CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761338Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Office of Therapeutic Biologics and Biosimilars
Clinical, Cross-Discipline Team Leader, and Division Memo

Date	See Electronic Stamp Date
From	Juwaria Waheed, MD (Clinical Reviewer, OTBB) Thomas Herndon, MD (CTL, CDTL, OTBB) Tatiana Oussova, MD (Division Signatory, DDD, OII)
Subject	Request for Approval for Interchangeability - Cross-Discipline Review of amendment to the BLA 761338 Original 2
Application Type	351(k) BLA
BLA/Supplement Number	BLA 761338/Original 2
Received Date	January 23, 2025
Target Action Date	April 30, 2025
Division/Office	Division of Dermatology and Dentistry (DDD)
Proprietary Name	Steqeyma
Proper Name	ustekinumab-stba
Product Code	CT-P43
Reference Product	US-licensed Stelara (ustekinumab)
Pharmacologic Class	Human interleukin-12 and -23 antagonist
Applicant	Celltrion Inc.
Approved Indication(s)	Adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis (UC) Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA)
Purpose of the Submission	Approval of Steqeyma (ustekinumab-stba) injection as interchangeable with US-Stelara (ustekinumab) as follows per the provisional determination letter for BLA 761338/Original 2 dated December 17, 2024: • Steqeyma injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use

	• Steqeyma injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use • Steqeyma injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use
Recommendation on Regulatory Action	Approval of the following as interchangeable products: • Approval of Steqeyma (ustekinumab-stba) injection 45 mg/0.5 mL and 90 mg/mL single-dose prefilled syringe (PFS) for subcutaneous use • Approval of Steqeyma (ustekinumab-stba) injection 130 mg/26 mL single-dose vial for intravenous use

1. Introduction

The subject of this review is the amendment to BLA 761338/Original 2 to seek approval for interchangeability of all products under the application that previously received a provisional determination on December 17, 2024.

On June 30, 2023, Celltrion Inc. (hereafter referred to as "the Applicant") submitted a Biologics License Application (BLA) 761338 under section 351(k) of the Public Health Service (PHS) Act seeking licensure of Steqeyma (proper name: ustekinumab-stba; product code: CT-P43) as a biosimilar product to US-Stelara. On November 20, 2023, the Applicant amended 351(k) BLA-761338 to support the claim for CT-P43 as a proposed interchangeable biosimilar product to US-Stelara as follows:

- Steqeyma injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as biosimilar to and interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
- Steqeyma injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as biosimilar to and interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
- Steqeyma injection 130 mg/26 mL single-dose vial for intravenous use as biosimilar to and interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use

The data and information in the original BLA, including the resubmission in response to the September 30, 2024 Complete Response, supported licensure of Steqeyma as a biosimilar product. The Applicant included a scientific justification that Steqeyma will produce the same clinical result in any given patient for each condition of use for which licensure is sought and for which US-Stelara has been approved, a scientific justification for extrapolating data and information to support licensure of Steqeyma as an interchangeable for each indication for which licensure is sought and for which US-Stelara has been previously approved, and use-related risk analyses and comparative analyses for the PFS platforms. The data and information in the BLA demonstrated that Steqeyma can be expected to produce the same clinical result as US-Stelara in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Steqeyma and US-Stelara is not greater than the use of US-Stelara without such alternation or switch.

However, data submitted in the application were not sufficient to support a conclusion that the manufacture of CT-P43 was well-controlled and would lead to a product that is pure and potent for the duration of the shelf-life. Multiple product quality deficiencies were identified and listed in the OPQ Executive Summary. Therefore, the FDA review team recommended a complete response. A complete response letter was sent to the Applicant on September 30, 2024.

The Applicant resubmitted BLA 761338 on October 16, 2024. The resubmission included responses to the deficiencies cited in the complete response letter. Upon review of the resubmission, the review team concluded that the resubmission adequately addressed the deficiencies in the complete response letter.
After reviewing the resubmitted BLA, FDA did not identify any deficiencies that would justify a second complete response action. FDA considered whether any unexpired first interchangeable exclusivity precluded approval of any products in the original application as interchangeable. The Steqeyma (ustekinumab-stba) injection 45 mg/0.5 mL and 90 mg/mL prefilled syringe (PFS) for subcutaneous use, and 130 mg/26 mL single-dose vial for intravenous use could not be approved as interchangeable due to unexpired first interchangeable exclusivity for Wezlana (ustekinumab-auub) injection 45 mg/0.5 mL and 90 mg/mL for subcutaneous use, and 130 mg/26 mL (5 mg/mL) for intravenous use. Refer to the Purple Book at https://purplebooksearch.fda.gov for more information about unexpired first interchangeable exclusivity.

BLA 761338 was administratively split to facilitate the following:

- An approval action for BLA 761338/Original 1
    - Steqeyma injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as biosimilar to US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
    - Steqeyma injection 90 mg/mL single-dose prefilled syringe for subcutaneous use as biosimilar to US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
    - Steqeyma injection 130 mg/26 mL single-dose vial for intravenous use as biosimilar to US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use
- A provisional determination for BLA 761338/Original 2
    - Steqeyma injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use would be interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
    - Steqeyma injection 90 mg/mL single-dose prefilled syringe for subcutaneous use would be interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
    - Steqeyma injection 130 mg/26 mL single-dose vial for intravenous use would be interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use

The “Biosimilar Multidisciplinary Evaluation and Review” (BMER) documenting the Agency’s review of the original application dated September 30, 2024 and the CDTL memo dated December 17, 2024 documenting the Agency’s review of the resubmission in response to the complete response action, respectively, are incorporated herein by reference. Refer to them for additional information.

The Original 1 application received an approval letter dated December 17, 2024, and the Original 2 application received a provisional determination letter dated December

17, 2024.

The provisional determination letter instructed the Applicant to submit an amendment no more than six months prior to the date it believed that the application would be eligible for approval.

To obtain approval of Steqeyma (ustekinumab-stba) injection 45 mg/0.5 mL and 90 mg/mL prefilled syringes for subcutaneous use, and Steqeyma (ustekinumab-stba) injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable products, the Applicant submitted an amendment, “Request for Approval” on January 23, 2025, which is the subject of this review.

2. Background

Steqeyma (proper name: ustekinumab-stba; product code: CT-P43) was approved as a biosimilar to US-Stelara (ustekinumab) on December 17, 2024. Refer to the BMER dated September 30, 2024, and the CDTL memo dated December 17, 2024, for background information, including a summary of key regulatory interactions.

3. Product Quality

No new product quality information was submitted nor required for this amendment. There are no product quality issues that would preclude approval of this application. Refer to the BMER dated September 30, 2024, and the CDTL memo dated December 17, 2024. All facilities remain compliant to support approval of this supplement.

The review team considered and determined that there are no new product quality information or updates since the provisional determination letter was issued (December 17, 2024) that would impact the provisional determination of interchangeability. The Applicant also confirmed the same in its request for approval dated January 23, 2025.

4. Clinical and Statistical Evaluation and Recommendations

No new clinical efficacy and safety or statistical information was submitted nor required for this amendment. There are no clinical efficacy and safety or statistical issues that would preclude approval of this application. Refer to the BMER dated September 30, 2024, and the CDTL memo dated December 17, 2024.

The review team considered and determined that there are no new safety information or updates since the provisional determination letter was issued (December 17, 2024) that would impact the provisional determination of interchangeability. The Applicant also confirmed the same in its April 17, 2025 response to an information request (IR).

5. Labeling

Labeling for the original application was reviewed and agreed upon with the Applicant during FDA's review of BLA 761338/Original 1. No changes to the labeling are necessary for the approval of BLA 761338/Original 2. The final labeling will be attached to the approval letter.

The review team determined that there are no new labeling updates since the provisional determination letter was issued (December 17, 2024) that would impact the provisional determination of interchangeability. The Applicant also confirmed the same in in its request for approval dated January 23, 2025.

6. Summary Assessment

The PD letter issued December 17, 2024, states, "In addition to a safety update, the amendment should also identify changes, if any, in the application, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS)."

In its Request for Approval dated January 23, 2025, the Applicant confirmed that there were no additional changes in the application. An information request (IR) was sent to the Applicant on April 9, 2025 to confirm if any safety updates have occurred to BLA 761338 from FDA's issuance of the PD letter that could impact the provisional determination of interchangeability.

The review team determined that there are no changes or updates to the application and/or supplements including safety, labeling, and CMC data and interim supplement approvals or expected supplement approvals (when applicable) since the issuance of the PD letter (December 17, 2024) and until the expiration of the FIE, April 30, 2025 that would impact the provisional determination of interchangeability. The Applicant confirmed the same in its request for approval dated January 23, 2025 and its April 17, 2025 response to the IR, dated.

7. Pediatrics

The following PREA-PMR previously issued (December 17, 2024) that has not yet been fulfilled remains in place:

> 4765-1 Develop a presentation that can be used to accurately administer Steqeyma (ustekinumab-stba) to pediatric patients who weigh less than 60 kg.
>
> Final Report Submission: 06/2025

Refer to the BMER dated September 30, 2024 and CDTL memo dated December 17, 2024, for more information.

8. REMS and Postmarketing Requirements and Commitments

Previously issued PMCs that have not yet been fulfilled remain in place. Refer to the approval letter for BLA 761338/Original 1 dated December 17, 2024. There are no REMS, PMRs, or PMCs associated with this amendment to BLA 761338/Original 2.

Refer to the CDTL memo dated December 17, 2024, for more information.

9. Other Regulatory Issues

None.

10. Recommended Regulatory Action

The data and information in BLA 761338, including the information submitted by the Applicant with this amendment, are sufficient to maintain FDA's determination that Steqeyma can be expected to produce the same clinical result as US-Stelara in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Steqeyma and US-Stelara is not greater than the use of US-Stelara without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that:

- Steqeyma injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use meets the statutory standards to be interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
- Steqeyma injection 90 mg/mL single-dose prefilled syringe for subcutaneous use meets the statutory standards to be interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
- Steqeyma injection 130 mg/26 mL single-dose vial for intravenous use meets the statutory standards to be interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use

These Steqeyma (ustekinumab-stba) products have met the statutory interchangeability requirements for the following indications for which US-Stelara has been previously approved:

Adult patients with:

- moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis (PsA)
- moderately to severely active Crohn's disease (CD)
- moderately to severely active ulcerative colitis (UC)

Pediatric patients 6 years and older with:

- moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis (PsA)

As noted in the Purple Book (https://purplebooksearch.fda.gov), the first interchangeable exclusivity expiration date is as follows:

- April 30, 2025 – Wezlana (ustekinumab-auub) injection 45 mg/0.5 mL and 90 mg/mL for subcutaneous use, and 130 mg/26 mL (5 mg/mL) for intravenous use.

The recommended regulatory action is approval of the following:

- BLA 761338 Original 2:
  - Steqeyma injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use is interchangeable with US-Stelara injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use
  - Steqeyma injection 90 mg/mL single-dose prefilled syringe for subcutaneous use is interchangeable with US-Stelara injection 90 mg/mL single-dose prefilled syringe for subcutaneous use
  - Steqeyma injection 130 mg/26 mL single-dose vial for intravenous use is interchangeable with US-Stelara injection 130 mg/26 mL single-dose vial for intravenous use

11. Recommended Comments to the Applicant

None.

12. Division Director or Designated Signatory Comments

I concur with the review team's assessment of the data and information submitted in this amendment and support the regulatory action.

13. Appendices

None.

14. References

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Cross-Discipline Team Leader and Multidisciplinary Evaluation and Review Memo

Application Type	BLA
Application Number	761338
Received Date	Resubmission received October 16, 2024
BsUFA Goal Date	April 16, 2025
Division/Office	Division of Dermatology and Dentistry /Office of Immunology and Inflammation (OII) in collaboration with the Division of Rheumatology and Transplant Medicine (DRTM)/OII and Division of Gastroenterology (DG)/OII
Review Completion Date	See DARRTS stamp date
Product Code Name	CT-P43
Proposed Nonproprietary Name[1]	Ustekinumab-stba
Proposed Proprietary Name[1]	Steqeyma
Pharmacologic Class	IL12/23 BLOCKER
Applicant	Celltrion Inc.
Applicant Proposed Indication(s)	• Moderate to severe plaque psoriasis (PsO) in adult patients and pediatric patients 6 years of age and older who are candidates for phototherapy or systemic therapy; • Active psoriatic arthritis (PsA) in adult patients and pediatric patients 6 years of age and older; • Moderately to severely active Crohn's Disease (CD) in adults • Moderately to severely active Ulcerative Colitis (UC) in adults
Recommendation on Regulatory Action	Approval of CT-P43 as biosimilar to U.S.-Stelara. Provisional determination that CT-P43 is interchangeable with U.S.-Stelara (ustekinumab), as described in Section 13 of this memorandum. Approval for interchangeability is precluded due to unexpired first interchangeable exclusivity for Wezlana.

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review entered in DARRTS on September 30, 2024 discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

Reviewers of the Cross Discipline Team Leader and Multidisciplinary Evaluation and Review Memo

Regulatory Project Manager	HF Van Horn/Susan Rhee
Nonclinical Pharmacology/Toxicology Reviewer(s)	Jianyong Wang
Nonclinical Pharmacology/Toxicology Team Leader(s)	Barbara Hill
Clinical Pharmacology Reviewer(s)	Sanjida Mahjabeen
Clinical Pharmacology Team Leader(s)	Chinmay Shukla
Office of Therapeutic Biologics and Biosimilars	Frances Andrada, Nina Brahme, Jessica Tyson, Angela LaPier, Jacquelyn Rosenberger
Clinical Reviewer(s)	Maryjoy Mejia
Clinical Team Leader(s)	Hamid Tabatabai
Clinical Statistics Reviewer(s)	Guoying Sun
Clinical Statistics Team Leader(s)	Wanjie Sun
Cross-Discipline Team Leader(s) (CDTL(s))	Hamid Tabatabai
Designated Signatory Authority	Tatiana Oussova

Signatures

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/Approved
Clinical Reviewer	Maryjoy Mejia, MD	Division of Dermatology and Dentistry (DDD)	Authored 1, 6, 7, 10, 11, 12, 13
	Signature: Maryjoy G. Mejia -S Digitally signed by Maryjoy G. Mejia -S Date: 2024.12.17 10:16:59 -05'00'		
Clinical Team Leader	Hamid Tabatabai, MD	DDD	Approved 1, 6, 7, 10, 11, 12, 13
	Signature: HAMID TABATABAI -S Digitally signed by HAMID TABATABAI -S Date: 2024.12.17 11:15:41 -05'00'		
Clinical Reviewer (Division of Rheumatology, Collaborative Review Division)	Emily Gotschlich, MD	DRTM	13
	Signature: Suzette Peng on behalf of Emily Gotschlich SUZETTE W. PENG -S Digitally signed by SUZETTE W. PENG -S Date: 2024.12.17 11:23:32 -05'00'		
Clinical Team Leader (Division Rheumatology, Collaborative Review Division)	Suzette Peng, MD	DRTM	13
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Clinical Reviewer (Division of Gastroenterology, Collaborative Review Division)	Sandhya Apparaju, PhD	DG	13
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Clinical Team Leader (Division of Gastroenterology, Collaborative Review Division)	Suno Seo, MD, MSc	DG	13
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Cross-Discipline Team Leader	Hamid Tabatabai, MD	DDD	Approved 1-13
	Signature: HAMID TABATABAI -S Digitally signed by HAMID TABATABAI -S Date: 2024.12.17 11:16:44 -05'00'		
Designated Signatory Authority	Tatiana Oussova, MD, MPH	DDD	N/A
	Signature: Tatiana Oussova -S Digitally signed by Tatiana Oussova -S Date: 2024.12.17 12:00:06 -05'00'		

1. Introduction

Celltrion Inc. (hereafter referred to as "the Applicant") resubmitted a Biologic License Application (BLA) 761338 under section 351(k) of the Public Health Service (PHS) Act for CT-P43 (non-proprietary name: ustekinumab-stba; proprietary name: Steqeyma) on October 16, 2024 in response to the Agency's Complete Response (CR) letter dated September 30, 2024. Multiple product quality-related major deficiencies including inadequate qualification of reference standards, inadequate control of drug product, and insufficient data to support sterility assurance of the CT-P43 130 mg/26 mL (5 mg/mL) single-dose vial drug product, precluded approval.

The Applicant's resubmission includes responses to the deficiencies cited in the CR letter. No new clinical study information is included in the Applicant's resubmission as the final safety data from all clinical studies were submitted in the original BLA submission. The Safety Update contains updated cumulative patient exposure and safety data from worldwide post-marketing experience with CT-P43 since the international birth date (IBD) of June 12, 2024 through to September 20, 2024.

CT-P43 is a proposed interchangeable biosimilar to US-licensed Stelara (US-Stelara, ustekinumab). CT-P43 is a recombinant human immunoglobulin isotype class G subclass 1 kappa monoclonal antibody (mAb) that belongs to the pharmacologic class of Interleukin-23 (IL-23) and Interleukin-12 (IL-12) antagonists.

The Applicant is seeking licensure of CT-P43 injection for the same indications for which US-licensed Stelara is approved, as well as for the following strengths, dosage form, and routes of administration:

- CT-P43 injection 45 mg/0.5 mL prefilled syringe (PFS) for subcutaneous use as an interchangeable biosimilar with US-licensed Stelara injection 45 mg/0.5 mL PFS for subcutaneous use
- CT-P43 injection 90 mg/mL PFS for subcutaneous use as an interchangeable biosimilar with US-licensed Stelara injection 90 mg/mL PFS for subcutaneous use
- CT-P43 injection 130 mg/26 mL single-dose vial for intravenous (IV) use as an interchangeable biosimilar with US-licensed Stelara injection 130 mg/26 mL single-dose vial for IV use

FDA agreed to the Applicant's deferral plan for the development of a 45 mg/0.5 mL single dose vial presentation for subcutaneous use for pediatric patients weighing less than 60 kg.

As described in this memo, the Office of Pharmaceutical Quality (OPQ) reviewers concluded that the resubmission adequately addresses the product quality-related major deficiencies cited in the CR letter. The OPQ team recommends an approval action (see the OPQ Executive Summary dated December 13, 2024), the Office of Pharmaceutical Quality Assessment III (OPQA III) review dated November 25, 2024, and the Office of Pharmaceutical Manufacturing Assessment (OPMA) review dated December 13, 2024). The CDTL and Division Signatory concur with the assessment and recommendations. See Section 13 below for more information.

2. Product Quality

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761338 for CT-P43 manufactured by Celltrion Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of CT-P43 is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that CT-P43 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information is included in this resubmission. There are no nonclinical pharmacology/toxicology issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on September 30, 2024.

4. Clinical Pharmacology

No new clinical pharmacology information is included in this resubmission. There are no new clinical pharmacology issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on September 30, 2024.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

No new efficacy data are included in this resubmission. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on September 30, 2024.

7. Safety

During the review of the original BLA, the review team determined that the data submitted by the Applicant demonstrated that CT-P43 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components, and that there were no clinically meaningful differences between CT-P43 and US-licensed Stelara in terms of the safety, purity, and potency of the product. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on September 30, 2024.

The Safety Update contains updated cumulative patient exposure and safety data from worldwide post-marketing experience with CT-P43 since the international birth date (IBD) of June 12, 2024 through to September 20, 2024. Since June 12, 2024, CT-P43 has been approved in the European Union (EU) & European Economic Area (EEA), United Kingdom (UK), South Korea, Canada, and Australia with the brand name Steqeyma. The total estimated cumulative exposure for Steqeyma from the June 12, 2024 to September 20, 2024 was approximately (b) (4) patient-years (PY) based on sales data received from 2 countries; there were no sales data from the remaining countries. Based on this post-marketing data, there have been no fatal or serious adverse events. A total of 2 non-serious adverse events were reported, both of which were considered unrelated: 1 event of “intentional deviation from dosage regimen” was reported for Steqeyma and the other event of “treatment failure” was reported without specifying the ustekinumab brand name. Additionally, there has been no new significant immunogenicity information.

There are no clinical safety issues that would preclude approval of this resubmission.

8. Advisory Committee Meeting

Not applicable.

9. Other Relevant Regulatory Issues

FDA received a Citizen Petition requesting that “FDA refuse to license any biosimilar version of Ustekinumab as interchangeable with the brand-name reference product that is manufactured using a Chinese hamster ovary (“CHO”) cell-line system—and in particular Ustekinumab-ttwe—unless and until the Agency has evaluated and concluded that the differences in sialyation between the proposed interchangeable biosimilar and the reference product, Stelara (ustekinumab), do not have the potential to adversely affect half-life and clinical effectiveness—particularly with respect to therapeutic response durability.” This application seeks licensure of the proposed products as both biosimilar to and interchangeable with Stelara. As the Citizen Petition is specific to licensure of products as interchangeable, the determination of biosimilarity is not implicated by the Citizen Petition.

Refer to the "Decision of Provisional Determination for BLA 761338/Original 2 in light of Citizen Petition Docket No. FDA-2024-P-4538" memorandum dated 12/17/2024 in DARRTS for additional information regarding the implication of the Citizen Petition to the determination of interchangeability of the proposed products in this application.

10. Labeling

Nonproprietary Name
The Applicant's proposed nonproprietary name, ustekinumab-stba, was conditionally accepted by the Agency (DMEPA reviews dated April 4, 2024, and December 13, 2024).

Proprietary Name
The proposed proprietary name for CT-P43 is conditionally approved as STEQEYMA. The name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the name was acceptable (DMEPA reviews dated September 27, 2023 and December 10, 2024).

Other Labeling Recommendations
It has been determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

11. Pediatrics

This resubmission includes the Agreed Initial Pediatric Study Plan, wherein the Agency agreed to the deferral for the 45mg/0.5ml vial presentation on March 28, 2022. Following this agreement, several revised versions of the Agreed Initial Pediatric Study Plan were subsequently submitted. This resubmission also includes the most recent amended iPSP, submitted on August 30, 2024, in which the Applicant requested to retract the deferral plan for the 45 mg vial presentation, because they had completed studies on the 45 mg vial presentation. However, because the amended iPSP was submitted after the submission of the original BLA, a post-marketing requirement (PMR) to develop the 45 mg/0.5ml vial presentation that can be used to accurately administer CT-P43 to pediatric patients who weigh less than 60 kg will be issued. Refer to Section 12.

In the amended iPSP, the Applicant included assessment via extrapolation for pediatric patients ages 6-17 years with plaque psoriasis and psoriatic arthritis. They also referenced the guidance for industry, *Questions and Answers on Biosimilar Development and the BPCI Act*, and noted the labeling for US-Stelara does not include adequate pediatric information and is not licensed for the treatment of:

- Plaque psoriasis in pediatric patients < 6 years of age
- Psoriatic arthritis in pediatric patients < 6 years of age
- Crohn's disease in pediatric patients 0-17 years of age
- Ulcerative colitis in pediatric patients 0-17 years of age

Because the Applicant has not submitted a 45 mg/0.5 mL single-dose vial presentation in this resubmission, weight-based dosing of plaque psoriasis and psoriatic arthritis patients 6 years and older is limited to 60 kg and above.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. A biosimilar biological product is considered to have a new active ingredient for purposes of PREA (21 U.S.C. 355c(l)).

At the time of this review, Wezlana (ustekinumab-auub), has been approved as an interchangeable biosimilar and has qualified for First Interchangeable Exclusivity (FIE). FDA has previously determined that FIE for the Wezlana products will expire on April 30, 2025.[2] Therefore, because CT-P43 will be approved as a biosimilar (and not as interchangeable), this biologic will be considered to have a new active ingredient.

12. Postmarketing Requirements (PMRs) and Commitments (PMCs)

The current CT-P43 presentations are not designed to allow for accurate administration of doses less than 45 mg, which impacts children who weigh less than 60 kg. For accurate weight-based dosing, an age-appropriate formulation (presentation) is required by PREA. Therefore, a PREA PMR is necessary for the development of a formulation (presentation) that can be used to safely administer CT-P43 in patients who weigh less than 60 kg.

The Applicant agreed to the following PMR:

PMR 4765-1: Develop a presentation that can be used to accurately administer CT-P43 to pediatric patients who weigh less than 60 kg.

Final Report Submission: June 2025

The Applicant also agreed to the following PMC developed by OPQ:

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

PMR 4765-02: Repeat the bacterial retention study [redacted] (b) (4) with CT-P43 drug product (5 mg/mL) to verify that the bacterial retention performance [redacted] (b) (4) is not impacted by contact with the drug product solution [redacted] (b) (4)

Final report submission: March 2025

13. Recommended Regulatory Action

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that CT-P43 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P43 and US-licensed Stelara in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that CT-P43 can be expected to produce the same clinical result as US-licensed Stelara in any given patient and that the risk in terms of safety of diminished efficacy of alternating or switching between use of CT-P43 and US-licensed Stelara is not greater than the risk of using US-licensed Stelara without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that CT-P43 is biosimilar to US-Stelara, and supports a provisional determination under section 351(k)(4) of the Public Health Service (PHS) Act that CT-P43 is interchangeable with US-Stelara, as follows:

- CT-P43, 45 mg/0.5 mL PFS for subcutaneous use is an interchangeable biosimilar with US-Stelara 45 mg/0.5 mL PFS for subcutaneous use
- CT-P43, 90 mg/mL PFS for subcutaneous use is an interchangeable biosimilar with US-Stelara 90 mg/mL PFS for subcutaneous use
- CT-P43, 130 mg/26 mL single-dose vial for intravenous (IV) use is interchangeable biosimilar with US-Stelara 130 mg/26 mL single-dose vial for IV use

for the following indications for which US-Stelara has previously been approved and for which the Applicant is seeking licensure:

- moderate to severe plaque psoriasis (Ps) in adult patients and pediatric patients 6 years and older, who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis (PsA) in adult patients and pediatric patients 6 years and older
- moderately to severely active Crohn's disease (CD) in adults
- moderately to severely active ulcerative colitis in adults

The Applicant is not seeking licensure of CT-P43 in a 45 mg/0.5 mL single-dose vial for subcutaneous use. US-Stelara is available in a 45 mg/0.5 mL single-dose vial for

subcutaneous use for weight-based dosing of pediatric patients with a body weight of less than 60 kg. Section 2 of the Prescribing Information for CT-P43 will note that there is no dosage form of the product that allows weight-based dosing for pediatric patients below 60 kg (132 pounds). Refer to Sections 11 and 12 above for more information on the Applicant's plans to develop the vial.

Although the Division of Dermatology and Dentistry (DDD) is the lead division for this application and provided the written clinical review memo for the resubmission, clinical concurrence pertaining to their respective indications was obtained from the Division of Gastroenterology (DG) and the Division of Rheumatology and Transplant Medicine (DRTM) in the BMER dated September 30, 2024, during the original review cycle

FDA has not identified any deficiencies that would justify a complete response action and has provisionally determined that this submission meets the statutory interchangeability criteria for any condition of use as described above. However, pursuant to section 351(k)(6) of the PHS Act, FDA is unable to make such determination because of unexpired first interchangeable exclusivity for US-licensed Wezlana.

Therefore, the FDA review team recommended that BLA 761338 be administratively split to facilitate an approval action for CT-P43 as a biosimilar product ("Original 1") and a provisional determination that CT-P43 is an interchangeable biosimilar product ("Original 2"), as described above. The Applicant is expected to submit an amendment seeking approval no more than six months prior to the expiration of such exclusivity (or when the Applicant believes that BLA 761338 Original 2 will become eligible for approval).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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12/17/2024 01:16:49 PM

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