CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761338Orig1s000
761338Orig2s000

OTHER REVIEW(S)

LABEL, LABELING, AND HUMAN FACTORS 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 23, 2025
Requesting Office or Division:	Office of Therapeutic Biologics and Biosimilars (OTBB)
Application Type and Number:	BLA 761338/Ori-2
Product Name, Dosage Form, and Strength:	Steqeyma (ustekinumab-stba) injection, Prefilled syringe: 45 mg/0.5 mL and 90 mg/mL Vial: 130 mg/26 mL (5 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Celltrion, Inc.
FDA Received Date:	January 23, 2025
TTT ID #:	2025-13032
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP
DMEPA 1 Human Factors Team Leader	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 INTRODUCTION

As part of the approval process for Steqeyma (ustekinumab-stba) injection BLA 761338/Original 2 for interchangeability designation of Steqeyma prefilled syringes (45 mg/0.5 mL and 90 mg/mL) and vial (130 mg/26 mL), the Office of Therapeutic Biologics and Biosimilars (OTBB) requested that we review the proposed Steqeyma 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. This review also discusses the human factors (HF) data requirements for the Steqeyma prefilled syringe (PFS) presentations based on our previous HF review.[a]

1.1 BACKGROUND

Steqeyma (ustekinumab-stba) is a proposed 351(k)(4) interchangeable and the US-licensed Reference Product (RP) is Stelara (ustekinumab), BLA 125261 and BLA 761044.

2 HUMAN FACTORS (HF) DISCUSSION

On June 30, 2023, under BLA 761338, Celltrion, Inc. submitted the use-related risk analysis (URRA) and comparative analyses (CA) as a justification for not submitting HF validation study results to support their marketing application for Steqeyma (ustekinumab-stba) injection, 45 mg/0.5 mL and 90 mg/mL PFS, as a proposed biosimilar to Stelara.

On January 24, 2024, the DMEPA 1 HF team reviewed the URRA and CA. The DMEPA 1 HF team determined Celltrion, Inc. did not need to submit HF validation results to support their marketing application for Steqeyma (ustekinumab-stba) injection, 45 mg/0.5 mL and 90 mg/mL PFS as a proposed biosimilar to Stelara.[b]

Celltrion, Inc. confirmed that that there are no additional changes in the application.[c] As such, the DMEPA 1 HF team determined that Celltrion, Inc. does not need to submit comparative use human factors (CUHF) study results with their marketing application for the proposed Steqeyma (ustekinumab-stba) injection, 45 mg/0.5 mL and 90 mg/mL PFS as a proposed interchangeable biosimilar to Stelara.

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[a] Mwangi, F. Use-Related Risk Analysis and Comparative Analyses Review Memorandum for CT-P43 (Ustekinumab-xxxx) injection, 45 mg/0.5 mL and 90 mg/mL PFS. (BLA 761338). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 24 January 2024. TTT No.: 2023-5400.

[b] Mwangi, F. Use-Related Risk Analysis and Comparative Analyses Review Memorandum for CT-P43 (Ustekinumab-xxxx) injection, 45 mg/0.5 mL and 90 mg/mL PFS. (BLA 761338). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 24 January 2024. TTT No.: 2023-5400.

[c] BLA 761338/Ori-2 Cover Letter - Licensure of Interchangeability of Steqeyma. Incheon (ROK): Celltrion, Inc. 2023 Jan 23. Available from: \\CDSESUB1\EVSPROD\bla761338\0044\m1\us\cover-letter.pdf

3 CONCLUSION

From an HF perspective, we determined that Celltrion, Inc. does not need to submit CUHF results with their marketing application for the proposed Steqeyma (ustekinumab-stba) injection, 45 mg/0.5 mL and 90 mg/mL PFS.

Additionally, the Steqeyma Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling remain unchanged from DMEPA's prior label and labeling review conducted for BLA 761338/Ori-1.[d,e] We have no Human Factors (HF) and labeling recommendations at this time.

[d] Patel, M. Label and Labeling Review for Steqeyma (BLA 761338). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAR 29. TTT ID No.: 2023-5397.

[e] Patel, M. Review of Revised Label and Labeling for Steqeyma (BLA 761338). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 DEC 04. TTT ID No.: 2023-5397-3.

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/s/

MADHURI R PATEL
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04/23/2025 02:10:54 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:	December 11, 2024
To:	H.F. Van Horn Senior 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)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Quynh-Nhu Capasso, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	STEQEYMA (ustekinumab-stba)[1]
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 761338
Applicant:	Celltrion, Inc.

[1]STEQEYMA has been developed as a proposed biosimilar to US-licensed STELARA (ustekinumab). The proprietary name, STEQEYMA, was found conditionally acceptable on October 16, 2024. The nonproprietary name, ustekinumab-stba, was found conditionally acceptable on April 9, 2024.

1 INTRODUCTION

On October 16, 2024, Celltrion, Inc. submitted for the Agency's review a Class 2 resubmission to their proposed Biologics License Application (BLA) 761338 for STEQEYMA **(**ustekinumab-stba**)** injection a proposed biosimilar product to US-licensed STELARA (ustekinumab) injection (BLA 125261). This submission is in response to the Agency's Complete Response (CR) letter dated September 30, 2024.

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 on November 19, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for STEQEYMA (ustekinumab-stba) injection, for subcutaneous or intravenous use.

2 MATERIAL REVIEWED

- Draft STEQEYMA (ustekinumab-stba) MG and IFU received on October 16, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 29, 2024.
- Draft STEQEYMA (ustekinumab-stba) Prescribing Information (PI) received on October 16, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 29, 2024.
- Approved US-licensed STELARA (ustekinumab) injection labeling dated November 15, 2024.

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%.

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 Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG are 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 is consistent with the approved labeling for the 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 are 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/

MARIA T NGUYEN
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DMPP-OPDP review of ustekinumab-stba (STEQEYMA) BLA 761338 MG and IFU

QUYNH-NHU D CAPASSO
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12/11/2024 02:46:53 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:	December 11, 2024
To:	H.F. Van Horn Senior 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)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Quynh-Nhu Capasso, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	STEQEYMA (ustekinumab-stba)[1]
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 761338
Applicant:	Celltrion, Inc.

[1]STEQEYMA has been developed as a proposed biosimilar to US-licensed STELARA (ustekinumab). The proprietary name, STEQEYMA, was found conditionally acceptable on October 16, 2024. The nonproprietary name, ustekinumab-stba, was found conditionally acceptable on April 9, 2024.

1 INTRODUCTION

On October 16, 2024, Celltrion, Inc. submitted for the Agency's review a Class 2 resubmission to their proposed Biologics License Application (BLA) 761338 for STEQEYMA **(**ustekinumab-stba**)** injection a proposed biosimilar product to US-licensed STELARA (ustekinumab) injection (BLA 125261). This submission is in response to the Agency's Complete Response (CR) letter dated September 30, 2024.

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 on November 19, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for STEQEYMA (ustekinumab-stba) injection, for subcutaneous or intravenous use.

2 MATERIAL REVIEWED

- Draft STEQEYMA (ustekinumab-stba) MG and IFU received on October 16, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 29, 2024.
- Draft STEQEYMA (ustekinumab-stba) Prescribing Information (PI) received on October 16, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 29, 2024.
- Approved US-licensed STELARA (ustekinumab) injection labeling dated November 15, 2024.

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%.

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- simplified wording and clarified concepts where possible
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- removed unnecessary or redundant information
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- 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 is consistent with the approved labeling for the 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 are 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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MARIA T NGUYEN
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DMPP-OPDP review of ustekinumab-stba (STEQEYMA) BLA 761338 MG and IFU

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

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

Memorandum

Date: December 5, 2024

To: H.F. Van Horn, Senior Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for STEQEYMA (ustekinumab-stba) injection, for subcutaneous or intravenous use [resubmission]

BLA: 761338

Background:
In response to DDD's consult request dated November 19, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original BLA resubmission for STEQEYMA (ustekinumab-stba) injection, for subcutaneous or intravenous use.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 27, 2024, and we do not have any comments at this time.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on November 27, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov.

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QUYNH-NHU D CAPASSO
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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)

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

Date of This Review:	December 4, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761338
Product Name, Dosage Form, and Strength:	Steqeyma (ustekinumab-stba) injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringe, 130 mg/26 mL (5 mg/mL) vial
Applicant Name:	Celltrion, Inc.
FDA Received Date:	December 2, 2024
TTT ID #:	2023-5397-3
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Celltrion, Inc. submitted revised container labels and carton labeling received on December 2, 2024 for Steqeyma. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Steqeyma (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

Celltrion, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel, M. Review of Revised Label and Labeling for Steqeyma (BLA 761338). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 NOV 26. TTT ID: 2023-5397-3.

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/s/

MADHURI R PATEL
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YEVGENIYA M KOGAN
12/05/2024 01:37:27 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)

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

Date of This Review:	November 26, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761338
Product Name, Dosage Form, and Strength:	Steqeyma[a] (ustekinumab-stba)[b] injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringe, 130 mg/26 mL (5 mg/mL) vial
Applicant Name:	Celltrion, Inc.
FDA Received Date:	October 16, 2024
TTT ID #:	2023-5397-2
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

[a] The proprietary name for this product has not yet been determined; therefore, the placeholder Steqeyma is used throughout this review to refer to the proprietary name for this product.

[b] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder ustekinumab-stba is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 PURPOSE OF MEMORANDUM

As part of the approval process for Steqeyma (ustekinumab-stba) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Steqeyma Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) and revised container label(s) and carton labeling (Appendix A) for areas of vulnerability that may lead to medication errors. The revisions to the container labels and carton labeling are in response to recommendations that we made during a previous label and labeling review.[c]

1.1 REGULATORY HISTORY

Celltrion, Inc. previously submitted BLA 761338 on June 30, 2023, which received a Complete Response (CR) letter on September 30, 2024 due to issues with product quality.[d]

Thus, Celltrion, Inc. submitted a Class 2 Resubmission on October 16, 2024.[e] We note our recommendation made during a previous label and labeling review memo was not conveyed prior to the CR and have included the recommendation below.[f]

2 CONCLUSION

We evaluated the proposed Steqeyma Prescribing Information (PI) and Medication Guide (MG), and determined that they are acceptable from a medication error perspective.

However, the proposed Steqeyma 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 for the Division of Dermatology and Dentistry (DDD) in Section 3 and for Celltrion, Inc. in Section 4..

3 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. Instructions for Use (IFU)

1. We note the strength in 'Figure A' is presented with a trailing zero (i.e. 90 mg/1.0 mL), which is also inconsistent with the product strength of 90 mg/mL. Inconsistent strength presentations may lead to wrong strength and wrong dose medication errors. Revise [redacted] (b) (4) to "90 mg/mL".

[c] Patel, M. Label and Labeling Review for Steqeyma (BLA 761338). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAR 29. TTT ID: 2023-5397.

[d] Rhee, S on behalf of Oussova, T. Complete Response for BLA 761338. Silver Spring (MD): FDA, CDER, OND, Division of Dermatology and Dentistry (DDD) (US); 2024 SEP 30.

[e] Resubmission of BLA 761338 (CT-P43). Incheon (ROK): Celltrion, Inc.; 2024 OCT 16. Available from: \\CDSESUB1\EVSPROD\bla761338\0033\m1\us\cover-letter.pdf.

[f] Patel, M. Review of Revised Label and Labeling for Steqeyma (BLA 761338). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 16. TTT ID: 2023-5397-1.

4 RECOMMENDATIONS FOR CELLTRION, INC.

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

1. For the prefilled syringe container labels and carton labeling, the route of administration statement contains the word (b) (4). We reserve the use of the word (b) (4) when there is (b) (4) We recommend revising the route of administration statement so that it reads “For subcutaneous use”.

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YEVGENIYA M KOGAN
11/26/2024 04:34:04 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:	May 17, 2024
To:	Qianyiren Song 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)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Quynh-Nhu Capasso, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
	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 (established name):	STEQEYMA (ustekinumab-stba)
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 761338
Applicant:	Celltrion, Inc.

1 INTRODUCTION

On June 30, 2023, Celltrion, Inc. submitted for the Agency's review Biologics License Application (BLA) 761338 for STEQEYMA **(**ustekinumab-stba**)** injection, a proposed biosimilar product to US-licensed STELARA (ustekinumab) injection (BLA 125261).

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 on August 17, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for STEQEYMA (ustekinumab-stba) injection, for subcutaneous or intravenous use.

2 MATERIAL REVIEWED

- Draft STEQEYMA (ustekinumab-stba) MG and IFU received on June 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 8, 2024.
- Draft STEQEYMA (ustekinumab-stba) Prescribing Information (PI) received on June 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 8, 2024.
- Approved US-licensed STELARA (ustekinumab) injection labeling dated March 18, 2024.

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%.

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 Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG are 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 is consistent with the approved labeling for the 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 are 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.

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/s/

MARIA T NGUYEN
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DMPP-OPDP review of ustekinumab-stba (STEQEYMA) BLA 761338 MG and IFU

QUYNH-NHU D CAPASSO
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MONTHERSON L SAINT JUSTE
05/22/2024 08:53:45 AM

LASHAWN M GRIFFITHS
05/22/2024 08:58:16 AM

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

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

Memorandum

Date: May 21, 2024

To: Qianyiren Song, Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

CC: Adewale Adeleye, Team Leader, OPDP
James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for STEQEYMA (ustekinumab-stba) injection, for subcutaneous or intravenous use

BLA: 761338

Background:
In response to DDD's consult request dated August 17, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for STEQEYMA (ustekinumab-stba) injection, for subcutaneous or intravenous use.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 8, 2024, and our comments are provided below.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on May 8, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov.

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/s/

QUYNH-NHU D CAPASSO
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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)

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Date of This Review:	May 16, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761338
Product Name, Dosage Form, and Strength:	Steqeyma (ustekinumab-stba) injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringe and 130 mg/26 mL (5 mg/mL) vial
Applicant Name:	Celltrion Inc.
FDA Received Date:	April 11, 2024
TTT ID #:	2023-5397-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Celltrion Inc. submitted revised container labels and carton labeling received on April 11, 2024 for Steqeyma. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Steqeyma (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

Celltrion Inc. implemented all of our recommendations. However, we have one additional recommendation. The container labels and carton are unacceptable from a medication error perspective.

3 RECOMMENDATIONS FOR CELLTRION INC.

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

1. For the prefilled syringe container labels and carton labeling, the route of administration statement contains the word (b) (4). We reserve the use of the word (b) (4) when there is (b) (4) We recommend revising the route of administration statement so that it reads “For subcutaneous use”.

[a] Patel, M. Label and Labeling Review for Steqeyma (BLA 761338). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAR 29. TTT ID: 2023-5397.

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/s/

MADHURI R PATEL
05/16/2024 07:50:24 AM

YEVGENIYA M KOGAN
05/16/2024 12:35:46 PM

M E M O R A N D U M

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

DATE: April 1, 2024

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

FROM: Melkamu Kebtie Getie, Ph.D., R.Ph.
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 Analytical Inspection of (b) (4) (b) (4)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of study CT-P43 1.2 (BLA 761338) conducted at (b) (4) (b) (4)

Form FDA 483 was issued at the inspection close-out. In addition, one discussion item was presented. Based on the inspection observations, exhibits, and the firm's response to Form FDA 483 and discussion item, I recommend the following.

a) OSIS concludes that the (b) (4) (b) (4)

b) The review division evaluate whether (b) (4) (b) (4)

2. Inspected Study

BLA 761338

Study Number: CT-P43 1.2
Study Title: "Phase 1, randomized, double-blind, parallel group, single dose study to compare the pharmacokinetics, safety, and immunogenicity of three subcutaneous injection formulation of ustekinumab (CT-P43, EU - approved Stelara and US - licensed Stelara) in healthy Japanese male subjects"
Dates of clinical study conduct: 8/17/2022 – 3/4/2023
Dates of sample analysis:

- PK: [redacted]
- ADA
- NAb

Analytical site: [redacted]

3. Inspectional Findings

[redacted]

3.1 Previous Inspection(s)

This was the first OSIS inspection of [redacted] under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing study related records and interviewing the firm's management and staff.

3.3 Inspection finding(s)

At the conclusion of the inspection, Form FDA 483 was issued to the analytical site. In addition, one discussion item was presented. The Form FDA 483 observation(s) (**Attachment 1**), the firm's response dated 2/15/2024 (**Attachment 2**), and my evaluation are presented below.

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(b) (4)

OSIS Evaluation of Firm's Response: After r
response, my evaluation remains unchanged. (b) (4)
(b) (4)

3.3.2. Discussion Item

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Attachment(s)
Attachment 1: Form FDA 483 observations
Attachment 2: Response to Form FDA 483 ns
Attachment 3: Storage information for (b) (4)

Melkamu Getie-Kebtie, R.Ph., Ph.D.,
Pharmacologist

Draft: MG 3/26/24, 3/27/24, 3/28/24, 3/29/24, 4/1/24
Edit: SA 3/26/24, 3/27/24, 3/28/24, 3/29/24, 4/1/24; JC 3/28/24, 3/29/24

OSIS File #: BE (b) (4)

eNSpect Assignment ID: (b) (4)
eNSpect OpID: (b) (4)

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/s/

MELKAMU GETIE KEBTIE
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STANLEY AU
04/01/2024 02:40:51 PM
Secondary reviewer

SEONGEUN CHO
04/01/2024 02:42:03 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:	March 29, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761338
Product Name, Dosage Form, and Strength:	Steqeyma (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:	Celltrion Inc.
FDA Received Date:	June 30, 2023
TTT ID #:	2023-5397
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 Steqeyma (ustekinumab-xxxx) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Steqeyma 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 REGULATORY HISTORY

BLA 761338 is a 351(k) BLA and proposed biosimilar to US-licensed Stelara (ustekinumab), BLA 125261 and BLA 761044.

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*	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 Celltrion Inc..

4 RECOMMEDATIONS 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 (PI), Medication Guide (MG), and Instructions for Use (IFU) – General Issues			
1.	The nonproprietary name suffix is denoted by the placeholder '-xxxx' or '(ustekinumab)'.	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 and including the nonproprietary name suffix in all other instances where appropriate.

5 RECOMMENDATIONS FOR CELLTRION INC.

Table 3. Identified Issues and Recommendations for Celltrion 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 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 (b) (4) (b) (4) which is inconsistent with the product strength of 90 mg/mL.	Inconsistent strength presentations may lead to wrong strength medication errors.	Revise (b) (4) to "90 mg/mL".
3.	The 45 mg/0.5 mL strength is not clearly differentiated due to the (b) (4)	Lack of adequate differentiation may contribute to wrong strength errors. (b) (4)	We recommend revising the (b) (4) of the 45 mg/0.5 mL strength or the proprietary name and non-proprietary

Table 3. Identified Issues and Recommendations for Celltrion Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) for the proprietary name for the prefilled syringes and the proprietary name and nonproprietary name for the vial.	(b) (4) is most effective when the (b) (4) used has no association with a particular feature and there is no pattern in the application of the (b) (4) scheme.	name such that the strengths and the names appear in their own unique (b) (4) .
4.	There is inadequate differentiation between the 90 mg/mL and 130 mg/26 mL (5 mg/mL) strengths.	Lack of adequate differentiation may contribute to wrong strength medication errors.	We recommend using different colors, boxing, or some other means to ensure adequate differentiation between the strengths for the container labels and carton labeling. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*
5.	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

Table 3. Identified Issues and Recommendations for Celltrion Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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 *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*
6.	For the vial container label and carton labeling, the terminology within the statement of dosage statement (i.e., "usual dosage") 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".
Carton Labeling			
1.	For the prefilled syringe carton labeling, the terminology within the statement of dosage statement (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, "Recommended Dosage: see Prescribing Information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Steqeyma that Celltrion Inc. submitted on June 30, 2023, and Stelara.

Table 4. Relevant Product Information for Listed Drug and Steqeyma		
Product Name	Stelara[b]	Steqeyma
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.	
Route of Administration	subcutaneous, intravenous	
Dosage Form	injection	

[b] Stelara [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. March 2023. [cited 2024 FEB 16]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125261s158lbl.pdf.

Table 4. Relevant Product Information for Listed Drug and Steqeyma		
Product Name	Stelara[b]	Steqeyma
Strength	Subcutaneous: Prefilled syringe: 45 mg/0.5 mL, 90 mg/mL Vial: 45 mg/0.5 mL Intravenous: 130 mg/26 mL (5 mg/mL)	Subcutaneous: Prefilled syringe: 45 mg/0.5 mL, 90 mg/mL Intravenous: 130 mg/26 mL (5 mg/mL)

<table>
<tr><th colspan="3">Table 4. Relevant Product Information for Listed Drug and Steqeyma</th></tr>
<tr><td>Product Name</td><td>Stelara[b]</td><td>Steqeyma</td></tr>
<tr><td>Dose and Frequency</td><td>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.

Psoriatic Arthritis (PsA)
<u>Subcutaneous Adult:</u></td><td>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>-</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 STEQEYMA that allows weight-based dosing for pediatric patients below 60 kg.

Psoriatic Arthritis (PsA)
<u>Subcutaneous Adult:</u></td></tr>
</table>

<table>
<tr><th colspan="3">Table 4. Relevant Product Information for Listed Drug and Steqeyma</th></tr>
<tr><td>Product Name</td><td>Stelara[b]</td><td>Steqeyma</td></tr>
<tr><td></td><td>

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
<u>Intravenous Induction Adult</u>:
</td><td>

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>-</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>
* There is no dosage form for STEQEYMA that allows weight-based dosing for pediatric patients below 60 kg.

Crohn's Disease (CD) and Ulcerative Colitis
<u>Intravenous Induction Adult</u>:
</td></tr>
</table>

<table>
<tr><th colspan="3">Table 4. Relevant Product Information for Listed Drug and Steqeyma</th></tr>
<tr><td>Product Name</td><td>Stelara[b]</td><td>Steqeyma</td></tr>
<tr><td></td><td>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 55 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.</td><td>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 55 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.</td></tr>
</table>

Table 4. Relevant Product Information for Listed Drug and Steqeyma		
Product Name	Stelara[b]	Steqeyma
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> *Prefilled Syringes* • 45 mg/0.5 mL (NDC 57894-(b) (4) • 90 mg/mL (NDC 57894 (b) (4) (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. *Single-dose Vial* • 45 mg/0.5 mL (NDC 57894-(b) (4) <u>For Intravenous Infusion</u> *Single-dose Vial* • 130 mg/26 mL (5 mg/mL) (NDC 57894-(b) (4)	sterile, preservative-free, colorless to pale 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> *Prefilled Syringes* • 45 mg/0.5 mL (NDC 72606-027-01) • 90 mg/mL (NDC 72606-028-01) Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover. <u>For Intravenous Infusion</u> *Single-dose Vial* • 130 mg/26 mL (5 mg/mL) (NDC 72606-029-01)

Table 4. Relevant Product Information for Listed Drug and Steqeyma		
Product Name	Stelara[b]	Steqeyma
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.	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 vials and prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to (b) (4) days in the original carton to protect from light. Record the date when the vial or the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a vial or a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the vial or syringe if not used within (b) (4) days at room temperature storage. Do not use after the expiration date on the carton or on the vial or 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 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover Vial: N/A

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 16, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, 'BLA 761338'. Our search identified one previous review[c], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Mwangi, F. Use-Related Risk Analysis and Comparative Analyses Review Memorandum for CT-P43 (BLA 761338). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 24. TTT ID No.: 2023-5400.

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,[d] along with postmarket medication error experiences with similar products, we reviewed the following Steqeyma labels and labeling submitted by Celltrion Inc..

- Container labels received on June 30, 2023
- Carton labeling received on June 30, 2023
- Prescribing Information, Medication Guide, Instructions for Use (Images not shown) received on June 30, 2023, available from \\CDSESUB1\EVSPROD\bla761338\0001\m1\us\draft-labeling-text-track.docx

F.2 Label and Labeling Images

Container labels

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[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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M E M O R A N D U M

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

DATE: February 29, 2024

TO: Shari Targum, MD.
Deputy Division Director
Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (DDI)
Office of New Drug (OND)

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspection of Kitasato University, Kitasato Institute Hospital, Tokyo, Japan, and Medical Corporation Heishinkai OPHAC Hospital, Osaka, Japan.

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of Study CT-P43 1.2 (BLA 761338) conducted at Kitasato University, Kitasato Institute Hospital, Tokyo, Japan, and Medical Corporation Heishinkai OPHAC Hospital, Osaka, Japan.

No items were discussed, no objectionable conditions were observed, and no Form FDA 483 was issued at the inspection close-out of both sites.

Based on the inspection findings, there are no identified concerns for Kitasato University, Kitasato Institute Hospital and Medical Corporation Heishinkai OPHAC Hospital regarding reliability of the data and human subject protection for inspected study CT-P43 1.2 (BLA 761338) for the review division consideration.

2. Inspected Studies:

BLA 761338

Study Number: CT-P43 1.2
Study Title: "A Phase I, Randomized, Double-Blind, Parallel Group, Single-Dose Study to Compare the Pharmacokinetics, Safety, and Immunogenicity of Three Subcutaneous Injection Formulations of Ustekinumab (CT-P43, EU approved Stelara, and US-licensed Stelara) in Healthy Japanese Male Subjects"

Dates of study conduct: 08/17/2022 – 03/04/2023

Clinical site# 4304: Kitasato University, Kitasato Institute Hospital (Site PI: Dr. Lim Lay Ah Young)
5-9-1 Shiro Kane, Minato-ku,
Tokyo, Japan

Clinical site# 4305: Medical Corporation Heishinkai OPHAC Hospital (Site PI: Dr. Michio Yagi)
4-1-29 Miyahara Yodogawa-ku, Medical Corporation Hei Shinkai OPHAC Hospital
Osaka-shi, Osaka, Japan

3. Inspectional Findings at Kitasato University Kitasato Institute Hospital, Tokyo, Japan (site# 4304)

ORA investigators Brandy D. Brown and Gabrielle Swain inspected Kitasato University, Kitasato Institute Hospital, Tokyo, Japan from January 15-19, 2024.

3.1 Previous Inspection(s)

This was the first OSIS inspection of Kitasato University, Kitasato Institute Hospital under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs)
-Informed consent forms and process
-Protocol deviations
-Institutional review board approvals
-Training records of study personnel
-Test article accountability and storage
-Randomization
-Adverse events

3.3 Inspection finding(s)

At the conclusion of the inspection, there were no discussion items. The investigators Brandy D. Brown and Gabrielle Swain did not observe any objectionable conditions and did not issue Form FDA 483 to the Kitasato University, Kitasato Institute Hospital, Tokyo, Japan.

4. Inspectional Findings at Medical Corporation Heishinkai OPHAC Hospital, Osaka, Japan (site# 4305)

ORA investigators Brandy D Brown and Gabrielle Swain inspected Medical Corporation Heishinkai OPHAC Hospital, Osaka, Japan from January 22-25, 2024.

4.1 Previous Inspection(s)

This was the first OSIS inspection of Medical Corporation Heishinkai OPHAC Hospital under the BA/BE program.

4.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs)
-Informed consent forms and process
-Protocol deviations
-Institutional review board approvals
-Training records of study personnel
-Test article accountability and storage
-Randomization
-Adverse events

4.3 Inspection finding(s)

At the conclusion of the inspection, there were no discussion items. The investigators Brandy D. Brown and Gabrielle Swain did not observe any objectionable conditions and did not issue Form FDA 483 to the Medical Corporation Heishinkai OPHAC Hospital.

Hasan A. Irier, Ph.D.
Pharmacologist
OSIS/DGDSI

Draft: HAI 02/20/2024
Edit: MO 02/20/2024; KAB 02/28/2024

OSIS File #: BE 10002

eNSpect Assignment ID: 227663
eNSpect OpID: 258450 (Kitasato University, Kitasato Institute Hospital)
eNSpect OpID: 258434 (Medical Corporation Heishinkai OPHAC Hospital)

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/s/

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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	2/8/2024		
To:	Melinda Bauerlien		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Michael Lancina OPEQ/OHT3/DHT3C		
Through (Division): ***optional**	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: Please review the following - The PFS-S is fitted with a safety guard. The safety guard is a single-use, disposable device to protect users from needle stick injury after injection….. . The same safety guards are used for both CT-P43 45 mg and 90 mg PFS-S." PFS has a staked needle with a safety cover.		
Recommendation:	Completed, No Deficiencies		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (optional)**
Michael G. Lancina -S Digitally signed by Michael G. Lancina -S Date: 2024.02.08 16:16:38 -05'00'	Shruti N. Mistry -S 2024.02.08 16:46:45 -05'00'	

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR#00941465
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/5003d000009AUatAAG/view
ICC tracking #	2300781
Submission Number	BLA 761338
Sponsor	Celltrion
Drug/Biologic	CT-P43
Indications for Use	Psoriasis, Crohn's disease, Ulcerative colitis
Device Constituent	PFS with safety feature
Related Files	(b) (4) 510(k) summary

2. CDRH REVIEW

ICC Review Request from CDER/OPQ, Choose an item.:	Please review the following - The PFS-S is fitted with a safety guard. The safety guard is a single-use, disposable device to protect users from needle stick injury after injection….. . The same safety guards are used for both CT-P43 45 mg and 90 mg PFS-S." PFS has a staked needle with a safety cover.
Device Presentation(s) being evaluated:	45 and 90mg PFS-S
Objective of this Memo:	Review of PFS safety feature
Review Comments:	The safety device is a cleared device being used within its indications for use
Review Recommendation:	No approvability issues

Device Description

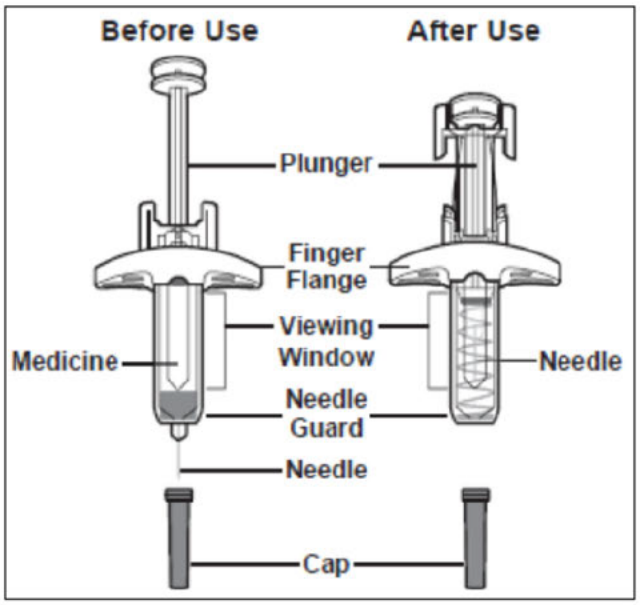

Figure 3.2.P.7-6: Schematic Diagram of CT-P43 PFS-S as Used in the Instruction for Use

The combination product uses the [redacted] (b) (4) passive needle guard. The device is cleared under 510k [redacted] (b) (4) The device has the following indications for use:

Indications for Use:

[redacted] (b) (4)

The submission initially only included a certificate of conformance in **3.2.P.7 Appendix 6.** The certificate states that the following characteristics were evaluated and found to conform to the specifications and/or drawings in effect:
- Visual
- Dimensional

- Functional:
    - Activation force
    - Separation force
    - Compression force
    - Spring force
    - Syringe Spin
    - Control Triggering
    - Pin Gauge

In response to IR #1 included in the appendix below, the sponsor supplied additional design verification documentation from (b) (4) The new verification document included the following summary performance data:

(b) (4)

[redacted]

The product has a stated shelf life of 48 months at 5°C. (b) (4) testing data includes rea-time aging of the safety device for 5 years. Stability testing of the safety device for the combination product is not necessary.

(b) (4) also supplied shipping validation data for the needle safety device, but the sponsor has conducted their own shipping validation study of the combination product, which is included below.

Shipping Validation

Shipping validation was carried out on three validation lots of material. Packages were shipped on the following routes:

Table 3.2.P.3.5.2-14 Validated Shipping Route and Location of the Sites

Transport Means	Route
Road Carriage	(b) (4)
Air Carriage	
Air Carriage	
Road Carriage	
Air Carriage	
Air Carriage	
Road Carriage	
Road Carriage (Shipment Recovery)	

Test Item	Acceptance Criteria[1]	Test Result[2]		
		Run 1	Run 2	Run 3
Activation Force	≤ (b) (4) N	11	12	11
Lock Out Force	≥ (b) (4) N	93.0	93.2	93.7
Stopper Movement	< (b) (4) mm	0	0	0

[1] The acceptance criteria are those in place at the time of the study.

[2] The results are the minimum or maximum values of the test samples taken from all outer boxes in a container.

Shipping validation results showed that the needle safety device maintained essential performance specifications.

Appendix

IR communicated after mid-cycle meeting:

(b) (4)

---END OF REVIEW---

Clinical Inspection Summary

Date	01/18/2024
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	Sena Lee, MD, Clinical Reviewer Amy Woitach, MD, Clinical Team Leader Qianyiren Song, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
BLA #	761338
Applicant	Celltrion, Inc.
Drug	CT-P43 (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	8/29/2023
Summary Goal Date	3/30/2024
Action Goal Date	6/30/2024
PDUFA Date	6/30/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Celltrion, Inc., submitted clinical data from Study CT-P43 3.1 (NCT04673786) to support a Biologics License Application (BLA 761338) for CT-P43 (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. Jaworski and Daniluk) were selected for clinical inspections. The inspections did not find significant concerns regarding the oversight of the clinical trial or GCP or regulatory compliance. Based on the results of these inspections, data generated by the inspected clinical investigators appear acceptable in support of the proposed indication.

II. BACKGROUND

Celltrion, Inc. seeks approval of a BLA for CT-P43 (ustekinumab-xxxx). In support of the BLA, the Applicant submitted clinical data from Study CT-P43 3.1, a phase 3 study. The following is a summary of the study protocol and key study information relevant to the clinical inspections.

Study Design

This was a randomized, active-controlled, double-blind, multicenter, Phase 3 study designed to evaluate the efficacy, pharmacokinetics, quality of life, and overall safety of CT-P43 compared to European Union (EU)-Stelara in patients with moderate to severe plaque psoriasis, who were candidates for phototherapy or systemic therapy. Patients received either CT-P43 or EU-Stelara subcutaneously at Weeks 0, 4, 16, 28, and 40.

Objectives and Endpoints

The primary objective of the study was to demonstrate that CT-P43 is equivalent to EU-Stelara in terms of efficacy.

The primary endpoint was the Psoriasis Area and Severity Index (PASI) mean percent improvement from Baseline to Week 12. The PASI is a measure of average redness/erythema, induration/thickness, and scaling of the lesions, weighted by the area of involvement. The lesions were scored for four anatomical regions: head, upper limbs, trunk, and lower limbs.

Eligibility Criteria

Key eligibility criteria included:

- Age 18 to 80 years old
- Diagnosis of plaque-type psoriasis for at least 24 weeks before the first administration of study drug on Day 1
- Stable moderate to severe chronic plaque psoriasis at both Screening and Day 1 as defined by the following:
    - PASI score ≥12
    - Involved body surface area (BSA) ≥10%
    - Static Physician's Global Assessment (sPGA) score ≥3
- Candidate for phototherapy or systemic therapy
- None of the following:
    - Diagnosis of other forms of psoriasis such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin condition like eczema at the time of Screening that would interfere with evaluation.
    - Previous receipt of ustekinumab, biosimilar of ustekinumab, or any drug targeting IL-12 or IL-23.
    - Prior exposure to two or more biologic agents approved for the treatment of

psoriasis.
- Current or chronic inflammatory or autoimmune disease or symptoms other than psoriasis and psoriatic arthritis that might have confounded study evaluations.
- Current or history of HIV; hepatitis B or C (unless resolved); herpes zoster or serious infection requiring hospitalization or antibiotics within 8 weeks of study drug administration, current or past granulomatous infection or other severe and/or chronic/recurrent infections (unless completely resolved).
- Current or history of active tuberculosis (TB) or untreated latent TB, signs or symptoms of active TB, or recent exposure to person with active TB.

Study Conduct

Thirty-four study centers in four countries (Estonia, Korea, Poland, and Ukraine) screened 574 subjects and enrolled 509 subjects.

III. RESULTS

1. **Dr. Janusz Jaworski (Site 2510)**
   Klinika Reuma Park Sp Z O.O. Sp. K., Aleja Wilanowska 333
   Warsaw, Mazowieckie, 02-0665 Poland

   Inspection Dates: November 6 – 10, 2023

   This investigator was inspected as a routine BsUFA inspection for Study CT-P43 3.1. The investigator was previously inspected February 2015, without significant findings identified.

   At this site, of the 72 subjects screened, 66 subjects were enrolled and completed the study. Signed informed consent forms (ICFs), paper source records for PASI, and adverse event (AE) reporting were reviewed for all enrolled subjects. A full review of 29 subjects' source records was also performed. Records were reviewed for eligibility, patient demographics, disposition, medical history, protocol adherence, safety assessments, study visit procedures, concomitant medication documentation, and investigational product (IP) accountability. Case report forms, questionnaires, progress notes, and nurses' notes were also reviewed.

   Study-related records reviewed included: ethics committee approval letters and correspondence, monitoring reports, laboratory certifications, financial disclosure forms, IP accountability logs, signature and responsibility logs, and training documentation.

   There were no discrepancies in the submitted data when compared to the source data. The Week 12 PASI scores were verifiable. No unusual enrollment practice or patterns were identified.

2. **Dr. Stefan Daniluk (Site 2511)**
   Ul. Stoleczna 7 Lok. 200
   Bialystok, Podlaskie, 15-879 Poland

   Inspection Dates: December 11 – 14, 2023

   This investigator was inspected as a routine BsUFA inspection for Study CT-P43 3.1. The investigator was previously inspected April 2017, during which erroneous enrollment and randomization was observed.

   Nineteen subjects were screened at the site, and the records of all 19 subjects were reviewed. Subject-related records reviewed included those for confirming subject eligibility, informed consent, dosing, AE reporting, and efficacy.

   Study-related records and procedures reviewed included: the protocol, pharmacy manual, financial disclosure reports, consent procedures, stratification and randomization procedures, and ethic committee approvals.

   There were no discrepancies in the submitted data when compared to the source data. The Week 12 PASI scores were verifiable. No issues were identified related to subject selection, stratification, or randomization.

{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.
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OSI/Office Director/David Burrow
OSI/ GCP Program Analysts/Yolanda Patague

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/s/

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