could not be accomplished due to limited resources available to accomplish the inspection prior to the user fee goal date. An OSIS remote regulatory assessment (RRA) is not possible at this time either due to resource constraints.

Therefore, we note OSIS's inspection history for the site below:

SocraTec Probandenstation Erfurt: The Office of Regulatory Affairs (ORA) inspected the clinical site in (b) (4). The inspection was conducted under the following submission: (b) (4).

OSIS concluded that data from the reviewed studies were reliable.

Therefore, based on the information above, a clinical site inspection will not be conducted.

Site

Facility Type	Facility Name	Facility Address
Clinical	SocraTec Probandenstation Erfurt	Mainzerhofplatz 14, Erfurt, Thuringia, Germany

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/s/

NICOLA M FENTY-STEWART
08/02/2024 10:07:00 AM

MEMORANDUM

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

DATE: July 19, 2024

TO: Shari Targum, MD
Director (Acting)
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs

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

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

SUBJECT: Review of remote regulatory assessment (RRA) conducted
at (b) (4)

1. RRA Summary

OSIS conducted an RRA of the analytical portion of study # FYB202-01-02 performed at (b) (4). The study was submitted in support of BLA 761379 (FYB202 [Ustekinumab]).

During the RRA, I observed and communicated the following two objectionable conditions to (b) (4)

(b) (4)

Based on the evaluation of RRA observations, exhibits, and written response to the observations by (b) (4) there are no concerns with reliability of measured concentration data from 101 runs and the results of neutralizing antibodies analyzed in subject samples from study # FYB202-01-02.

- Despite of reporting incorrect LQC concentration data for 101 out of 594 analytical runs, the correct LQC measured concentrations were used to accept or reject analytical runs. Therefore, the measured concentration data of subject samples from study # FYB202-01-02 are reliable.
- The written response submitted post-RRA includes newly validated freeze-thaw stability data supporting up to eight freeze-thaw cycles at -20°C. Thus, the new freeze-thaw stability assessment adequately covers the number of freeze-thaw cycles experienced by subject samples. Therefore, the reviewed results of neutralizing antibodies analyzed in subject samples from study # FYB202-01-02 are reliable.

2. Reviewed Study:

BLA 761379

Study Number: FYB202-01-02

Study Title: "A randomized, double-blind, single-dose, three-arm, parallel-group phase 1 study to demonstrate pharmacokinetic equivalence of FYB202 and Stelara (Ustekinumab) administered as a single subcutaneous injection to healthy volunteers."

Dates of Pharmacokinetic Sample Analysis: December 16, 2022 to March 17, 2023.

Dates of Neutralizing Antibody Sample Analysis: March 23 to April 20, 2023.

Analytical site: (b) (4)

3. Scope of RRA

OSIS scientist Gajendiran Mahadevan, Ph.D. reviewed the analytical portion of the above study performed at (b) (4)

3.1 Previous Inspection

The previous OSIS inspection of (b) (4) was conducted from (u) (4) At the conclusion of the inspection, no objectionable conditions were observed, and no

Form FDA 483 was issued. In addition, no items were discussed with (b) (4)

3.2 Current RRA

The current RRA included opening and close-out meetings with (b) (4). Requests for study documents were made via communication letters. (b) (4) directly uploaded the requested documents in FDA's Cloud File Sharing (CFS) service facilitated by Box.com. During the record audit, screen sharing was used to review study data when clarifications were needed.

The RRA covered the following items:

- Study records.
- Method validation of pharmacokinetic and neutralizing antibody studies.
- Sample analysis of pharmacokinetic and neutralizing antibody studies.
- Study relevant SOPs.
- Organizational charts.
- Training records of study personnel.

3.3 RRA Observations

At the conclusion of the RRA, I discussed two objectionable conditions with the site's management. The observations

(b) (4)

(b) (4)

y

Draft: GM 7/15/2024; 7/16/2024; 7/17/2024
Edits: RCA 7/16/2024, 7/17/2024; AD 7/17/2024

OSIS File #: (b) (4)

eNSpect Assignment ID: (b) (4)

eNSpect Op ID: (b) (4)

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/s/

GAJENDIRAN MAHADEVAN
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ARINDAM DASGUPTA
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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:	July 1, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761379
Product Type:	Combination Product (Biologic-Device)
Product Name, Dosage Form and Strength:	FYB202 ^a (ustekinumab-xxxx) ^b injection, 45 mg/0.5 mL and 90 mg/mL
Device Constituent:	Prefilled Syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Formycon AG
Submission Date:	September 28, 2023; December 11, 2023; March 26, 2024
OSE TTT #:	2023-6567
DMEPA 1 Safety Evaluator:	Lisa Huang, PharmD, MPH
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

^a FYB202 has been developed as a proposed biosimilar and interchangeable to US-licensed Stelara (ustekinumab) (hereafter, called Stelara). At the time this review was written, the proprietary name Otulfi was found conditionally acceptable on January 12, 2024. However, the proprietary name placeholder FYB202, is used throughout the review.

^b The proposed nonproprietary name suffix has not yet been conditionally accepted. We therefore refer to the proposed product as “ustekinumab-xxxx” throughout this review in place of the nonproprietary name for this product.

1. REASON FOR REVIEW

On September 28, 2023, Formycon AG submitted Biologics License Application (BLA) under BLA 761379 that included a comparative analyses (CA) and justification for not submitting Human Factors (HF) Validation study and Comparative Use Human Factors (CUHF) study results to support their marketing application for FYB202 (ustekinumab-xxxx) injection, 45 mg/0.5 mL and 90 mg/mL as a proposed biosimilar and interchangeable biosimilar to US-Licensed Stelara (hereafter, called Stelara).

2. BACKGROUND

FYB202 is a single ingredient combination product with a single-dose prefilled syringe (PFS) device constituent part. FYB202 is a human interleukin-12 and -23 antagonist indicated for the treatment of:

- Adult patients with moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy
- Adult patients with active psoriatic arthritis (PsA)
- Adult patients with moderately to severely active Crohn's disease (CD)
- Adult patients with moderately to severely active ulcerative colitis
- Pediatric patients 6 years and older who weigh 60 kg or more with moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy
- Pediatric patients 6 years and older who weigh 60 kg or more active psoriatic arthritis (PsA)

On December 20, 2021, Formycon AG submitted a Use-related Risk Analysis (URRA), CA, and justification for not submitting HF validation study results under IND 141478 to support their future marketing application for FYB202 45 mg/0.5 mL and 90 mg/mL PFS, as a proposed biosimilar to Stelara PFS.

On March 1, 2022, we reviewed the URRA, CA, and justification for not submitting HF validations results. We determined Formycon AG does not need to submit HF validation study results to support their future marketing application for FYB202 PFS device constituents. We also stated that if Formycon AG modified the product user interface, additional human factors considerations may apply.^c

On September 28, 2023, Formycon AG submitted their marketing application under BLA 761379 for FYB202 PFS, as proposed biosimilar and interchangeable to Stelara. The submission included a CA and justification for not submitting HF validation study results to support their marketing

^c Flint, J. Use-Related Risk Analysis and Comparative Analyses review for FYB202 Injection, 45 mg/0.5 mL and 90 mg/mL (IND 141478). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 01 MAR 2022. TTT No.: 2021-2478.

application. However, it was not clear if the product user interface of the proposed FYB202 PFS evaluated in the CA and justification submitted on September 28, 2023, under BLA 761379, was identical to the product user interface of the proposed FYB202 PFS injections evaluated in the URR, CA and justification submitted on December 20, 2021, under IND 141478. Additionally, Formycon AG did not indicate whether the commercial product user interface had been modified since the December 20, 2021, submission. As such, we issued information requests (IR) on December 7, 2023, and March 22, 2024, respectively, asking Formycon AG to clarify the following:

- *“if the product user interface of your proposed FYB202 (ustekinumab) 45 mg/0.5 mL and 90 mg/mL PFS injections evaluated in your December 20, 2021, submission is identical to the product user interface of the FYB202 (ustekinumab) 45 mg/0.5 mL and 90 mg/mL PFS injections proposed in your September 28, 2023, submission.*
- *if the CA and justification evaluated in your December 20, 2021, submission is identical to the CA and justification submitted in your September 28, 2023, submission.”*
- *“confirm that you have not made any changes to the URR since our review dated March 1, 2022, for FYB202 (ustekinumab) PFS injections under IND 141478. If there are any changes, please indicate what changes you made to the URR.”*

Subsequently, on December 11, 2023, and March 26, 2024, respectively, Formycon AG indicated in their IR responses that they made the following changes to the FYB202 PFS injection product user interfaces, URR, CA and labeling:

URR

- Updated the URR to reflect the completed design verification, design validation and risk control measures information. The rationale for the update was done because the design verification and validation were not completed when the URR/CA was submitted on December 20, 2021.

Labeling

- The PFS images were updated to reflect change in plunger rod color (b) (4). The rationale for the change is to align with the intend to market artworks and labeling.
- Carton box labeling, container labels, medication guide, patient package insert design and information were added as the information was not available when the URR/CA was submitted on December 20, 2021.

CA

- The plunger rod length dimensions were updated (b) (4) to 61.09 mm to include front part with thread in the overall length. The rationale for the change is to align with the intend to market artworks and labeling.
- Wording for task 2.3 was changed from, (b) (4) to “Open the Carton Box” to reflect implicit task.

- Wording for task 4.3 included an additional instruction, *“Do not give an injection in an area of the skin that is tender, bruised, red or hard.”*
- Wording for tasks 5.1, 5.2, 5.3, 6.1, 6.2, 6.5, and 7.1 was changed to align with wording used in the Stelara IFU.
- Table 13 Part C, instructions for use (IFU) were updated to include weight in kilograms, visual appearance of medication color of PFS, and the text *“Do not use the prefilled syringe if it is dropped onto a hard surface”* this was added to reflect (b) (4) instructions for use for the syringe. Additionally, the latex warning was removed as latex is not contained in the container of FYB202.
- IFU images changed, but the text remained the same.

Additionally, Formycon AG stated, *“The user interface as proposed in the December 20, 2021, submission is almost identical to the product user interface of the FYB202 (ustekinumab) 45 mg/0.5 mL and 90 mg/mL PFS injections proposed in our September 28, 2023, submission. The only change introduced was the change in the plunger rod color not affecting the overall plunger rod and interface design.”*

Furthermore, based on the physical design differences, label and labeling changes, we note there are differences between the proposed product PFS, labels and labeling, and the reference product Stelara PFS and labels and labeling. Based on our independent expert review, we determined that these physical design and labeling differences are unlikely to negatively impact user’s ability to complete the critical tasks needed to use this product safely and effectively in the context of a proposed interchangeable biosimilar product to Stelara. Therefore, we determine that these labeling differences do not warrant data from a HF validation and comparative use human factors study.

3. CONCLUSION

Based on the aforementioned information, we maintain that Formycon AG does not need to submit human factors validation study results with their marketing application under BLA 761379 for FYB202 (ustekinumab-xxxx) injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringes, a proposed biosimilar to Stelara. Additionally, regarding interchangeability, based on our URRA and CA review we have determined that Formycon AG does not need to submit comparative use human factors study results as part of their marketing application to support interchangeability to US-licensed Stelara. We have no HF recommendations for this marketing application.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A.

Comparative Analyses is accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761379\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hf\hf-hf-validation-report.pdf>

Use-Related Risk Analysis is accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761379\0018\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hf\hf-other-risk.pdf>

APPENDIX B. INFORMATION REQUEST ISSUED DURING THIS REVIEW

On December 7, 2023, we issued an information request asking Formycon AG to clarify the following:

We note you submitted a URRA, CA, and justification for not submitting HF validation study results under IND 141478 and a CA and the aforementioned justification under BLA 761379 for FYB202 (ustekinumab) 45 mg/0.5 mL and 90 mg/mL PFS injections. However, it is not clear if the CA and justification you submitted on December 20, 2021, for IND 141478, is the same as the CA and justification you submitted on September 28, 2023, for BLA 761379.

Additionally, it is not clear if the product user interface of the FYB202 (ustekinumab) 45 mg/0.5 mL and 90 mg/mL PFS injections for your URRA, CA, and justification submitted on December 20, 2021, under IND 141478, is identical to the product user interface of your FYB202 (ustekinumab) 45 mg/0.5 mL and 90 mg/mL PFS injections for your CA and justification submitted on September 28, 2023.

As such, to facilitate an efficient and comprehensive review of all the changes, we request you submit the following:

- Specify if the CA and justification evaluated in your December 20, 2021, submission is identical to the CA and justification submitted in your September 28, 2023, submission. If there are any changes, please specify the changes you made in a red-lined, annotated version of your September 28, 2023, CA submission that identifies any changes made after our March 1, 2022, URRA and CA review.
- Specify if the product user interface of your proposed FYB202 (ustekinumab) 45 mg/0.5 mL and 90 mg/mL PFS injections evaluated in your December 20, 2021, submission is identical to the product user interface of the FYB202 (ustekinumab) 45 mg/0.5 mL and 90 mg/mL PFS injections proposed in your September 28, 2023, submission. If there are any changes, please indicate what changes you made to the user interface."

Formycon AG provided an acceptable response on December 11, 2023, that can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761379\0008\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hf\hf-validation-report-redline.pdf>

On March 22, 2024, we issued an information request asking Formycon AG to clarify the following:

We note in your December 11, 2023, Response to HF Information Request, you specified the changes made in the CA and product user interface since our URR and CA review dated March 1, 2022, for FYB202 (ustekinumab) PFS injections under IND 141478. However, it is not clear if you made changes to the URR since our review.

As such, we are unable to adequately review your CA. Please confirm that you have not made any changes to the URR since our review dated March 1, 2022, for FYB202 (ustekinumab) PFS injections under IND 141478. If there are any changes, please indicate what changes you made to the URR.

Formycon AG provided an acceptable response on March 26, 2024, that can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761379\0018\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hf\hf-other-response.pdf>

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/s/

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JASON A FLINT
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Clinical Inspection Summary

Date	April 29, 2024
From	Roy Blay, Ph.D. Michele Fedowitz, M.D. Jenn Sellers, M.D., Ph.D. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Shari Targum, M.D., Deputy Division Director Snezana Trajkovic, M.D., Clinical Team Leader Felisa Lewis, M.D., Reviewing M.O. Kimberle Searcy, P.M. Division of Dermatology and Dentistry
BLA	761379
Applicant	Formycon AG
Drug	Ustekinumab
NME	No
Therapeutic Classification	Cytokine modulator (human monoclonal antibody, IL-12 and -23 antagonist)
Proposed Indication(s)	Treatment of moderate to severe plaque psoriasis
Consultation Request Date	20 Nov 2023
Summary Goal Date	28 Jul 2024
Action Goal Date	27 Sep 2024
PDUFA Date	28 Sep 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Protocol FYB202-03-01 were submitted to the Agency in support of BLA 761379 for the use of ustekinumab for the treatment of moderate to severe plaque psoriasis. Two clinical investigators, Dr. Kapinska-Mrowiecka and Dr. Pirowska were inspected in support of this BLA.

Based on the results of these inspections, Study FYB202-03-01 appears to have been conducted adequately and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

Protocol FYB202-03-01: A Randomised, Double-blind, Parallel-group, Phase 3 Study to Compare the Efficacy, Safety and Immunogenicity of Proposed Biosimilar Ustekinumab FYB202 to Stelara in Moderate-to-Severe Plaque Psoriasis Patients

This protocol was a multicenter, randomised, double-blind, parallel-group Phase 3 trial whose primary efficacy objective was to evaluate and compare percent improvement in Psoriasis Area and Severity Index (PASI) score over 12 weeks.

The study consisted of eight clinic visits over a period of 52 weeks. Eligible subjects were randomized in a 1:1 ratio to receive subcutaneous injections of either FYB202 or Stelara 45 mg at weeks 0 and 4 and at 12-week intervals thereafter (weeks 16, 28, and 40); the end of study visit was at week 52. Randomisation was stratified by prior inadequate response or intolerance to a systemic biological treatment in the opinion of the investigator.

Patients not achieving a $\geq 75\%$ improvement in PASI score (PASI 75) from baseline at week 28 were considered non-responders and discontinued from study intervention. At week 28, patients were re-randomised in a blinded fashion. Patients initially randomised to the Stelara treatment arm were re-randomised 1:1 so that 50% of patients in the original Stelara arm would then receive FYB202 and 50% would continue receiving Stelara. Patients originally randomised to FYB202 would continue to receive FYB202.

The primary efficacy endpoint was the percent improvement in PASI score from baseline (Week 0) to Week 12.

The study was conducted at 27 sites in four countries. The first subject's first visit was on 23 Sep 2020, and the last subject's last visit was on 21 Mar 2022. A total of 392 subjects were enrolled, randomized, treated, and analyzed, with 197 subjects receiving FYB202 and 195 subjects receiving Stelara EU.

1. Monika Kapinska-Mrowiecka, MD

Ul. Henryka Sienkiewicza 23
Krakow, NA 30-033
Poland

Site: 311

Inspection Dates: 22-23 Jan 2024

Dr. Kapinska-Mrowiecka was inspected for the conduct of Protocol FYB202-03-01. This was the first inspection of Dr. Kapinska-Mrowiecka.

At this site for Protocol FYB202-03-01, 28 subjects were screened, 25 subjects were enrolled and treated, with 23 subjects completing the study. Two subjects withdrew from the study: one subject withdrawing permission and the other experiencing a severe adverse event of renal cancer.

The primary efficacy endpoint (the Psoriasis Area and Severity Index (PASI) at Week 12) and adverse event reporting were verified for all enrolled subjects, as well as PASI scores at screening, baseline, and Weeks 4, 16, 28, 40, and 52. Subject records reviewed included signed informed consent forms and visit documentation.

Study-related documents reviewed included SOPs, correspondence between the sponsor, site, and the ethics committee, training documentation including eCRF data entry training, delegation logs, investigational product (IP) shipping, dispensing, storage, and accountability records, and financial disclosures.

Because of the abbreviated nature of the inspection, subject eligibility records, maintenance of IP blinding, and reporting of concomitant medications were not reviewed.

The inspection compared the primary efficacy endpoint and adverse event reporting source documents with the data listings and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

2. Magdalena Pirowska, MD

Ul. Rogozinskiego 6/Lokal U3
KRAKOW, NA 31-559
Poland

Site: 312:

Inspection Dates: 18-21 Mar 2024

Dr. Pirowska was inspected for the conduct of Protocol FYB202-03-01. This was the first inspection of Dr. Pirowska. At this site for Protocol FYB202-03-01, 37 subjects were screened, 10 subjects were screen failures, 27 subjects were enrolled, and 26 subjects completed the study.

The study files of all 27 enrolled subjects were reviewed, including primary efficacy endpoint and adverse event reporting. Subject records reviewed included study eligibility, medical histories, informed consent, and protocol deviations.

Study-related documents reviewed included ethics committee correspondence and approvals, training documentation, delegation logs, IP shipment, receipt, storage, accountability, and dispensation records, sponsor and monitor correspondence, and financial disclosures. Source records were in paper format that was then entered into an electronic database capture (EDC) system.

The inspection compared the source records with the data listings and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
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:
Central Doc. Rm.
DO/Division Director/Jill Lindstrom
DO/Deputy Director/Shari Targum
DO/Medical Team Leader/Snezana Trajkovic
DO/MO/Felisa Lewis
DO/Project Manager/Kimberle Searcy
OSI/Office Director/David Burrow
OSI/Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Michele Fedowitz
OSI/DCCE/GCPAB Reviewer/Roy Blay
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/

ROY A BLAY
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MICHELE B FEDOWITZ
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JENN W SELLERS
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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:	April 12, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761379
Product Name, Dosage Form, and Strength:	Otulfu (ustekinumab-xxxx) ^a injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringe and 130 mg/26 mL (5 mg/mL) vial
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Formycon AG
FDA Received Date:	September 28, 2023
TTT ID #:	2023-6565
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

^a The 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 Otulfi (ustekinumab-xxxx) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Otulfi 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 – N/A
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. 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 Formycon AG. Note that DMEPA 1 is evaluating the Human Factors (HF) data under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming

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			

Table 2. Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The nonproprietary name suffix is denoted by the placeholder ‘-xxxx’.	A distinguishable nonproprietary name will facilitate accurate identification of the biological product by healthcare providers and patients.	We recommend replacing ‘-xxxx’ with the conditionally acceptable nonproprietary name suffix when it is determined.

5 RECOMMENDATIONS FOR FORMYCON AG

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors data.

Table 3. Identified Issues and Recommendations for Formycon AG (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently presented, the placeholder ‘xxxx’ for the suffix is present as part of the nonproprietary name on the principal display panel.	A distinguishable nonproprietary name will facilitate accurate identification of the biological product by healthcare providers and patients.	Once a nonproprietary name is found conditionally acceptable for your proposed product, revise the nonproprietary name on all labels and labeling to incorporate the FDA-designated nonproprietary name suffix throughout the labels and labeling.
2.	The strength is presented as “90 mg/1 mL”, which is inconsistent with the product strength of 90 mg/mL.	Inconsistent strength presentations may lead to wrong strength medication errors.	Revise “90 mg/1 mL” to “90 mg/mL”.
3.	The 45 mg/0.5 mL strength is not clearly differentiated due to the similarity between the	Lack of adequate differentiation may contribute to wrong strength errors. Color	We recommend revising the color scheme of the 45 mg/0.5 mL strength or the proprietary and non-proprietary names

Table 3. Identified Issues and Recommendations for Formycon AG (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) color which overlaps with the font colors used for the proprietary and nonproprietary names.	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.	such that the strengths and the names appear in their own unique colors that do not overlap.
4.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See <i>Guidance for Industry: Product Identifiers under the Drug Supply Chain</i>

Table 3. Identified Issues and Recommendations for Formycon AG (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			<i>Security Act - Questions and Answers (June 2021).</i>
5.	For the vial container label and carton labeling, the terminology within the statement of dosage statement (i.e., (b) (4) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage statement to read, "Dosage: see Prescribing Information" or "Recommended Dosage: see Prescribing Information".
Container Label(s)			
1.	The first temperature numerical is missing the degree symbol, as well as the unit of temperature [e.g., Fahrenheit symbol (F) and Centigrade symbol (C)].	Lack of clarity.	Revise '36-46°F' read '36°F to 46°F' and revise '2-8C°' read '2°C to 8°C'.
Carton Labeling			
1.	For the prefilled syringe carton labeling, the terminology within the statement of dosage statement "See package insert for dosing information" is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage statement to read, "Recommended Dosage: see Prescribing Information."
2.	The net quantity statement does not appear on the principal display panel. Additionally, the discard statement "Discard unused portion" is not	Failure to include the net quantity statement on the principal display panel may result in confusion regarding the contents of the carton.	We recommend revising the statements 'Single-Dose vial' and 'Single-Dose prefilled syringe' on the principal display panel to include a net quantity statement and discard statement [e.g., 'One single-

Table 3. Identified Issues and Recommendations for Formycon AG (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	present next to the package type term “single-dose [vial/prefilled syringe]”.		dose vial. Discard unused portion.’ or ‘1 single-dose vial. Discard unused portion.’] and ensure it is located away from and less prominent than the product strength. See <i>Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> .
3.	As currently presented the prefilled syringe cartons have the statement (b) (4) ”.	Improperly storing this product (i.e., not protecting from freezing) could lead to deteriorated drug medication errors.	Revise this statement to read, “Keep in carton to protect from light.”

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Otulfi that Formycon AG submitted on September 28, 2023, and Stelara.

Table 4. Relevant Product Information for Listed Drug and Otulfi		
Product Name	Stelara ^b	Otulfi
Initial Approval Date	September 25, 2009 (BLA 125261) September 23, 2016 (BLA 761044)	N/A
Active Ingredient	ustekinumab	ustekinumab-xxxx
Indication	Psoriasis (Ps) treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Psoriatic Arthritis (PsA) treatment of patients 6 years or older with active psoriatic arthritis. Crohn's Disease (CD) treatment of adult patients with moderately to severely active Crohn's disease. Ulcerative Colitis treatment of adult patients with moderately to severely active ulcerative colitis.	Psoriasis (Ps) treatment of patients 6 years or older and weighing 60 kg or more with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Psoriatic Arthritis (PsA) treatment of patients 6 years or older and weighing 60 kg or more with active psoriatic arthritis. Crohn's Disease (CD) treatment of adult patients with moderately to severely active Crohn's disease. Ulcerative Colitis treatment of adult patients with moderately to severely active ulcerative colitis.
Route of Administration	subcutaneous, intravenous	

^b Stelara [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. March 2023. [cited 2024 FEB 21]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125261s158lbl.pdf.

Table 4. Relevant Product Information for Listed Drug and Otulfi		
Product Name	Stelara ^b	Otulfi
Dosage Form	injection	
Strength	<u>Subcutaneous:</u> Prefilled syringe: 45 mg/0.5 mL, 90 mg/mL Vial: 45 mg/0.5 mL <u>Intravenous:</u> 130 mg/26 mL (5 mg/mL)	<u>Subcutaneous:</u> Prefilled syringe: 45 mg/0.5 mL, 90 mg/mL <u>Intravenous:</u> 130 mg/26 mL (5 mg/mL)

Table 4. Relevant Product Information for Listed Drug and Otulfi

Product Name	Stelara ^b	Otulfi														
Dose and Frequency	Psoriasis (Ps) <u>Subcutaneous Adult:</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:</u> Administer subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter. The recommended dose for pediatric patients (6-17 years old) based on body weight is shown below. <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>0.75 mg/kg</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> *For pediatric patients weighing less than 60 kg... withdraw the appropriate volume from the single-dose vial.	Body Weight of Patient at the Time of Dosing	Recommended Dose	less than 60 kg*	0.75 mg/kg	60 kg to 100 kg	45 mg	more than 100 kg	90 mg	Psoriasis (Ps) <u>Subcutaneous Adult:</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:</u> Administer subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter. The recommended dose for pediatric patients (6-17 years old, who weigh 60 kg or more) based on body weight is shown below. <table><tr><th>Body Weight of Patient at the Time of Dosing</th><th>Recommended Dose</th></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> Note: There is no dosage form for Otulfi that allows weight-based dosing for pediatric patients (6-17 years old) weighing less than 60 kg.	Body Weight of Patient at the Time of Dosing	Recommended Dose	60 kg to 100 kg	45 mg	more than 100 kg	90 mg
Body Weight of Patient at the Time of Dosing	Recommended Dose															
less than 60 kg*	0.75 mg/kg															
60 kg to 100 kg	45 mg															
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Body Weight of Patient at the Time of Dosing	Recommended Dose															
60 kg to 100 kg	45 mg															
more than 100 kg	90 mg															

Table 4. Relevant Product Information for Listed Drug and Otulfi

Product Name	Stelara ^b	Otulfi														
	Psoriatic Arthritis (PsA) <u>Subcutaneous Adult:</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:</u> Administer subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter. The recommended dose for pediatric patients (6-17 years old) based on body weight is shown below. <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>0.75 mg/kg</td></tr><tr><td>60 kg or more</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> *For pediatric patients weighing less than 60 kg... withdraw the appropriate volume from the single-dose vial. Crohn's Disease (CD) and Ulcerative Colitis	Body Weight of Patient at the Time of Dosing	Recommended Dose	less than 60 kg*	0.75 mg/kg	60 kg or more	45 mg	greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg	Psoriatic Arthritis (PsA) <u>Subcutaneous Adult:</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:</u> Administer subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter. The recommended dose for pediatric patients (6-17 years old, who weigh 60 kg or more) based on body weight is shown below. <table><tr><th>Body Weight of Patient at the Time of Dosing</th><th>Recommended Dose</th></tr><tr><td>60 kg or more</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> Note: There is no dosage form for Otulfi that allows weight-based dosing for pediatric patients (6-17 years old) weighing less than 60 kg. Crohn's Disease (CD) and Ulcerative Colitis	Body Weight of Patient at the Time of Dosing	Recommended Dose	60 kg or more	45 mg	greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg
Body Weight of Patient at the Time of Dosing	Recommended Dose															
less than 60 kg*	0.75 mg/kg															
60 kg or more	45 mg															
greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg															
Body Weight of Patient at the Time of Dosing	Recommended Dose															
60 kg or more	45 mg															
greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg															

Table 4. Relevant Product Information for Listed Drug and Otulfi

Product Name	Stelara ^b	Otulfi																								
	<u>Intravenous Induction Adult:</u> A single intravenous infusion dose using the weight-based dosage regimen. <table> <tr> <th>Body Weight of Patient at the time of dosing</th><th>Dose</th><th>Number of 130 mg/26 mL (5 mg/mL) vials</th></tr> <tr> <td>55 kg or less</td><td>260 mg</td><td>2</td></tr> <tr> <td>more than 55 kg to 85 kg</td><td>390 mg</td><td>3</td></tr> <tr> <td>more than 85 kg</td><td>520 mg</td><td>4</td></tr> </table> <u>Subcutaneous Maintenance Adult:</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.	Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) vials	55 kg or less	260 mg	2	more than 55 kg to 85 kg	390 mg	3	more than 85 kg	520 mg	4	<u>Intravenous Induction Adult:</u> A single intravenous infusion dose using the weight-based dosage regimen. <table> <tr> <th>Body Weight of Patient at the time of dosing</th><th>Dose</th><th>Number of 130 mg/26 mL (5 mg/mL) vials</th></tr> <tr> <td>55 kg or less</td><td>260 mg</td><td>2</td></tr> <tr> <td>more than 55 kg to 85 kg</td><td>390 mg</td><td>3</td></tr> <tr> <td>more than 85 kg</td><td>520 mg</td><td>4</td></tr> </table> <u>Subcutaneous Maintenance Adult:</u> The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.	Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) vials	55 kg or less	260 mg	2	more than 55 kg to 85 kg	390 mg	3	more than 85 kg	520 mg	4
Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) vials																								
55 kg or less	260 mg	2																								
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Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) vials																								
55 kg or less	260 mg	2																								
more than 55 kg to 85 kg	390 mg	3																								
more than 85 kg	520 mg	4																								

Table 4. Relevant Product Information for Listed Drug and Otulfi		
Product Name	Stelara ^b	Otulfi
How Supplied	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 <u>For Subcutaneous Use</u> <i>Prefilled Syringes</i> • 45 mg/0.5 mL (NDC 57894-(b) (4)) • 90 mg/mL (NDC 57894-(b) (4)) 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. <u>Single-dose Vial</u> • 45 mg/0.5 mL (NDC 57894-(b) (4)) <u>For Intravenous Infusion</u> <i>Single-dose Vial</i> • 130 mg/26 mL (5 mg/mL) (NDC 57894-(b) (4))	sterile, preservative-free, colorless to slightly brown-yellow solution. 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 XXXXX XXX XX) • 90 mg/mL (NDC XXXXX XXX XX) Each prefilled syringe is equipped with a 29 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that is not made with natural rubber <u>For Intravenous Infusion</u> <i>Single-dose Vial</i> • 130 mg/26 mL (5 mg/mL) (NDC XXXXX XXX XX)

Table 4. Relevant Product Information for Listed Drug and Otulfi		
Product Name	Stelara ^b	Otulfi
Storage	vials and prefilled syringes must be refrigerated at 2°C to 8°C (36°F to 46°F). Store 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 after the expiration date on the carton or on the prefilled syringe.	
Container Closure	Prefilled Syringe: 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 Vial: N/A	Prefilled Syringe: Each prefilled syringe is equipped with a 29 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that is not made with natural rubber Vial: N/A

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,^c along with postmarket medication error experiences with similar products, we reviewed the following Otulfi labels and labeling submitted by Formycon AG.

- Container labels received on September 28, 2023
- Carton labeling received on September 28, 2023
- Prescribing Information, Medication Guide, Instructions for Use (Images not shown) received on September 28, 2023, available from <\\CDSESUB1\EVSPROD\bla761379\0001\m1\us\114-labeling\listed-drug\annotated\annotated-comparison-stelara-otulfi.pdf>

F.2 Label and Labeling Images



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

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/

MADHURI R PATEL
04/12/2024 11:51:39 AM

YEVGENIYA M KOGAN
04/12/2024 04:06:00 PM