

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761338Orig1s000

761338Orig2s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary

Assessment Date: 12/09/2024

1. Application/Product Information

BLA number	761338
Submission Type	Resubmission
Regulatory Pathway	351(a)
Associated IND/BLA	IND 146085
Review Designation	Standard Complete Response Resubmission
Applicant	Celltrion Inc.
Indication	- 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
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Steqeyma
	Non-proprietary Name/Code Name Ustekinumab-stba
	OBP Naming MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [CT-P43]
Drug Product Description	Steqeyma (CT-P43, ustekinumab-stba) drug product is a sterile, preservative-free, clear to slight opalescent, colorless to pale yellow solution and may contain a few small translucent or white particles with pH 5.7 for subcutaneous injection or intravenous infusion. Steqeyma is a proposed biosimilar to US-licensed Stelara. - Steqeyma for subcutaneous injection is supplied in a single-dose prefilled syringe (PFS) containing 45 mg or 90 mg of CT-P43 in 0.5 mL or 1 mL, respectively. The excipient concentrations of CT-P43 in the PFS are histidine and L-histidine hydrochloride monohydrate (1.27 mg/mL), polysorbate 80 (0.04 mg/mL), and sucrose (76 mg/mL). - Steqeyma for intravenous infusion is supplied in a single-dose vial containing 130 mg of CT-P43 in 26 mL (5 mg/mL CT-P43), edetate disodium ((b) (4) mg),

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	histidine (9.36 mg), L-histidine hydrochloride monohydrate (23.66 mg), methionine (10.56 mg), polysorbate 80 (10.37 mg) and sucrose (1976 mg). Ustekinumab- stba is a human immunoglobulin G1 kappa monoclonal antibody produced in CHO cells consisting of 1324 amino acids and an estimated molecular weight of 145 kDa. Ustekinumab is an antagonist of human interleukin 12 (IL-12) and interleukin 23 (IL-23) cytokines. It binds to the p40 subunit shared by IL-12 and IL-23 and prevents IL-12 and IL-23 from binding to their receptor.		
Dosage Form	Injection		
Strength	For subcutaneous injection: 90 mg/mL (90 mg/1.0 mL PFS, 45 mg/0.5 mL PFS) For intravenous infusion: 130 mg/26 mL (5 mg/1.0 mL) vial		
Route of Administration	- Subcutaneous injection - Intravenous infusion		
Primary Container Closure System	45 mg/0.5 mL and 90 mg/1 mL PFS: 1 mL Type (b) (4) glass syringe with a staked-in-place stainless steel needle and closed with a (b) (4) elastomeric plunger-stopper and an elastomeric needle shield (cap). 130 mg/26 mL vial: 30mL Type I glass vial closed with a 20 mm elastomeric stopper and flip-off seal		
Device Information	The PFS has a 27-gauge fixed ½ inch staked-in-place stainless steel needle and is assembled with a finger flange, plunger rod and fitted with a passive safety guard.		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Zhong Zhao (1 st review cycle)/ João Pedras-Vasconcelos	Hailin (Sheena) Wang
	Drug product		
	Comparative analytical assessment		
	Immunogenicity Assay	Sujin Hwang	Daniela Verthelyi
	Facility/ Microbiology	DS: Zonglin (Tony) Hu	Madu Dharmasena
		DP: Jiangsong Jiang	Virginia Carroll

	OPQAI II labeling	Jennifer Kim
	RBPM	Melinda Bauerlien
	ATL	Hailin (Sheena) Wang
	Tertiary	Frances Namuswe
OPQ Issued Consults	The final recommendation from CDRH is that the device safety feature of the combination product is acceptable. There are no PMC/PMR from CDRH.	

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761338 for Steqeyma manufactured by Celltrion Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Steqeyma is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Steqeyma 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. CMC Information for Action Letter

a. Manufacturing Location:

- Drug Substance: CELLTRION, Inc. (b) (4) 20, Academy-ro 51 beongil, Yeonsugu, Incheon, 22014, Republic of Korea; FEI:3005241015
- Drug Product:
 - For 45 mg/0.5mL and 90 mg/mL PFS, CELLTRION, Pharm, Inc., 82, Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju, Chungcheongbuk-do, 28117, Republic of Korea; FEI: 3012279978.
 - For 130 mg/26 mL vial: (b) (4)

b. Fill size and dosage form:

- Single-dose prefilled syringe (PFS) containing 45 mg/0.5 mL
- Single-dose PFS containing 90 mg/1.0 mL
- Single-dose vial containing 130 mg/26 mL

c. Dating Period:

- Drug Substance: (b) (4) months at (b) (4) °C
- Drug Product: 36 months at 5±3°C for both PFS and vial presentations
- For packaged products: Not packaged
- Stability Option: N/A

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d. Exempt from lot release:

- Yes
- Rationale, if exempted: Stegeyma is exempted from lot release per FR 95-29960. The overall control strategy, including manufacturing and release controls, is adequate to control lot-to-lot variability and product quality over the proposed shelf-life.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable:

CMC PMC#1 (4765-2): To repeat the bacterial retention study (b) (4) with CT-P43 drug product (5 mg/mL) to verify that the bacterial retention performance (b) (4) is not impacted by contact with the drug product solution (b) (4)

Final report submission date: March 2025

4. Basis for Recommendation

a. Summary:

The original BLA 761338 submission received a complete response recommendation due to multiple quality deficiencies related to 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.

In the BLA resubmission on Oct. 16, 2024, the Applicant adequately addressed the complete response comments and additional comments provided in the Complete Response Action Letter on September 30, 2024, and updated the Chemistry, Manufacturing, and Controls module of the BLA accordingly.

CT-P43 (ustekinumab- stba) is a recombinant human IgG1 directed against the shared p40 subunit of IL-23 and IL-12 cytokines. It is a proposed interchangeable biosimilar to US-Stelara for the same indications as US-Stelara including moderate to severe PsO, PsA, CD and UC. Ustekinumab binds to the p40 subunits of IL-12 and IL-23, blocking IL-12 and IL-23 from binding to the shared IL-12 receptor subunit beta 1; thereby, disrupting IL-12 and IL-23 mediated signaling events and cytokine cascades. Potency of CT-P43 is controlled using a cell-based assay that monitors inhibition of IL-12 mediated signaling during drug substance (DS) and drug product (DP) release and stability testing. Ustekinumab binds to the shared P40 subunit of IL-12 or IL-23 and is unable to bind to the IL-12 or IL-23 molecule already

bound to its receptor complex, and thus is not likely to mediate Fc effector functions.

The totality of the evidence from the comparative analytical assessment supports that CT-P43 (ustekinumab- stba) is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. Celltrion adequately established a three-way scientific bridge between CT-P43, US-Stelara, and EU-Stelara to support the relevance of the data generated from studies using EU-Stelara as a comparator in the assessment of biosimilarity. The strengths of CT-P43 (ustekinumab- stba) 45 mg/0.5mL and 90 mg/mL in the single-dose PFS for subcutaneous infusion and 130mg/26mL (5mg/mL) in a single-dose vial for intravenous infusion are the same as those of US-Stelara in the same presentations and routes of administration. The Applicant plans to develop the 45 mg/0.5 mL in a single-dose vial presentation for the subcutaneous injection, which is also approved for US-Stelara, post-marketing. Refer to Appendix of the previous Quality Executive Summary for BLA 761338 checked in DARRTS on 09/27/2024 for detailed summary of the comparative analytical assessment.

The CT-P43 DS manufacturing process consists of

(b) (4)

(b) (4)

The overall CT-P43 (ustekinumab- stba) control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for CT-P43 (ustekinumab- stba) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern.

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The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for CELLTRION, Inc. (FEI: 3005241015) proposed for DS manufacture and CELLTRION Pharm, Inc. (FEI: 3012279978) and (b) (4) proposed for CT-P43 (ustekinumab- stba) DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

The BLA is recommended for approval from a product quality, immunogenicity, facility, microbiology, and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assays	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the Applicant and deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for Steqeyma (i.e., there is no specific test method described in regulation for Steqeyma that establishes an official standard of potency). We next considered whether potency is a factor for Steqeyma within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if “potency is a factor” and “no U.S. standard of potency has been prescribed.” We have determined that potency is not a factor for Steqeyma for purposes of § 610.61(r) because lot variability is not a concern for Steqeyma as Steqeyma’s manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

Comments: N/A

b. Drug Substance:

i. Protocols approved:

(b) (4)



- ii. Residual risk: None
- iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:

- 1. Post-approval Stability Protocol: 3.2.P.8.2 Drug product post-approval stability protocol and stability commitment
- 2. Shipping validation protocol for DS and DP: 3.2.P.9 Shipping validation for change in shipping conditions.

- ii. Residual risk: None
- iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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/

HAILIN WANG
12/13/2024 10:42:57 AM

FRANCES NAMUSWE
12/13/2024 01:48:50 PM

**PRODUCT QUALITY MICROBIOLOGY/FACILITY
ASSESSMENT****Memorandum of Review to the File**

Application ID	BLA 761338
Submission Type	Original BLA/ resubmission
Drug Product Name	CT-P43 (Biosimilar to ustekinumab, Stelara®)
Strengths	PFS: 45 mg/0.5 mL, 90 mg/1 mL; IV vial: 130 mg/26 mL
Dosage Form	Solution for Injection
Administration Route	Subcutaneous, Intravenous
Indication	Psoriasis, Psoriatic Arthritis, Crohn's Disease, Ulcerative Colitis
Applicant Name	CELLTRION, Inc.
US License Number	1996
Application Type	351 (k)
Primary Reviewer	Jiangsong Jiang, CDER/OPQ/OPMA/DPMVI
Secondary Reviewer	Virginia Carroll, CDER/OPQ/OPMA/DPMVI
Goal Date	04/16/2025

Recommendation for Approvability:

- This BLA resubmission was reviewed from a sterility assurance perspective and is recommended for Approval with the following post-marketing commitment(s):

To repeat the bacterial retention study (b) (4) with CT-P43 drug product (5 mg/mL) to verify that the bacterial retention performance (b) (4) is not impacted by contact with the drug product solution (b) (4). The (b) (4) final report will be submitted by March 2025.

- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OPQAIII.

List of Submissions Assessed (Table):

Document Description (Sequence #)	Date Received
Resubmission (sequence #0033)	10/16/2024
IR Response (sequence #0037)	11/29/2024
IR Response (sequence #0040)	12/10/2024

Application Submission Background**Reviewer's Comment: For Information**

This is a resubmission of BLA 761338. Refer to original OPMA assessment for CT-P43 drug product dated 06/25/2024. During the previous review cycle, the following microbiology deficiencies and additional comments were included in the CR letter for the applicant:

CR deficiencies:

- The bacterial retention study is inadequate (b) (4) for the CT-P43 IV drug product (5 mg/mL). (b) (4)

(b) (4)

(b) (4) Repeat the bacterial retention study of the

(b) (4)

for CT-P43 IV drug product vial (5 mg/mL).

2. The container closure integrity test (CCIT) dye ingress method used for stability testing of CT-P43 IV drug product vials is not validated to ensure reproducibility of results between different analysts. The validation summary for the dye ingress method in Table 3.2.P.5.3-59 includes results for sensitivity, specificity, and robustness, however the reproducibility of the visual detection method between different analysts is not addressed. According to FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics (2015), for non-compendial method, validation data are needed to support the reproducibility of the method. Provide evidence of the reproducibility of the visual inspection method to detect breach sizes at the limit of detection with multiple analysts. Alternatively, measure all samples by spectrophotometry and provide an updated method description with acceptance criteria and submit additional method validation data accordingly.

Additional comments to the CR letter (not approvability issues):

1. The sensitivity of the dye ingress method used to demonstrate container closure integrity (CCI) (b) (4) is unclear. Additional information is needed to confirm that the (b) (4) parameters will result in integral vials. The method description in section 3.2.P.2.5.4 states that (b) (4)

(b) (4)

(b) (4) If not, provide additional CCI test results from vials (b) (4)

(b) (4) The method used during (b) (4) should be demonstrated to be sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns).

(b) (4)

2.

3. The acceptance criteria for the post-use integrity test (b) (4) for 5 mg/mL CT-P43 IV drug product listed in section 3.2.P.3.4 are based on the (b) (4) (b) (4) Update section 3.2.P.3.4 with the (b) (4) prior to integrity testing, as (b) (4) product could impact results of the test. The post-use integrity test result should be accurate to support sterility assurance of the product.
4. The sterilization validation summary for stoppers used for CT-P43 IV drug product vial does not specify the actual sterilization parameters used during the studies. The sterilization validation parameters are needed to ensure that a sterility assurance level of 10^{-6} is demonstrated for the stoppers. (b) (4) (b) (4)
5. It is unclear whether the depyrogenation/sterilization validation studies for glass vials were designed to evaluate the worst-case locations in the (b) (4) (b) (4)
6. Additional (b) (4) results to validate the (b) (4) for CT-P43 IV drug product at (b) (4) were planned to be submitted by June 25, 2024, however these results were not reviewed. In the resubmission, provide summary data from at least one (b) (4) run with the container closure system of CT-P43 IV drug product to support validation of the (b) (4) (b) (4)
7. (b) (4) (b) (4)

In the current resubmission, the applicant provides their responses to these issues.



Jiangsong
Jiang

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Virginia
Carroll

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U.S. FOOD & DRUG
ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING ASSESSMENT

Date of Assessment:	December 13, 2024
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Joao Pedras-Vasconcelos, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XV
Application:	BLA 761338
Applicant:	CELLTRION Inc.
Submission Date:	October 16, 2024
Product:	Steqeyma (ustekinumab-stba)
Dosage form(s):	Injection
Strength and Container-Closure:	45 mg/0.5 mL (90 mg/mL) in a single-dose pre-filled syringe with safety guard 90 mg/1 mL (90 mg/mL) in a single-dose pre-filled syringe with safety guard 130 mg/26 mL (5 mg/mL) solution in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of Steqeyma (ustekinumab-stba) for treatment of plaque psoriasis, psoriatic arthritis, crohn's disease and ulcerative colitis as a biosimilar to the reference product Stelara (Ustekinumab) BLA 125261 and 761044.
Recommendations:	The prescribing information, medication guide, instructions for use, container labels, and carton labeling are acceptable from an OPQA III labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

BLA 761338 was resubmitted on October 16, 2024, and Appendix B includes labeling comments that were communicated in the previous review cycle.

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

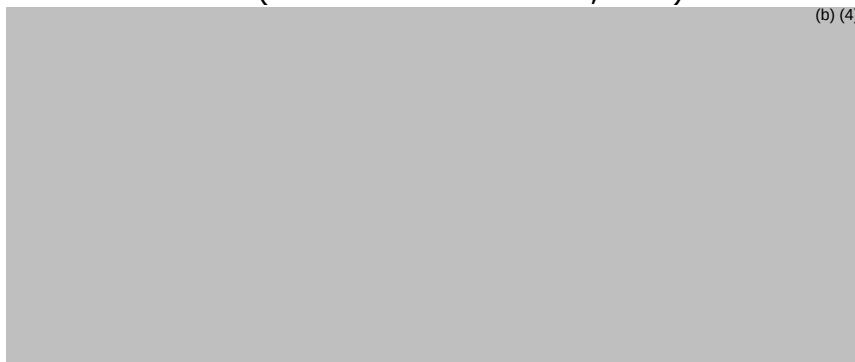
CONCLUSION

The prescribing information submitted on December 10, 2024, medication guide and instructions for use submitted on December 13, 2024, container labels and carton labeling submitted on December 2, 2024, were assessed, and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information, Medication Guide, and Instructions for Use (submitted on October 16, 2024)
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- Container Labels (submitted on October 16, 2024)



Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Proper Name (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S. license number for container bearing a partial label⁵)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Prefilled Syringe: <i>The label is small and could be considered a partial label. Thus, the qualifying phrase "Manufactured by" and the U.S. license number are not required per 21 CFR 610.60(c). The label displays the manufacturer's name.</i> Vial: The vial label displays the qualifying phrase "Manufactured by" and the U.S. license number.	

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

⁵ Per 21 CFR 610.60(c) *Partial Label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Lot number or other lot identification (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	☒ Yes ☐ No ☐ N/A

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022) USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Prefilled Syringe: Revise the product strength from (b) (4) to "90 mg/mL". <i>The applicant revised as requested.</i>	

Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No

<i>Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☐ N/A
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Medication Guide (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>The label is small and would be considered a partial label. Thus, a Medication Guide statement is not required per 21 CFR 610.60(a)(7).</i>	

No Package for container (container label)	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: The container is enclosed in a package.	

No container label (container label)	Acceptable
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: The product contains a container label.	

Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. <i>The applicant confirms that there is no text on the ferrule and cap overseal of the vials.</i>	

Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.	

The applicant confirms that sufficient area remains uncovered for 130 mg vial, and moreover, PFS-S label is all transparent except for the area where variable data is printed. Therefore, there is no problem with visual inspection.

(b) (4)

Route of administration (container label)	Acceptable
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

NDC numbers (container label)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Preparation instructions (container label)	Acceptable
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☐ Yes ☐ No ☒ N/A

Package type term (container label)	Acceptable
<i>Recommended labeling practices: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Prefilled Syringe: <i>The label is small and could be considered a partial label. Thus, a package type term statement is not required.</i>	

Vial: *The label provides a package type term statement.*

No misleading statements (container label)	Acceptable
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

Prominence of required label statements (container label)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: The label does not display text in Spanish.	

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.	

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Bar Code Label Requirements Questions and Answers (August 2011) Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>Prefilled Syringe: The label is small and could be considered a partial label. Thus, a dosage statement is not required.</i> <i>On the vial label, revise the dosage statement to read "Dosage: See prescribing information" to avoid clutter.</i> <i>The applicant revised as requested.</i>	

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: <i>The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.</i>	

Storage requirements (container label)	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>Prefilled Syringe: The label is small and could be considered a partial label. Thus, a storage statement is not required.</i>	

Revise the storage information to read "Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light."
The applicant revised as requested.

Dispensing container (container label)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package⁶ Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	☒ Yes ☐ No ☐ N/A

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A

⁶ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Beyond Use Date (Multiple-dose containers) (package labeling)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	Acceptable
Regulation: 21 CFR 610.61(e)	☒ Yes ☐ No ☐ N/A

Number of containers (package labeling)	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A

Product Strength (package labeling)	Acceptable
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Prefilled Syringe: Revise the product strength from (b) (4) to "90 mg/mL". <i>The applicant revised as requested.</i>	

Storage temperature/requirements (package labeling)	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the storage information to read "Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light." <i>The applicant revised as requested.</i>	

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	Acceptable
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	Acceptable
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Please revise the ingredient statements to read as follows: Prefilled Syringe 45 mg/0.5 mL: "Each 0.5 mL prefilled syringe delivers 45 mg ustekinumab-xxxx, histidine (0.18 mg), L-histidine hydrochloride monohydrate (0.46 mg), polysorbate 80 (0.02 mg), and sucrose (38 mg) in Water for Injection." Prefilled Syringe 90 mg/mL:	

"Each 1 mL prefilled syringe delivers 90 mg ustekinumab-xxxx, histidine (0.36 mg), L-histidine hydrochloride monohydrate (0.91 mg), polysorbate 80 (0.04 mg), and sucrose (76 mg) in Water for injection."

Vial:

"Each vial contains 26 mL of solution containing 130 mg of ustekinumab-xxxx, edetate disodium (0.47 mg), histidine (9.36 mg), L-histidine hydrochloride monohydrate (23.66 mg), methionine (10.56 mg), polysorbate 80 (10.37 mg) and sucrose (1,976 mg) in Water for Injection."

The applicant revised as requested.

Source of the product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: <i>The source of the product is not a safety concern.</i>	

Minimum potency of product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(r)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for ustekinumab products (i.e., there is no specific test method described in regulation for ustekinumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for this product because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.</i>	

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No

(Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☒ N/A
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Distributor (package labeling)	Acceptable
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☒ Yes ☐ No ☐ N/A

Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022)	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022) <i>USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Vial: <i>The end user is instructed to refer to the prescribing information.</i>	

Package type term (package labeling)	Acceptable
<i>Recommended labeling practices: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use</i> (October 2018) <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

No misleading statements (package labeling)	Acceptable
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

Prominence of required label statements (package labeling)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: The label does not display text in Spanish.	

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.	

Phenylalanine as a component of aspartame (package labeling)	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: The drug product does not contain phenylalanine.	

Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain sulfites.

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: On the vial carton labeling, revise the dosage statement to read "Dosage: See prescribing information" to avoid clutter. <i>The applicant revised as requested.</i> On the prefilled syringe carton labeling, revise the statement (b) (4) to read "Dosage: See prescribing information." <i>The applicant revised as requested.</i>	

Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☒ Yes ☐ No ☐ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	Acceptable
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv) <i>Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted</i>	☒ Yes ☐ No

<i>products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components</i> Draft Guidance <i>Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry</i> (January 2023)	☐ N/A
Comment/Recommendation: We revised to the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." per 21 CFR 201.57(c)(3)(iv). <i>The applicant revised as requested.</i>	

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use</i> (October 2018) <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
11 DESCRIPTION	Acceptable
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We deleted trailing zero. <i>The applicant revised as requested.</i> To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, edetate disodium, histidine, L-histidine monohydrochloride monohydrate, methionine, polysorbate (b) (4) and sucrose. Confirm if (b) (4) (b) (4) USP monograph. If so,	

(b) (4) (b) (4) Confirm the provided calculation and provide an updated Description and Composition Table in section 3.2.P.1 adding a footnote to Table 1 that includes the calculation between mg of (b) (4) (b) (4) The footnote should serve as a link between the name and quantity presented in section 3.2.P.1 (i.e., (b) (4)) to the name and quantity presented in the Prescribing Information, container label, and carton labeling (i.e., (b) (4)). <i>The applicant revised as requested.</i> We added the diluent. <i>The applicant revised as requested.</i>
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Full Prescribing Information	
15 & 16 Hazardous Drug	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures. ¹	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>Labeling submitted on October 16, 2024 includes revision of in-use storage condition for both vial and prefilled syringe at room temperature from (b) (4) days to 15 days. In the response to the complete response letter, the applicant submitted additional stability testing data, which support the proposed revision for in-use storage time, and this was confirmed by the product quality reviewer. This revision is acceptable from OPQA III Labeling perspective.</i>	

Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	Acceptable
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	☒ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	Acceptable
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>Labeling submitted on October 16, 2024 includes revision of in-use storage condition for both vial and prefilled syringe at room temperature from (b) (4) days to 15 days. In the response to the complete response letter, the applicant submitted additional stability testing data, which support the proposed revision for in-use storage time, and this was confirmed by the product quality reviewer. This revision is acceptable from OPQA III Labeling perspective.</i>	

MEDICATION GUIDE	
INGREDIENTS	Acceptable
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised the inactive ingredient name to its established name for drugs (i.e., drug products and ingredients), to ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e). We added the (b) (4) to the inactive ingredient list. <i>The applicant revised as requested.</i>	

MEDICATION GUIDE	
MANUFACTURER INFORMATION	Acceptable
21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	☒ Yes ☐ No ☐ N/A

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
<i>Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	Acceptable
<i>Recommended labeling practices for IFU: Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>Labeling submitted on October 16, 2024 includes revision of in-use storage condition for both vial and prefilled syringe at room temperature from (b) (4) days to 15 days. In the response to the complete response letter, the applicant submitted additional stability testing data, which support the proposed revision for in-use storage time and this was confirmed by the product quality reviewer. This revision is acceptable from OPQA III Labeling perspective.</i>	

INSTRUCTIONS FOR USE	
INGREDIENTS	Acceptable
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☐ Yes ☐ No ☒ N/A

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	Acceptable
21 CFR 201.1, 19 CFR 134.11	☒ Yes ☐ No ☐ N/A
Guidance for Industry <i>Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format</i> (July 2022). 21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	☒ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on December 10, 2024)
<\\CDSESUB1\EVSPROD\bla761338\0040\m1\us\draft-labeling-text-pi.docx>
- Medication Guide (submitted on December 13, 2024)
<\\CDSESUB1\EVSPROD\bla761338\0041\m1\us\draft-labeling-text-mg.docx>
- Instructions for Use (submitted on December 13, 2024)
<\\CDSESUB1\EVSPROD\bla761338\0041\m1\us\draft-labeling-text-ifu.docx>
- Container Labels (submitted on December 2, 2024)

(b) (4)



Joao
Pedras
Vasconcel

Digitally signed by Joao Pedras Vasconcel
Date: 12/13/2024 02:06:13PM
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Jennifer
Kim

Digitally signed by Jennifer Kim
Date: 12/13/2024 02:05:01PM
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BLA Executive Summary

Assessment Date: Original review: June 25, 2024, 07/26/2024

Amended: 09/27/2024 (due to change in facility status)

1. Application/Product Information

BLA number	761338
Submission Type	Original Submission
Regulatory Pathway	351(k) BLA
Associated IND/BLA	IND 146085
Review Designation	Standard
Applicant	Celltrion Inc.
Indication	- 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
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Steqeyma
	Non-proprietary Name/Code Name: Ustekinumab-stba
	OBP Naming: MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [CT-P43]
Drug Product Description	Steqeyma (CT-P43, ustekinumab- stba) drug product is a sterile, preservative-free, clear to slight opalescent, colorless to pale yellow solution and may contain a few small translucent or white particles with pH 5.7 for subcutaneous injection or intravenous infusion. Steqeyma is a proposed biosimilar to US-licensed Stelara. Steqeyma for subcutaneous injection is supplied in a single-dose prefilled syringe (PFS) containing 45 mg or 90 mg of CT-P43 in 0.5 mL or 1 mL, respectively. The excipient concentrations of CT-P43 in the PFS are histidine and L-histidine hydrochloride monohydrate

	(1.27 mg/mL), polysorbate 80 (0.04 mg/mL), and sucrose (76 mg/mL). Steqeyma for intravenous infusion is supplied in a single-dose vial containing 130 mg of CT-P43 in 26 mL (5 mg/mL CT-P43), edetate disodium (b) (4) mg), histidine (9.36 mg), L-histidine hydrochloride monohydrate (23.66 mg), methionine (10.56 mg), polysorbate 80 (10.37 mg) and sucrose (1976 mg). Ustekinumab- stba is a human immunoglobulin G1 kappa monoclonal antibody produced in CHO cells consisting of 1324 amino acids and an estimated molecular weight of 145 kDa. Ustekinumab is an antagonist of human interleukin 12 (IL-12) and interleukin 23 (IL-23) cytokines. It binds to the p40 subunit shared by IL-12 and IL-23 and prevents IL-12 and IL-23 from binding to their receptor.		
Dosage Form	Injection		
Strength	For subcutaneous injection: 90 mg/mL (90 mg/1.0 mL PFS, 45 mg/0.5 mL PFS) For intravenous infusion: 130 mg/26 mL (5 mg/1.0 mL) vial		
Route of Administration	- Subcutaneous injection - Intravenous infusion		
Primary Container Closure System	45 mg/0.5 mL and 90 mg/1 mL PFS: 1 mL Type (b) (4) glass syringe with a staked-in-place stainless steel needle and closed with a (b) (4) elastomeric plunger-stopper and an elastomeric needle shield (cap). 130 mg/26 mL vial: 30mL Type I glass vial closed with a 20 mm elastomeric stopper and flip-off seal		
Device Information	The PFS has a 27-gauge fixed ½ inch staked-in-place stainless steel needle and is assembled with a finger flange, plunger rod and fitted with a passive safety guard.		
Co-packaged Product Information	N/A		
	Discipline	Primary	Secondary
	Drug substance	Zhong Zhao	Hailin (Sheena)
	Drug product		Wang

OPQ Review Team	Comparative analytical assessment		
	Immunogenicity Assay	Sujin Hwang	Daniela Verthelyi
	Facility/ Microbiology	DS: Tony Hu	Madu Dharmasena
		DP: Jiangsong Jiang	Virginia Carroll
	RBPM	Melinda Bauerlien	
	ATL	Hailin (Sheena) Wang	
	Tertiary	Frances Namuswe	
OPQ Issued Consults	The final recommendation from CDRH is that the device safety feature of the combination product is acceptable. There are no PMC/PMR or CR deficiencies from CDRH.		

2. Recommendation and Conclusion on Approvability

Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761338 for Steqeyma manufactured by Celltrion Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Steqeyma is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Celltrion Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comments and Additional Comments (if applicable):

Product Quality Complete Response Comments:

- The bacterial retention study is inadequate (b) (4) for the CT-P43 IV drug product (5 mg/mL). (b) (4)
- Repeat the bacterial retention (b) (4) study of the (b) (4) for CT-P43 IV drug product vial (5 mg/mL).

2. The container closure integrity test (CCIT) dye ingress method used for stability testing of CT-P43 IV drug product vials is not validated to ensure reproducibility of results between different analysts. The validation summary for the dye ingress method in Table 3.2.P.5.3-59 includes results for sensitivity, specificity, and robustness, however the reproducibility of the visual detection method between different analysts is not addressed. According to FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics (2015), for non-compendial method, validation data are needed to support the reproducibility of the method. Provide evidence of the reproducibility of the visual inspection method to detect breach sizes at the limit of detection with multiple analysts. Alternatively, measure all samples by spectrophotometry and provide an updated method description with acceptance criteria and submit additional method validation data accordingly.

3. The proposed release and stability specification for clarity of (b) (4) (b) (4) for CT-P43 drug product (DP) [SCS] is not acceptable because it is not justified by your clinical and manufacturing experience. In your response to information request (IR), received on 05/13/2024, you proposed not to tighten this release and stability specification based on stability data under stress condition (40 ± 2 °C/ $75 \pm 5\%$ RH) for Lot No. 2NGP01 as justification. The proposed justification is not acceptable as it is not clinically relevant. Results from accelerated and stress conditions should not be used to support the release and long-term stability acceptance criteria. In addition, this specification is not supported by the updated full term (36 months) stability data from the primary stability (non-PPQ) batches provided in the same amendment in SN 0027, which consistently showed results are below (b) (4) NTU at all timepoints throughout the product shelf life. Tighten the release and stability acceptance criteria for clarity for CT-P43 [SCS] DP based on the historical release and long-term stability results to ensure consistent quality of CT-P43 DP [SCS].

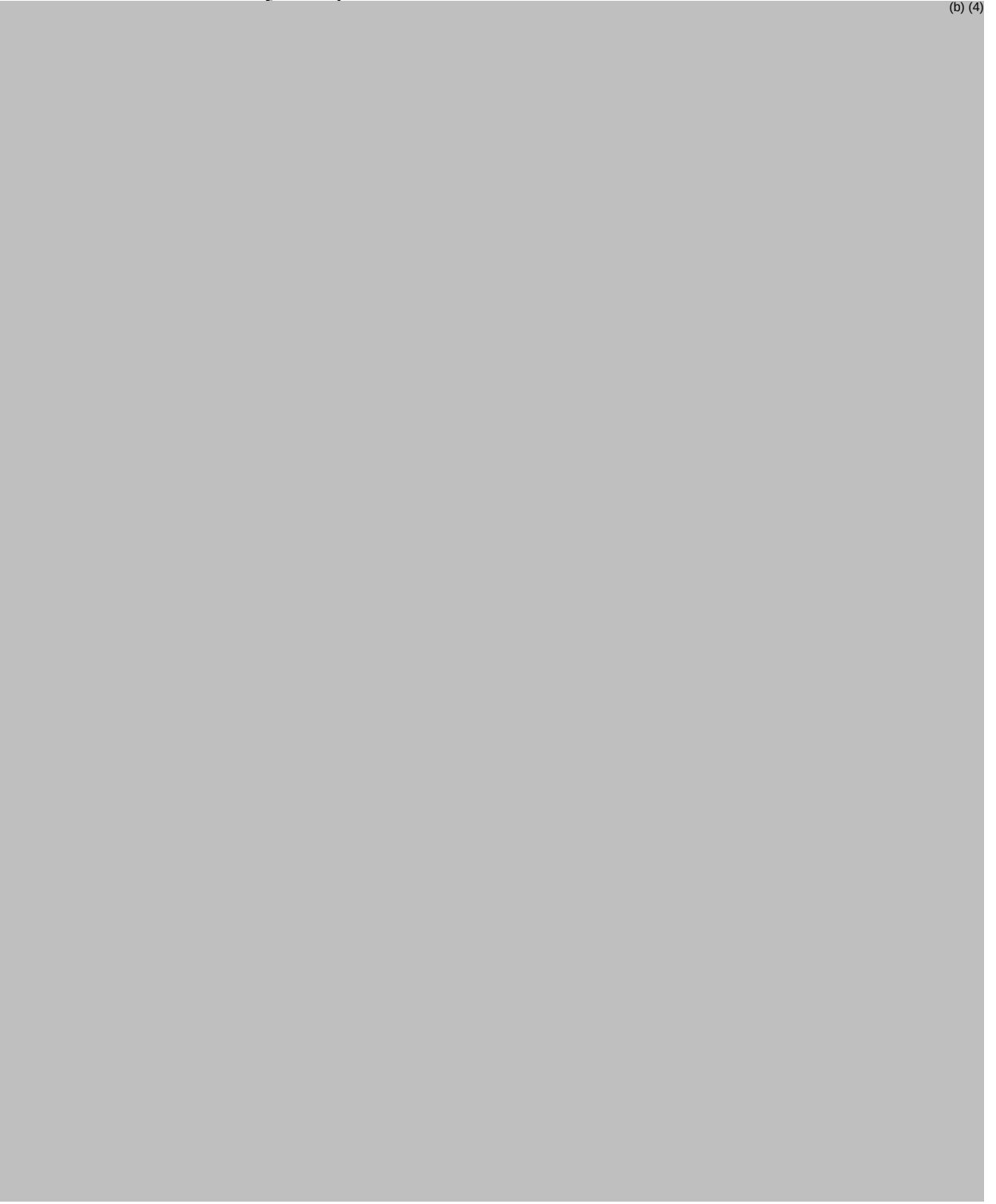
4. The proposed shelf-life limit of (b) (4) % for acidic peaks in CT-P43 PFS and Vial DP is not supported by your clinical and manufacturing experience. In the IR response received on 05/13/2024, you proposed not to tighten this shelf-life limit based on results from the stress and accelerated conditions. You described that the (b) (4) are associated with an (b) (4).

However, the proposed shelf-life limit does not reflect the clinical and manufacturing experience and is not supported by the updated full term stability results (all data points $\leq$ (b) (4) %). from the primary stability batches (non-PPQ) for both PFS and vial DP presentations provided in the same amendment in SN0027 Tighten the shelf-life acceptance criteria

for acidic peaks based on long term stability data to ensure the consistent CT-P43 DP quality over the shelf-life.

Additional Product Quality non-CR Comments:

(b) (4)



2. As indicated in the proposed labeling, individual pre-filled syringes or vials may be stored at room temperature up to 30 °C for a maximum single period of up to (b) (4) days in the carton. You provided the stability data under the accelerated 2 condition using representative DP lots to support the labeled in-use storage for CT-P43 at room temperature prior to administration or dilution. However, it appears end of shelf-life samples were not tested for in-use stability data under accelerated 2 condition. To ensure the in-use room temperature stability of CT-P43 PFS and vial DP, provide additional stability testing under the accelerated 2 condition using end of the shelf-life DP samples. In addition, to further support the in-use dilution stability of CT-P43 vial products and as recommended per ICH Q1A(R2), provide additional in-use stability testing of end of shelf-life DP vial samples after the maximum (b) (4) days room temperature storage.
3. We note that you only provided in-use compatibility study with (b) (4) IV bag. If you intend for the product to be used with other common bags such as (b) (4) or (b) (4) we recommend studies to support those.
4. The information for some responses in Section 1.11.1 in SN 0027 received on 05/13/2024 was incomplete and/or inaccurate. For example, response to information request 4 was not submitted while response to information request 2 was submitted twice in Quality Information Amendment 2 and 4. Revise the quality information amendment to provide accurate and complete responses to the quality information request dated 05/03/2024 in your BLA re-submission.
5. The sensitivity of the dye ingress method used to demonstrate container closure integrity (CCI) (b) (4) (b) (4) is unclear. Additional information is needed to confirm that the (b) (4) parameters will result in integral vials. The method description in section 3.2.P.2.5.4 states that (b) (4)

If not, provide additional CCI test results from vials (b) (4). The method used during (b) (4) should be demonstrated to be sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns).

(b) (4)

7. The acceptance criteria for the post-use integrity test (b) (4) for 5 mg/mL CT-P43 IV drug product listed in section 3.2.P.3.4 are based on the (b) (4) Update section 3.2.P.3.4 with the (b) (4) (b) (4) prior to integrity testing, as (b) (4) product could impact results of the test. The post-use integrity test result should be accurate to support sterility assurance of the product.

8. The sterilization validation summary for stoppers used for CT-P43 IV drug product vial does not specify the actual sterilization parameters used during the studies. The sterilization validation parameters are needed to ensure that a sterility assurance level of 10⁻⁶ is demonstrated for the stoppers. (b) (4)

(b) (4)

9. It is unclear whether the depyrogenation/sterilization validation studies for glass vials were designed to evaluate the worst-case locations in the (b) (4)

(b) (4)

10. Additional (b) (4) results to validate the (b) (4) for CT-P43 IV drug product at (b) (4) were planned to be submitted by June 25, 2024, however these results were not reviewed. In the resubmission, provide summary data from at least one (b) (4) run with the container closure system of CT-P43 IV drug product to support validation of the (b) (4) process.

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(b) (4)

(b) (4)

4. Basis for Recommendation

a. Summary:

CT-P43 is a recombinant human IgG1 directed against the shared p40 subunit of IL-23 and IL-12 cytokines. It is a proposed interchangeable biosimilar to US-Stelara for the same indications as US-Stelara including moderate to severe PsO, PsA, CD and UC. Ustekinumab binds to the p40 subunits of IL-12 and IL-23, blocking IL-12 and IL-23 from binding to the shared IL-12 receptor subunit beta 1; thereby, disrupting IL-12 and IL-23 mediated signaling events and cytokine cascades. Potency of CT-P43 is controlled using a cell-based assay that monitors inhibition of IL-12 mediated signaling during drug substance (DS) and drug product (DP) release and stability testing. Ustekinumab binds to the shared P40 subunit of IL-12 or IL-23 and is unable to bind to the IL-12 or IL-23 molecule already bound to its receptor complex, and thus is not likely to mediate Fc effector functions.

The totality of the evidence from the comparative analytical assessment supports that CT-P43 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. Celltrion adequately established a three-way scientific bridge between CT-P43, US-Stelara, and EU-Stelara to support the relevance of the data generated from studies using EU-Stelara as a comparator in the assessment of biosimilarity. The strengths of CT-P43 45 mg/0.5mL and 90 mg/mL in the single-dose PFS for subcutaneous infusion and 130mg/26mL (5mg/mL) in a single-dose vial for intravenous infusion are the same as those of US-Stelara in the same presentations and routes of administration. The Applicant plans to develop the 45 mg/0.5 mL in a single-dose vial presentation for the subcutaneous injection, which is also approved for US-Stelara, post-marketing. Refer to Appendix for detailed summary of the comparative analytical assessment.

The CT-P43 DS manufacturing process consists of

(b) (4)

(b) (4)

(b) (4)

OPQ identified multiple product quality deficiencies during the review of Module 3 of BLA 761338. The data and information provided do not support that the manufacture and testing of CT-P43 is well controlled and will lead to a product that is safe, pure, and potent for duration of the shelf-life. As indicated in the CR comments above, there is inadequate control of PFS and Vial DP, and insufficient information to support the sterility assurance of the CT-P43 DP in the vial presentation. Other product quality deficiencies include insufficient data to support the in-use stability of CT-P43 Vial DP and inadequate control of reference standard. As these deficiencies were not resolved during this review cycle, a CR action is recommended for this BLA.

Pre-license inspections of the drug substance and drug product manufacturing facilities were waived originally. However, GMP issues that impact this BLA were identified for the DS and PFS DP manufacturing site at CELLTRION, Inc. FEI:3005241015 when the site was inspected in Feb 2024 as a combined pre-license inspection for a different BLA and surveillance inspection. This facility issue was captured as CR issue in the original OPQ quality executive summary dated 07/26/2024 in DARRTS. Subsequently, the pOAI status from the Feb inspection was downgraded to VAI based on OMQ review of the firm's responses (Case #686453 in CMS). All proposed manufacturing and testing facilities are now considered acceptable based on their current CGMP compliance status and recent relevant inspectional coverage at the time of completion of the amended quality executive summary.

CDRH final recommendation is the needle safety device of the PFS combination product is approvable.

Overall, the information and data submitted in this application are not adequate to support a conclusion that the manufacture of CT-P43 DS and DP is well-controlled and will lead to a product that is safe, pure, and potent.

Therefore, from an OPQ perspective, this BLA is not recommended for approval in its present form until the above-mentioned quality deficiencies are satisfactorily resolved.

b. Subdiscipline Recommendation:

Drug Substance	-	Inadequate
Drug Product	-	Inadequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Inadequate

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the Applicant and deemed acceptable.

d. Potency Assessment for Labeling:

Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations

Not applicable as OPQ does not recommend approval of this application.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Appendix

II. Evaluation of the Comparative Analytical Assessment

A. Overview and Conclusions

Celltrion is seeking licensure of CT-P43 as an interchangeable biosimilar to U.S.-licensed Stelara (referred to hereafter as US-Stelara) for these strengths and presentations: 90 mg/1.0 mL (90 mg/mL) and 45 mg/0.5 mL (90 mg/mL) in a single-dose prefilled syringe (PFS) with safety guard for subcutaneous injection, and 130 mg/26 mL (5 mg/mL) in a single-dose vial for intravenous infusion. These are the same strengths currently available for US-Stelara.

To support a demonstration that CT-P43 is highly similar to US- Stelara and establish the analytical component of the scientific bridge, Celltrion performed a three-way comparative analytical assessment (CAA). The first sub-study compared the PFS presentations based on the following data:

- 10 lots of US-Stelara (7 lots of 45 mg/0.5 mL PFS, 3 lots of 90 mg/1.0 mL PFS) with expiration dates ranging from April 2023 through September 2024;
- 10 lots of E.U.-approved-Stelara (EU-Stelara) (8 lots of 45 mg/0.5 mL PFS, 2 lots of 90 mg/1.0 mL PFS) with expiration dates ranging from March 2023 through October 2024;
- 6 lots of CT-P43 PFS drug product (DP) (4 lots of 45 mg/0.5 mL PFS, 2 lots of 90 mg/1.0 mL PFS,) manufactured between April 2020 and May 2022 from 6 independent CT-P43 DS lots.
- For several assays not expected to be impacted by the DP manufacturing process, independent CT-P43 drug substance (DS) lots were included in the CAA if a DP lot manufactured from that DS lot was not available at the time of the assessment. Up to 4 DS lots manufactured between January 2020 and August 2021 were used in the final CAA.

In addition, Celltrion also performed a second comparative analytical assessment sub-study between CT-P43 and US-Stelara for the 130 mg/26 mL vial using the following:

- 6 lots of US-Stelara (130 mg/26 mL vial) with expiration dates ranging from June 2023 through July 2025. For assessment of protein concentration only, an additional 5 lots of US-Stelara were used for a total of 11 lots.
- 6 lots of CT-P43 130 mg/26 mL vial DP manufactured between December 2020 and April 2023 from the same 6 independent CT-P43 DS lots also used for in the manufacturing of 6 CT-P43 PFS drug product lots already included in the above CAA sub-study.

The DP lots used in clinical studies and the CT-P43 PPQ lots for all strengths are included in the CAA. The ages of US-Stelara and EU-Stelara at the time of testing were adequate to capture potential differences or variability over time for US-Stelara and EU-Stelara.

The CAA included comparison of physicochemical and functional quality attributes (QAs) of CT-P43, US-Stelara and EU-Stelara using orthogonal methods, as well as

comparison of their degradation profiles under forced degradation conditions. The CAA included a 3-way comparative assessment between the PFS presentations only since this presentation was used in the clinical studies and 2-way comparative assessment between the 130 mg/26 mL vials with the same methods. In addition, the Applicant conducted a comparability assessment between CT-P43 45 mg/0.5 mL SC PFS and CT-P43 IV 130 mg/26 mL vial DP and the data support that these are analytically comparable. Results from method validation or qualification studies support the suitability of the methods used in the analytical assessment. The Applicant used a criticality-based data analysis approach to evaluate the analytical results that was consistent with FDA recommendations. The approach included the following: QAs amenable to statistical analysis were compared to quality ranges (QRs) of mean $\pm$ 2 (very high criticality) or 3 (high and moderate criticality) * standard deviations (SD)) established from US-Stelara and EU-Stelara. In addition, for certain low criticality attributes, results are evaluated against the min-max ranges of US-Stelara and EU-Stelara to support similarity. If a result exceeded the min-max range, the magnitude and the criticality of the observed differences were discussed and justified. QAs not amenable to quantitative analysis or otherwise justified were analyzed by a qualitative comparison (e.g. visual comparison,). DP vial samples used in the 2-way CAA sub-study included non-independent DS lots from those used in the 3-way CAA sub-study; however quality attributes that could be impacted by the DP manufacturing process and difference in formulation were assessed using an adequate number of DP lots.

For the comparative stability studies, the Applicant conducted studies under forced degradation conditions (thermal stress at 55°C for up to 6 days, photo stress, oxidation and hydrolytic degradation). The comparative forced degradation studies show similar degradation pathways and degradation rate among CT-P43, US-Stelara and EU-Stelara.

Our assessment of the CT-P43 and US-Stelara comparative analytical data supports the determination that CT-P43 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. CT-P43 has the same strengths, dosage form and routes of administration as US-Stelara. The Applicant used a comprehensive set of analytical methods that were suitable to evaluate the critical quality attributes of CT-P43 and US-Stelara to support the demonstration that the products are highly similar. The number of lots tested and data analysis approaches used were appropriate or justified as needed to allow for a meaningful evaluation of the results of the analytical studies. The differences observed in a subset of the quality attributes do not preclude a determination that CT-P43 and US-Stelara are highly similar.

In addition, Celltrion used three-way pairwise comparisons of CT-P43, US-Stelara, and EU-Stelara to establish the analytical component of the scientific bridge between CT-P43, US-Stelara, and EU-Stelara to support the relevance of the data generated from clinical studies using EU-Stelara as the comparator in the assessment of biosimilarity. Our assessment of the data supports that the Applicant established the analytical component of the scientific bridge between CT-P43, US-Stelara, and EU-Stelara, using

the same methods and statistical approaches used to evaluate that CT-P43 is highly similar to US-Stelara. This supports the relevance of the data generated from clinical studies using EU-Stelara as the comparator for the assessment of biosimilarity.

B. Comparative Analytical Results

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Primary Structure	Amino acid sequence	Yes	Yes
	Intact molecular weight	Yes	Yes
	Reduced and deglycosylated mass of HC and LC	Yes	Yes
Post Translational Modifications	Methionine Oxidation	Yes	Yes
	Deamidation	Yes	Yes
	HC and LC Glycation	Yes	Yes
	Isomerization	Yes	Yes
	C-terminal Lys truncation	Yes	Yes
Purity and impurities	Size variants by SEC-HPLC	Yes	Yes
	Size variants by SEC-MALS		
	Size variants by SV-AUC	Yes	Yes
	Size variants by reduced CE-SDS	Yes	Yes
	Size variants by non-reduced CE-SDS	Yes	Yes
	Non-glycosylated HC	Yes	Yes
	Charge variants by IEC-HPLC	Yes	Yes
	Charge variants by IEC-HPLC	Yes	Yes
Glycosylation	Glycan map	Yes	Yes
	Afucosylation	Yes	Yes
	High Mannose	Yes	Yes
	β-Galactosylation	Yes	Yes
	α-Galactosylation	Yes	Yes
	Sialylation: levels and types (NANA, NGNA)	Yes	Yes
	Other glycans G0F, G1F, G2F	Yes	Yes
High Order Structure	Disulfide structure	Yes	Yes
	Free thiols	Yes	Yes
	Secondary structure FTIR and far UV spectra	Yes	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Biological activities	Tertiary Structure by near UV spectra	Yes	yes
	Tertiary structure by DSC	Yes	Yes
	Inhibition of IL-23 mediated STAT signaling	Yes	Yes
	Inhibition of IL-12 mediated STAT signaling	Yes	Yes
	Inhibition of binding of IL-23 to receptor IL-12R β 1	Yes	Yes
	Inhibition of binding of IL-12 to receptor IL-12R β 1	Yes	Yes
	IL-12/IL-23 p40 binding assay	Yes	Yes
Bioactivity – Fc mediated	-Inhibition of IL-23-induced and IL-12 induced IFN- γ release in PBMCs from a healthy donor; - Inhibition of IL-23-induced IL-17A secretion in PBMCs from a health donor.	Yes	Yes
	Lack of Antibody-dependent cell-mediated cytotoxicity (ADCC)	Yes	Yes
	Lack of Complement-dependent cytotoxicity (CDC)	Yes	Yes
	FcRn binding	Yes	Yes
	Fc γ RI binding	Yes	Yes
	Fc γ RIIa binding	Yes	Yes
	Fc γ RIIb binding	Yes	Yes
	Fc γ RIIIa (V158) binding	Yes	Yes
	Fc γ RIIIb binding	Yes	Yes
Drug Product Attributes	C1q binding	Yes	Yes
	Protein concentration	Yes	Yes
Forced degradation studies	Thermal Stress	Yes	Yes
	Photo degradation	Yes	Yes
	Chemical oxidation	Yes	Yes
	Hydrolytic degradation	Yes	Yes

C. Analytical Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

The clinical development of CT-P43 included three completed clinical studies that compared CT-P43 to US-Stelara and/or EU-Stelara.

- Study CT-P43 1.1 (comparative pharmacokinetics study not considered in support of biosimilarity. Refer to BMER for additional information on this PK study): A 2-part, randomized, double-blind, parallel-group, single-dose, PK similarity study to compare the pharmacokinetics, safety and immunogenicity of subcutaneously-administered CT-P43, US-Stelara and EU- Stelara in healthy male subjects.
- Study CT-P43 1.2 (comparative pharmacokinetics study): A randomized, double blind, parallel-group, single-dose PK similarity study to compare the pharmacokinetics, safety and immunogenicity of subcutaneously-administered CT-P43, US-Stelara and EU-Stelara in healthy Japanese male subjects
- Study CT-P43 3.1 (comparative efficacy and safety study): A randomized, active-controlled, double-blind comparative clinical study to compare the efficacy and safety of CT-P43 to EU-Stelara in patients with moderate to severe plaque psoriasis

To establish the analytical component of the scientific bridge to support the relevance of the clinical comparative data generated using EU-Stelara as a comparator product, Celltrion performed a three-way analytical assessment comparing CT-P43, US-Stelara, and EU-Stelara using a comprehensive set of analytical methods. The same analytical methods used for the assessment of highly similar between CT-P43 and US-Stelara were used for comparison of CT-P43 and EU-Stelara and EU-Stelara and US-Stelara. The differences observed in a subset of quality attributes in the comparative analytical studies (See section D below) do not preclude a determination that the analytical component of the scientific bridge is established.

D. Assessment of Comparative Analytical Study Results

Comparative analytical assessment criteria were met for all attributes evaluated with the following exceptions:

Critical Quality Attributes with Differences	Related Critical Quality Attributes
Glycosylation – Overall glycan map	The glycan map profiles show that several types of glycans are present among CT-P43, U.S.-Stelara, and E.U.-Stelara; however, there are several differences due to additional, missing, and different levels of glycan species in CT-P43 compared to U.S.-Stelara, and E.U.-Stelara. These differences can be attributed to different cell lines used in manufacturing. For example, some of the differences are due to the

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	presence of NANA-containing glycans in CT-P43 and NGNA-containing glycans in U.S.-Stelara and E.U.-Stelara, as a result of the different cell lines. However, these differences do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge as addressed below in the subsequent rows of this table for each glycan species with noted differences.
Afucosylation	The afucosylation levels in all 10 CT-P43 lots in the 3-way CAA sub-study (min-max: 3.33 – 4.27%) are higher and outside the quality range of both U.S.-Stelara (QR: 2.36 - 3.24%) and E.U.-Stelara (QR: 1.83 – 3.05%). The same trend where a higher level was observed in CT-P43 lots in the 2-way CAA sub-study was observed (and expected given this attribute is not expected to differ between the strengths or presentations). Afucosylated species may impact binding to Fcγ receptors, such as FcγRIIIa. A higher level of afucosylated glycans might result in increased Fc-mediated activities such as ADCC; however, no corresponding difference in Fcγ receptor binding was observed between the three products, suggesting that the magnitude of the difference observed was unlikely to translate into a meaningful difference in biological activity. Further, ustekinumab is not known to have effector function and the Applicant provided data showing that all three products lack effector function. Therefore, slight differences in attributes that can impact Fc-mediated functions are not expected to be meaningful. Given the foregoing, the noted differences are not expected to have a clinically meaningful impact. The observed differences in afucosylation do not preclude the demonstration that CT-P43 is highly similar to U.S.-Stelara or the establishment of the analytical component of the scientific bridge.
High Mannose	A higher level of high mannose (min-max: 2.17 – 3.19%) is observed in CT-P43 compared to U.S.-Stelara (QR: 0.98 -1.31%) and E.U.-Stelara (QR: 0.98 -1.35%) in the 3-way CAA. The same trend with a higher level of high mannose in CT-P43 DP lots was observed in the 2-way CAA sub-study (and expected given this attribute is not expected to differ between the strengths or presentations). The levels of all 10 CT-P43 SC lots are above the QRs of both U.S.-Stelara and E.U.-Stelara. High mannose may potentially impact the PK. In addition, high mannose species are a subset of afucosylated species and could impact ADCC activity. However, the increased high mannose in CT-P43 did not result in increased FcγRIIIa binding activity because CT-P43 has slightly lower FcγRIIIa binding activity and no ADCC activity. In addition, removal of high mannose from the three products by mannosidase treatment conducted by the Applicant did not impact biological activities (FcγRIIIa-V binding affinity, FcRn binding affinity, hIL-12 binding inhibition activity (CELISA) or hIL-12-mediated signaling inhibition activity (reporter

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	assay)) of these products in vitro. These data suggest that the < 2% higher level of high mannose glycans in CT-P43 should not impact these biological activities. Regarding the potential impact on PK, it is known that high mannose glycans of therapeutic monoclonal antibodies can increase serum clearance in human. Scientific literature also indicates that up to 5% difference in high mannose glycan differences does not significantly impact clearance of monoclonal antibodies [Goetze A.M. et al. Glycobiology, 21(7), 949–959; Welch J. et. al. Clinical Pharmacology & Therapeutics, 2022, 113(5), 1003-1010]. Therefore, the observed differences in high mannose do not preclude the demonstration that CT-P43 is highly similar to U.S.-Stelara or the establishment of the analytical component of the scientific bridge.
Sialylation	CT-P43 contains NANA-sialylation, consistent with sialylated glycans found in human glycoproteins, while US-Stelara and EU-Stelara contain non-human NGNA-sialylation. Non-human glycans could be associated with potential hypersensitivity. Therefore, change from the non-human to the human glycan form should not adversely impact the safety profile of CT-P43. In addition, NANA was detected in CT-P43 at a much lower level (1.00 – 1.35%) as compared to the combined NGNA levels detected in US-Stelara SC (20.29 – 29.11%) and EU-Stelara SC (20.48 – 28.40%). A potential role of sialylation in the biological activities of mAbs has been suggested. However, removal of sialic acid from the three products by sialidase treatment conducted by the Applicant did not result in differences in the biological activities (FcγRIIIa-V binding affinity, FcRn binding affinity, hIL-12 binding inhibition activity (CELISA) or hIL-12-mediated signaling inhibition activity (reporter assay)) of the three products in-vitro. These data suggest that the observed differences in the type and level of observed sialylated species should not impact these biological activities. Differences in sialylation could also influence the serum half-life of therapeutic proteins; for example, therapeutic proteins containing less sialylation could be cleared more rapidly through the asialoglycoprotein receptors than those containing more sialylation. However, a definitive role of sialylation in Fc region on serum PK for mAbs remains to be understood. There is currently no known bioactivity assay that can assess the impact of differences in sialylation on the PK of mAbs. The results from the PK similarity study CT-P43 1.2, considered in the context of other information submitted by the Applicant and the publicly available literature, have provided a framework for evaluating the

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	acceptable range of the differences observed in the comparative analytical assessment. On that basis, the observed differences in sialylated species between CT-P43 and US-Stelara do not preclude a demonstration of highly similar or the establishment of the analytical component of the scientific bridge. Thus, CT-P43 is highly similar to US-Stelara.
β-galactosylation	Overall, CT-P43 contained a significantly lower level of total galactosylated glycans at 45.1 – 54.5% than U.S.-Stelara (61.6 – 71.0 %) and E.U.-Stelara SC (62.7 – 71.0%). However, when terminal unsialylated galactose is considered, CT-P43 contains a slightly higher level of terminal galactosylated glycans at 44.10 – 53.18% than U.S.-Stelara (40.94 – 43.71%) and E.U.-Stelara (41.32 – 43.16%). Terminal galactose in mAbs is associated with C1q binding and CDC activity (Boyd et al., 1995, Hodoniczky et al., 2005). However, there was no difference in C1q binding of the three products. In an agalactosylation study conducted by the Applicant, a reduction in total galactose content (mole of total galactose content to mole of total glycan) correlated to a reduction in Fc binding affinity to FcγRIIIa-V, FcγRIIIb, FcγRIIb and FcγRI (SPR), but had no impact on Fab functionality or binding affinity to FcRn (SPR), hIL-12 binding inhibition activity (CELISA) or hIL-12-mediated signaling inhibition activity (inhibition reporter assay). However, ustekinumab does not mediate effector function such as ADCC or CDC (Benson et al., 2011). Thus, the observed difference in galactosylated glycans is not expected to have an adverse effect on potency in vivo. In addition, recent studies¹ indicate that galactosylation may play a role in antibody clearance. Antibodies containing lower galactosylation are cleared more rapidly than those containing more galactosylation. There is currently no known bioactivity assay that can assess the impact of differences in galactosylation on the PK of mAbs. The results from the PK similarity study CT-P43 1.2, considered in the context of other information submitted by the Applicant and the publicly available literature, have provided a framework for evaluating the acceptable range of the differences observed in the comparative analytical assessment. On that basis, the observed differences in galactosylation

¹ Literature reference is made to the following two articles:

- i. David Falck et al. Glycoform-resolved pharmacokinetic studies in a rat model employing glycoengineered variants of a therapeutic monoclonal antibody. MABS 2020, VOL. 13, NO. 1, e1865596.
- ii. David Falck et al. Clearance of therapeutic antibody glycoforms after subcutaneous and intravenous injection in a porcine model. MABS 2022, VOL. 14, NO. 1, e2145929.

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	between CT-P43 and US-Stelara do not preclude a demonstration of highly similar or the establishment of the analytical component of the scientific bridge. Thus, CT-P43 is highly similar to US-Stelara.
α-galactosylation	Due to differences in the cell line used, CT-P43 does not have α-galactosylation, which is present in U.S.-Stelara and E.U.-Stelara. α-gal has been associated with increased safety risk such as immunogenicity. Lack of α-galactosylation in CT-P43 is not expected to impact safety risks as lack of α-galactosylation in CT-P43 is not expected to increase immunogenicity. Therefore, the difference in α-galactosylation in this case does not preclude a demonstration that CT-P43 is highly similar to U.S.-Stelara or establishment of the analytical component of the scientific bridge.
FcγRIIIa binding	CT-P43 has lower relative FcγRIIIa (V158) binding activity (min-max: 84 -99%) compared to U.S.-Stelara (min-max: 111 -131 %) and E.U.-Stelara (min-max: 113 -136 %). The results for all CT-P43 lots are below the lower bound of the U.S.- and E.U.- Stelara. Lower FcγRIIIa (V158) binding activity is not attributed to the level of afucosylated glycans in CT-P43 which is higher than both US-Stelara and EU-Stelara. The Applicant suggests the lower FcγRIIIa-V binding affinity of CT-P43 may be due to the lower level of total galactose content shown by oligosaccharide profiling based on an agalactosylation study conducted by the Applicant. FcγRIIIa binding could impact ADCC activity. Lack of ADCC and ADCP activity was demonstrated for CT-P43, U.S.-Stelara, and E.U.-Stelara. In addition, the Applicant provided data showing that CT-P43 and ustekinumab are unable to bind to IL-12 or IL-23 that is already bound to its receptor complexes, supporting that they are not likely to mediate Fc effector functions. Therefore, the lower FcγRIIIa (V158) binding activity for CT-P43 is not expected to have an increased risk for unexpected effector functions and therefore the difference is not expected to be clinically significant and does not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.
FcγRIIIb binding	CT-P43 shows slightly lower binding affinity to FcγRIIIb (min-max: 92 - 101%) compared to U.S.-Stelara (min-max:103 – 117%) and E.U.-Stelara (min-max:100 – 119%). This is consistent with the results for FcγRIIIa binding and was also justified to be due to differences in galatose content based on the Applicant's agalactosylation study. However, as discussed above, this lower binding affinity is not considered clinically meaningful because effector function has not been demonstrated to play a role in the efficacy or safety of ustekinumab and lack of ADCC and ADCP activity was demonstrated for CT-P43, U.S.-Stelara, and E.U.-Stelara. Therefore, the noted differences do not

Critical Quality Attributes with Differences	Related Critical Quality Attributes
Post-translational modifications (PTMs)	preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge. The peptide map analysis shows significantly lower C-terminal Lysine levels in CT-P43 (16.7 -32.9%) compared to U.S.-Stelara (44.2 – 52.1%), and E.U.-Stelara (39.9 – 50.8%). However, lower levels of C-terminal lysine are not considered clinically significant because they did not impact potency, which is similar for CT-P43, U.S.-Stelara, and E.U.-Stelara. In addition, C-lysine truncation occurs readily in vivo; therefore, the differences are not expected to impact PK and safety. For other PTMs that do not meet the min-max range similarity criteria, the differences between CT-P43 and U.S.-Stelara, CT-P43 and E.U.-Stelara, and or U.S Stelara and E.U.-Stelara are small (~≤1%) and the level of these PTMs in all three products is low (<1 – 5%). Therefore, the differences in C-terminal lysine and other PTMs do not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.
Charge Variants	The IEC-HPLC results for CT-P43, U.S.-Stelara, and E.U.-Stelara before enzymatic treatments show lower levels of acidic species and lower levels of basic species for CT-P43. CT-P43 contained ~ 9 – 17% lower level of acidic peaks, 12 – 32% higher level of main peak, and 0 – 23% lower level of basic species compared to U.S.-Stelara and E.U.-Stelara. The IEC-HPLC profiles for the three products following enzyme treatment using carboxypeptidase B (CPB) and α2-3,6,8 neuraminidase (sialidase) suggests the difference in charge variant profile and the ratio of acidic and basic variants between CT-P43 and U.S-Stelara and E.U.-Stelara are predominantly due to the lower level of variants with C-terminal lysine in CT-P43 which results in lower levels of basic peaks, and the high level of sialic acids residues in US-Stelara and EU- Stelara which result in higher levels of acidic peaks for US-Stelara and EU-Stelara. Characterization of enriched charge variant fractions supports the following: Enriched IEC-HPLC fractions of acidic peaks, main peak, and basic peaks from the three products contain the same PTMs (oxidation, isomerization, deamidation, Lysine C, etc.) at the same amino acid residues and similar levels, except for unprocessed C-terminal lysine and deamidation at HC Asn327 (<1%), which are addressed above. The observed differences do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	• Acidic peaks in all three products are enriched with sialylated glycan-containing species with biological activity similar to that of unfractionated material. The observed differences do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge as discussed above. This is also consistent with the results of the study CT-P43 1.2, in which PK similarity is demonstrated between CT-P43, U.S.-Stelara, and E.U.-Stelara (see BMER). • The basic peaks in all three products are enriched with unprocessed HC C-terminal lysine and high mannose glycan-containing species and show biological activity that is similar to the unfractionated material. As discussed above, the observed differences do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge. Overall, the data support that the differences in charge variants are not expected to have a clinically meaningful impact and therefore do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.
Size variants by SEC-HPLC, reduced CE-SDS and non-reduced CE-SDS	<u>Reduced CE-SDS:</u> Purity (HC+LC) of most CT-P43 lots trends slightly lower and HMW species and NGHC higher (by <1%) than U.S.-Stelara and E.U.-Stelara of similar age. However, the levels of impurities in all products are low (<1.3%). Overall, the data support similar levels and types of the different size variants in CT-P43, U.S.-Stelara, and E.U.-Stelara. Minor differences in purity (HC+LC), NGHC and HMW species levels, between CT-P43 and U.S.-Stelara, and between CT-P43 and E.U.-Stelara do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.

E. Same Strength(s)

CT-P43 has the same dosage form and routes of administration as US-Stelara. Celltrion is seeking approval of 90 mg/ mL and 45 mg/0.5 mL CT-P43 in a single-dose prefilled syringe (PFS) for the subcutaneous route of administration, and 130 mg/26 mL CT-P43 in a single dose vial for the intravenous route of administration as an interchangeable biosimilar to US-Stelara. US-Stelara is available in these strengths². Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical

² "U.S. Prescribing Information, US-licensed Stelara. Accessed June 26, 2024 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125261s163lbl.pdf"

assessment. The deliverable volume (mL) and fill weight data were assessed (b) (4)
(b) (4) Based on the comparative analytical assessment and manufacturing data, the proposed strengths of CT-P43 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US- Stelara. The strengths of CT-P43 90 mg/1.0 mL and 45 mg/0.5 mL in the PFS, and 130 mg/26 mL in the single dose vial are the same as those of US-Stelara.

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/s/

HAILIN WANG
09/27/2024 05:09:50 PM

FRANCES NAMUSWE
09/27/2024 05:29:01 PM

BLA Executive Summary

Assessment Date: June 25, 2024, 07/26/2024

1. Application/Product Information

BLA number	761338
Submission Type	Original Submission
Regulatory Pathway	351(k) BLA
Associated IND/BLA	IND 146085
Review Designation	Standard
Applicant	Celltrion Inc.
Indication	- 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
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Steqeyma
	Non-proprietary Name/Code Name: Ustekinumab-stba
	OBP Naming: MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [CT-P43]
Drug Product Description	Steqeyma (CT-P43, ustekinumab-stba) drug product is a sterile, preservative-free, clear to slight opalescent, colorless to pale yellow solution and may contain a few small translucent or white particles with pH 5.7 for subcutaneous injection or intravenous infusion. Steqeyma is a proposed biosimilar to US-licensed Stelara. Steqeyma for subcutaneous injection is supplied in a single-dose prefilled syringe (PFS) containing 45 mg or 90 mg of CT-P43 in 0.5 mL or 1 mL, respectively. The excipient concentrations of CT-P43 in the PFS are histidine and L-histidine hydrochloride monohydrate

	(1.27 mg/mL), polysorbate 80 (0.04 mg/mL), and sucrose (76 mg/mL). Steqeyma for intravenous infusion is supplied in a single-dose vial containing 130 mg of CT-P43 in 26 mL (5 mg/mL CT-P43), edetate disodium ((b) (4) mg), histidine (9.36 mg), L-histidine hydrochloride monohydrate (23.66 mg), methionine (10.56 mg), polysorbate 80 (10.37 mg) and sucrose (1976 mg). Ustekinumab- stba is a human immunoglobulin G1 kappa monoclonal antibody produced in CHO cells consisting of 1324 amino acids and an estimated molecular weight of 145 kDa. Ustekinumab is an antagonist of human interleukin 12 (IL-12) and interleukin 23 (IL-23) cytokines. It binds to the p40 subunit shared by IL-12 and IL-23 and prevents IL-12 and IL-23 from binding to their receptor.		
Dosage Form	Injection		
Strength	For subcutaneous injection: 90 mg/mL (90 mg/1.0 mL PFS, 45 mg/0.5 mL PFS) For intravenous infusion: 130 mg/26 mL (5 mg/1.0 mL) vial		
Route of Administration	- Subcutaneous injection - Intravenous infusion		
Primary Container Closure System	45 mg/0.5 mL and 90 mg/1 mL PFS: 1 mL Type (b) (4) glass syringe with a staked-in-place stainless steel needle and closed with a (b) (4) elastomeric plunger-stopper and an elastomeric needle shield (cap). 130 mg/26 mL vial: 30mL Type I glass vial closed with a 20 mm elastomeric stopper and flip-off seal		
Device Information	The PFS has a 27-gauge fixed ½ inch staked-in-place stainless steel needle and is assembled with a finger flange, plunger rod and fitted with a passive safety guard.		
Co-packaged Product Information	N/A		
	Discipline	Primary	Secondary
	Drug substance	Zhong Zhao	Hailin (Sheena) Wang
	Drug product		

OPQ Review Team	Comparative analytical assessment		
	Immunogenicity Assay	Sujin Hwang	Daniela Verthelyi
	Facility/ Microbiology	DS: Tony Hu	Madu Dharmasena
		DP: Jiangsong Jiang	Virginia Carroll
	RBPM	Melinda Bauerlien	
	ATL	Hailin (Sheena) Wang	
	Tertiary	Frances Namuswe	
OPQ Issued Consults	The final recommendation from CDRH is that the device safety feature of the combination product is acceptable. There are no PMC/PMR or CR deficiencies from CDRH.		

2. Recommendation and Conclusion on Approvability
Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761338 for Steqeyma manufactured by Celltrion Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Steqeyma is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Celltrion Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comments and Additional Comments (if applicable):

Product Quality Complete Response Comments:

- Following a CGMP inspection of Celltrion, Inc., Incheon, Korea (FEI 3005241015), listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your pending application, therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002 for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a PAI/PLI of the facility.

Satisfactory outcomes of both the PAI/PLI and the CGMP surveillance inspections will be needed prior to an approval of the application.

2. The bacterial retention study is inadequate (b) (4) for the CT-P43 IV drug product (5 mg/mL). (b) (4)
- Repeat the bacterial retention study of the (b) (4) for CT-P43 IV drug product vial (5 mg/mL).
3. The container closure integrity test (CCIT) dye ingress method used for stability testing of CT-P43 IV drug product vials is not validated to ensure reproducibility of results between different analysts. The validation summary for the dye ingress method in Table 3.2.P.5.3-59 includes results for sensitivity, specificity, and robustness, however the reproducibility of the visual detection method between different analysts is not addressed. According to FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics (2015), for non-compendial method, validation data are needed to support the reproducibility of the method. Provide evidence of the reproducibility of the visual inspection method to detect breach sizes at the limit of detection with multiple analysts. Alternatively, measure all samples by spectrophotometry and provide an updated method description with acceptance criteria and submit additional method validation data accordingly.
4. The proposed release and stability specification for clarity of (b) (4) (b) (4) for CT-P43 drug product (DP) [SCS] is not acceptable because it is not justified by your clinical and manufacturing experience. In your response to information request (IR), received on 05/13/2024, you proposed not to tighten this release and stability specification based on stability data under stress condition ($40\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$) for Lot No. 2NGP01 as justification. The proposed justification is not acceptable as it is not clinically relevant. Results from accelerated and stress conditions should not be used to support the release and long-term stability acceptance criteria. In addition, this specification is not supported by the updated full term (36 months) stability data from the primary stability (non-PPQ) batches provided in the same amendment in SN 0027, which consistently showed results are below (b) (4) NTU at all timepoints throughout the

product shelf life. Tighten the release and stability acceptance criteria for clarity for CT-P43 [SCS] DP based on the historical release and long-term stability results to ensure consistent quality of CT-P43 DP [SCS].

5. The proposed shelf-life limit of (b) (4) % for acidic peaks in CT-P43 PFS and Vial DP is not supported by your clinical and manufacturing experience. In the IR response received on 05/13/2024, you proposed not to tighten this shelf-life limit based on (b) (4). You described that the (b) (4) are associated with an (b) (4)

However, the proposed shelf-life limit does not reflect the clinical and manufacturing experience and is not supported by the updated full term stability results (all data points $\leq$ (b) (4) %). from the primary stability batches (non-PPQ) for both PFS and vial DP presentations provided in the same amendment in SN0027 Tighten the shelf-life acceptance criteria for acidic peaks based on long term stability data to ensure the consistent CT-P43 DP quality over the shelf-life.

Additional Product Quality non-CR Comments:

1. (b) (4)

(b) (4)

2. As indicated in the proposed labeling, individual pre-filled syringes or vials may be stored at room temperature up to 30 °C for a maximum single period of up to (b) (4) days in the carton. You provided the stability data under the accelerated 2 condition using representative DP lots to support the labeled in-use storage for CT-P43 at room temperature prior to administration or dilution. However, it appears end of shelf-life samples were not tested for in-use stability data under accelerated 2 condition. To ensure the in-use room temperature stability of CT-P43 PFS and vial DP, provide additional stability testing under the accelerated 2 condition using end of the shelf-life DP samples. In addition, to further support the in-use dilution stability of CT-P43 vial products and as recommended per ICH Q1A(R2), provide additional in-use stability testing of end of shelf-life DP vial samples after the maximum (b) (4) days room temperature storage.
3. We note that you only provided in-use compatibility study with polypropylene IV bag. If you intend for the product to be used with other common bags such as polyolefin or PVC, we recommend studies to support those.
4. The information for some responses in Section 1.11.1 in SN 0027 received on 05/13/2024 was incomplete and/or inaccurate. For example, response to information request 4 was not submitted while response to information request 2 was submitted twice in Quality Information Amendment 2 and 4. Revise the quality information amendment to provide accurate and complete responses to the quality information request dated 05/03/2024 in your BLA re-submission.
5. The sensitivity of the dye ingress method used to demonstrate container closure integrity (CCI) (b) (4) is unclear. Additional information is needed to confirm that the (b) (4) parameters will result in integral vials. The method description in section 3.2.P.2.5.4 states that (b) (4)

(b) (4)

If not, provide

additional CCI test results from vials (b) (4) The method used during (b) (4) should be demonstrated to be sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns).

6.

(b) (4)

7. The acceptance criteria for the post-use integrity test (b) (4) for 5 mg/mL CT-P43 IV drug product listed in section 3.2.P.3.4 are based on the (b) (4) Update section 3.2.P.3.4 with the (b) (4) (b) (4) prior to integrity testing, as (b) (4) product could impact results of the test. The post-use integrity test result should be accurate to support sterility assurance of the product.

8. The sterilization validation summary for stoppers used for CT-P43 IV drug product vial does not specify the actual sterilization parameters used during the studies. The sterilization validation parameters are needed to ensure that a sterility assurance level of 10^{-6} is demonstrated for the stoppers. (b) (4)

(b) (4)

9. It is unclear whether the depyrogenation/sterilization validation studies for glass vials were designed to evaluate the worst-case locations in the (b) (4)

(b) (4)

(b) (4)

10. Additional (b) (4) results to validate the (b) (4) for CT-P43 IV drug product at (b) (4) were planned to be submitted by June 25, 2024, however these results were not reviewed. In the resubmission, provide summary data from at least one (b) (4) run with the container closure system of CT-P43 IV drug product to support validation of the (b) (4)

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(b) (4)

4. Basis for Recommendation

a. Summary:

CT-P43 is a recombinant human IgG1 directed against the shared p40 subunit of IL-23 and IL-12 cytokines. It is a proposed interchangeable biosimilar to US-Stelara for the same indications as US-Stelara including moderate to severe PsO, PsA, CD and UC. Ustekinumab binds to the p40 subunits of IL-12 and IL-23, blocking IL-12 and IL-23 from binding to the shared IL-12 receptor subunit beta 1; thereby, disrupting IL-12 and IL-23 mediated signaling events and cytokine cascades. Potency of CT-P43 is controlled using a cell-based assay that monitors inhibition of IL-12 mediated signaling during drug substance (DS) and drug product (DP) release and stability testing. Ustekinumab binds to the shared P40 subunit of IL-12 or IL-23 and is unable to bind to the IL-12 or IL-23 molecule already bound to its receptor complex, and thus is not likely to mediate Fc effector functions.

The totality of the evidence from the comparative analytical assessment supports that CT-P43 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. Celltrion adequately established a three-way scientific bridge between CT-P43, US-Stelara, and EU-Stelara to

support the relevance of the data generated from studies using EU-Stelara as a comparator in the assessment of biosimilarity. The strengths of CT-P43 45 mg/0.5mL and 90 mg/mL in the single-dose PFS for subcutaneous infusion and 130mg/26mL (5mg/mL) in a single-dose vial for intravenous infusion are the same as those of US-Stelara in the same presentations and routes of administration. The Applicant plans to develop the 45 mg/0.5 mL in a single-dose vial presentation for the subcutaneous injection, which is also approved for US-Stelara, post-marketing. Refer to Appendix for detailed summary of the comparative analytical assessment.

The CT-P43 DS manufacturing process consists of

(b) (4)

(b) (4)

OPQ identified multiple product quality deficiencies during the review of Module 3 of BLA 761338. The data and information provided do not support that the manufacture and testing of CT-P43 is well controlled and will lead to a product that is safe, pure, and potent for duration of the shelf-life.

As indicated in the CR comments above, there is inadequate control of PFS and Vial DP, and insufficient information to support the sterility assurance of the CT-P43 DP in the vial presentation. Other product quality deficiencies include insufficient data to support the in-use stability of CT-P43 Vial DP and inadequate control of reference standard. As these deficiencies were not resolved during this review cycle, a CR action is recommended for this BLA.

In addition, GMP issues that impact this BLA were identified for the DS and PFS DP manufacturing site at CELLTRION, Inc. FEI:3005241015 when the site was inspected in a combined pre-license inspection for a different BLA and surveillance inspection. There are significant, outstanding manufacturing risks that prevent approval of this application, and the facility recommendation is

withhold approval. Satisfactory resolution of the inspectional deficiencies cited during the recent FDA inspection at Celltrion, Inc. is required before this application may be approved. Therefore, the unacceptable status of the facility is considered a deficiency and will be communicated in the CR letter.

CDRH final recommendation is the needle safety device of the PFS combination product is approvable.

Overall, the information and data submitted in this application are not adequate to support a conclusion that the manufacture of CT-P43 DS and DP is well-controlled and will lead to a product that is safe, pure, and potent. Therefore, from an OPQ perspective, this BLA is not recommended for approval in its present form until the above-mentioned quality deficiencies are satisfactorily resolved.

b. Subdiscipline Recommendation:

Drug Substance	-	Inadequate
Drug Product	-	Inadequate
Immunogenicity Assay	-	Adequate
Facilities	-	Inadequate
Microbiology	-	Inadequate

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the Applicant and deemed acceptable.

d. Potency Assessment for Labeling:

Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations

Not applicable as OPQ does not recommend approval of this application.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Appendix

II. Evaluation of the Comparative Analytical Assessment

A. Overview and Conclusions

Celltrion is seeking licensure of CT-P43 as an interchangeable biosimilar to U.S.-licensed Stelara (referred to hereafter as US-Stelara) for these strengths and presentations: 90 mg/1.0 mL (90 mg/mL) and 45 mg/0.5 mL (90 mg/mL) in a single-dose prefilled syringe (PFS) with safety guard for subcutaneous injection, and 130 mg/26 mL (5 mg/mL) in a single-dose vial for intravenous infusion. These are the same strengths currently available for US-Stelara.

To support a demonstration that CT-P43 is highly similar to US-Stelara and establish the analytical component of the scientific bridge, Celltrion performed a three-way comparative analytical assessment (CAA). The first sub-study compared the PFS presentations based on the following data:

- 10 lots of US-Stelara (7 lots of 45 mg/0.5 mL PFS, 3 lots of 90 mg/1.0 mL PFS) with expiration dates ranging from April 2023 through September 2024;
- 10 lots of E.U.-approved-Stelara (EU-Stelara) (8 lots of 45 mg/0.5 mL PFS, 2 lots of 90 mg/1.0 mL PFS) with expiration dates ranging from March 2023 through October 2024;
- 6 lots of CT-P43 PFS drug product (DP) (4 lots of 45 mg/0.5 mL PFS, 2 lots of 90 mg/1.0 mL PFS,) manufactured between April 2020 and May 2022 from 6 independent CT-P43 DS lots.
- For several assays not expected to be impacted by the DP manufacturing process, independent CT-P43 drug substance (DS) lots were included in the CAA if a DP lot manufactured from that DS lot was not available at the time of the assessment. Up to 4 DS lots manufactured between January 2020 and August 2021 were used in the final CAA.

In addition, Celltrion also performed a second comparative analytical assessment sub-study between CT-P43 and US-Stelara for the 130 mg/26 mL vial using the following:

- 6 lots of US-Stelara (130 mg/26 mL vial) with expiration dates ranging from June 2023 through July 2025. For assessment of protein concentration only, an additional 5 lots of US-Stelara were used for a total of 11 lots.
- 6 lots of CT-P43 130 mg/26 mL vial DP manufactured between December 2020 and April 2023 from the same 6 independent CT-P43 DS lots also used for in the manufacturing of 6 CT-P43 PFS drug product lots already included in the above CAA sub-study.

The DP lots used in clinical studies and the CT-P43 PPQ lots for all strengths are included in the CAA. The ages of US-Stelara and EU-Stelara at the time of testing were adequate to capture potential differences or variability over time for US-Stelara and EU-Stelara.

The CAA included comparison of physicochemical and functional quality attributes (QAs) of CT-P43, US-Stelara and EU-Stelara using orthogonal methods, as well as

comparison of their degradation profiles under forced degradation conditions. The CAA included a 3-way comparative assessment between the PFS presentations only since this presentation was used in the clinical studies and 2-way comparative assessment between the 130 mg/26 mL vials with the same methods. In addition, the Applicant conducted a comparability assessment between CT-P43 45 mg/0.5 mL SC PFS and CT-P43 IV 130 mg/26 mL vial DP and the data support that these are analytically comparable. Results from method validation or qualification studies support the suitability of the methods used in the analytical assessment. The Applicant used a criticality-based data analysis approach to evaluate the analytical results that was consistent with FDA recommendations. The approach included the following: QAs amenable to statistical analysis were compared to quality ranges (QRs) of mean $\pm$ 2 (very high criticality) or 3 (high and moderate criticality) * standard deviations (SD)) established from US-Stelara and EU-Stelara. In addition, for certain low criticality attributes, results are evaluated against the min-max ranges of US-Stelara and EU-Stelara to support similarity. If a result exceeded the min-max range, the magnitude and the criticality of the observed differences were discussed and justified. QAs not amenable to quantitative analysis or otherwise justified were analyzed by a qualitative comparison (e.g. visual comparison,). DP vial samples used in the 2-way CAA sub-study included non-independent DS lots from those used in the 3-way CAA sub-study; however quality attributes that could be impacted by the DP manufacturing process and difference in formulation were assessed using an adequate number of DP lots.

For the comparative stability studies, the Applicant conducted studies under forced degradation conditions (thermal stress at 55°C for up to 6 days, photo stress, oxidation and hydrolytic degradation). The comparative forced degradation studies show similar degradation pathways and degradation rate among CT-P43, US-Stelara and EU-Stelara.

Our assessment of the CT-P43 and US-Stelara comparative analytical data supports the determination that CT-P43 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. CT-P43 has the same strengths, dosage form and routes of administration as US-Stelara. The Applicant used a comprehensive set of analytical methods that were suitable to evaluate the critical quality attributes of CT-P43 and US-Stelara to support the demonstration that the products are highly similar. The number of lots tested and data analysis approaches used were appropriate or justified as needed to allow for a meaningful evaluation of the results of the analytical studies. The differences observed in a subset of the quality attributes do not preclude a determination that CT-P43 and US-Stelara are highly similar.

In addition, Celltrion used three-way pairwise comparisons of CT-P43, US-Stelara, and EU-Stelara to establish the analytical component of the scientific bridge between CT-P43, US-Stelara, and EU-Stelara to support the relevance of the data generated from clinical studies using EU-Stelara as the comparator in the assessment of biosimilarity. Our assessment of the data supports that the Applicant established the analytical component of the scientific bridge between CT-P43, US-Stelara, and EU-Stelara, using

the same methods and statistical approaches used to evaluate that CT-P43 is highly similar to US-Stelara. This supports the relevance of the data generated from clinical studies using EU-Stelara as the comparator for the assessment of biosimilarity.

B. Comparative Analytical Results

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Primary Structure	Amino acid sequence	Yes	Yes
	Intact molecular weight	Yes	Yes
	Reduced and deglycosylated mass of HC and LC	Yes	Yes
Post Translational Modifications	Methionine Oxidation	Yes	Yes
	Deamidation	Yes	Yes
	HC and LC Glycation	Yes	Yes
	Isomerization	Yes	Yes
	C-terminal Lys truncation	Yes	Yes
Purity and impurities	Size variants by SEC-HPLC	Yes	Yes
	Size variants by SEC-MALS		
	Size variants by SV-AUC	Yes	Yes
	Size variants by reduced CE-SDS	Yes	Yes
	Size variants by non-reduced CE-SDS	Yes	Yes
	Non-glycosylated HC	Yes	Yes
	Charge variants by IEC-HPLC	Yes	Yes
	Charge variants by IEC-HPLC	Yes	Yes
Glycosylation	Glycan map	Yes	Yes
	Afucosylation	Yes	Yes
	High Mannose	Yes	Yes
	β-Galactosylation	Yes	Yes
	α-Galactosylation	Yes	Yes
	Sialylation: levels and types (NANA, NGNA)	Yes	Yes
	Other glycans G0F, G1F, G2F	Yes	Yes
High Order Structure	Disulfide structure	Yes	Yes
	Free thiols	Yes	Yes
	Secondary structure FTIR and far UV spectra	Yes	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Biological activities	Tertiary Structure by near UV spectra	Yes	yes
	Tertiary structure by DSC	Yes	Yes
	Inhibition of IL-23 mediated STAT signaling	Yes	Yes
	Inhibition of IL-12 mediated STAT signaling	Yes	Yes
	Inhibition of binding of IL-23 to receptor IL-12R β 1	Yes	Yes
	Inhibition of binding of IL-12 to receptor IL-12R β 1	Yes	Yes
	IL-12/IL-23 p40 binding assay	Yes	Yes
Bioactivity – Fc mediated	-Inhibition of IL-23-induced and IL-12 induced IFN- γ release in PBMCs from a healthy donor; - Inhibition of IL-23-induced IL-17A secretion in PBMCs from a health donor.	Yes	Yes
	Lack of Antibody-dependent cell-mediated cytotoxicity (ADCC)	Yes	Yes
	Lack of Complement-dependent cytotoxicity (CDC)	Yes	Yes
	FcRn binding	Yes	Yes
	Fc γ RI binding	Yes	Yes
	Fc γ RIIa binding	Yes	Yes
	Fc γ RIIb binding	Yes	Yes
	Fc γ RIIIa (V158) binding	Yes	Yes
	Fc γ RIIIb binding	Yes	Yes
Drug Product Attributes	C1q binding	Yes	Yes
	Protein concentration	Yes	Yes
Forced degradation studies	Thermal Stress	Yes	Yes
	Photo degradation	Yes	Yes
	Chemical oxidation	Yes	Yes
	Hydrolytic degradation	Yes	Yes

C. Analytical Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

The clinical development of CT-P43 included three completed clinical studies that compared CT-P43 to US-Stelara and/or EU-Stelara.

- Study CT-P43 1.1 (comparative pharmacokinetics study not considered in support of biosimilarity. Refer to BMER for additional information on this PK study): A 2-part, randomized, double-blind, parallel-group, single-dose, PK similarity study to compare the pharmacokinetics, safety and immunogenicity of subcutaneously-administered CT-P43, US-Stelara and EU- Stelara in healthy male subjects.
- Study CT-P43 1.2 (comparative pharmacokinetics study): A randomized, double blind, parallel-group, single-dose PK similarity study to compare the pharmacokinetics, safety and immunogenicity of subcutaneously-administered CT-P43, US-Stelara and EU-Stelara in healthy Japanese male subjects
- Study CT-P43 3.1 (comparative efficacy and safety study): A randomized, active-controlled, double-blind comparative clinical study to compare the efficacy and safety of CT-P43 to EU-Stelara in patients with moderate to severe plaque psoriasis

To establish the analytical component of the scientific bridge to support the relevance of the clinical comparative data generated using EU-Stelara as a comparator product, Celltrion performed a three-way analytical assessment comparing CT-P43, US-Stelara, and EU-Stelara using a comprehensive set of analytical methods. The same analytical methods used for the assessment of highly similar between CT-P43 and US-Stelara were used for comparison of CT-P43 and EU-Stelara and EU-Stelara and US-Stelara. The differences observed in a subset of quality attributes in the comparative analytical studies (See section D below) do not preclude a determination that the analytical component of the scientific bridge is established.

D. Assessment of Comparative Analytical Study Results

Comparative analytical assessment criteria were met for all attributes evaluated with the following exceptions:

Critical Quality Attributes with Differences	Related Critical Quality Attributes
Glycosylation – Overall glycan map	The glycan map profiles show that several types of glycans are present among CT-P43, U.S.-Stelara, and E.U.-Stelara; however, there are several differences due to additional, missing, and different levels of glycan species in CT-P43 compared to U.S.-Stelara, and E.U.-Stelara. These differences can be attributed to different cell lines used in manufacturing. For example, some of the differences are due to the

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	presence of NANA-containing glycans in CT-P43 and NGNA-containing glycans in U.S.-Stelara and E.U.-Stelara, as a result of the different cell lines. However, these differences do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge as addressed below in the subsequent rows of this table for each glycan species with noted differences.
Afucosylation	The afucosylation levels in all 10 CT-P43 lots in the 3-way CAA sub-study (min-max: 3.33 – 4.27%) are higher and outside the quality range of both U.S.-Stelara (QR: 2.36 - 3.24%) and E.U.-Stelara (QR: 1.83 – 3.05%). The same trend where a higher level was observed in CT-P43 lots in the 2-way CAA sub-study was observed (and expected given this attribute is not expected to differ between the strengths or presentations). Afucosylated species may impact binding to Fcγ receptors, such as FcγRIIIa. A higher level of afucosylated glycans might result in increased Fc-mediated activities such as ADCC; however, no corresponding difference in Fcγ receptor binding was observed between the three products, suggesting that the magnitude of the difference observed was unlikely to translate into a meaningful difference in biological activity. Further, ustekinumab is not known to have effector function and the Applicant provided data showing that all three products lack effector function. Therefore, slight differences in attributes that can impact Fc-mediated functions are not expected to be meaningful. Given the foregoing, the noted differences are not expected to have a clinically meaningful impact. The observed differences in afucosylation do not preclude the demonstration that CT-P43 is highly similar to U.S.-Stelara or the establishment of the analytical component of the scientific bridge.
High Mannose	A higher level of high mannose (min-max: 2.17 – 3.19%) is observed in CT-P43 compared to U.S.-Stelara (QR: 0.98 -1.31%) and E.U.-Stelara (QR: 0.98 -1.35%) in the 3-way CAA. The same trend with a higher level of high mannose in CT-P43 DP lots was observed in the 2-way CAA sub-study (and expected given this attribute is not expected to differ between the strengths or presentations). The levels of all 10 CT-P43 SC lots are above the QRs of both U.S.-Stelara and E.U.-Stelara. High mannose may potentially impact the PK. In addition, high mannose species are a subset of afucosylated species and could impact ADCC activity. However, the increased high mannose in CT-P43 did not result in increased FcγRIIIa binding activity because CT-P43 has slightly lower FcγRIIIa binding activity and no ADCC activity. In addition, removal of high mannose from the three products by mannosidase treatment conducted by the Applicant did not impact biological activities (FcγRIIIa-V binding affinity, FcRn binding affinity, hIL-12 binding inhibition activity (CELISA) or hIL-12-mediated signaling inhibition activity (reporter

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	assay)) of these products in vitro. These data suggest that the < 2% higher level of high mannose glycans in CT-P43 should not impact these biological activities. Regarding the potential impact on PK, it is known that high mannose glycans of therapeutic monoclonal antibodies can increase serum clearance in human. Scientific literature also indicates that up to 5% difference in high mannose glycan differences does not significantly impact clearance of monoclonal antibodies [Goetze A.M. et al. Glycobiology, 21(7), 949–959; Welch J. et. al. Clinical Pharmacology & Therapeutics, 2022, 113(5), 1003-1010]. Therefore, the observed differences in high mannose do not preclude the demonstration that CT-P43 is highly similar to U.S.-Stelara or the establishment of the analytical component of the scientific bridge.
Sialylation	CT-P43 contains NANA-sialylation, consistent with sialylated glycans found in human glycoproteins, while US-Stelara and EU-Stelara contain non-human NGNA-sialylation. Non-human glycans could be associated with potential hypersensitivity. Therefore, change from the non-human to the human glycan form should not adversely impact the safety profile of CT-P43. In addition, NANA was detected in CT-P43 at a much lower level (1.00 – 1.35%) as compared to the combined NGNA levels detected in US-Stelara SC (20.29 – 29.11%) and EU-Stelara SC (20.48 – 28.40%). A potential role of sialylation in the biological activities of mAbs has been suggested. However, removal of sialic acid from the three products by sialidase treatment conducted by the Applicant did not result in differences in the biological activities (FcγRIIIa-V binding affinity, FcRn binding affinity, hIL-12 binding inhibition activity (CELISA) or hIL-12-mediated signaling inhibition activity (reporter assay)) of the three products in-vitro. These data suggest that the observed differences in the type and level of observed sialylated species should not impact these biological activities. Differences in sialylation could also influence the serum half-life of therapeutic proteins; for example, therapeutic proteins containing less sialylation could be cleared more rapidly through the asialoglycoprotein receptors than those containing more sialylation. However, a definitive role of sialylation in Fc region on serum PK for mAbs remains to be understood. There is currently no known bioactivity assay that can assess the impact of differences in sialylation on the PK of mAbs. The results from the PK similarity study CT-P43 1.2, considered in the context of other information submitted by the Applicant and the publicly available literature, have provided a framework for evaluating the

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	acceptable range of the differences observed in the comparative analytical assessment. On that basis, the observed differences in sialylated species between CT-P43 and US-Stelara do not preclude a demonstration of highly similar or the establishment of the analytical component of the scientific bridge. Thus, CT-P43 is highly similar to US-Stelara.
β-galactosylation	Overall, CT-P43 contained a significantly lower level of total galactosylated glycans at 45.1 – 54.5% than U.S.-Stelara (61.6 – 71.0 %) and E.U.-Stelara SC (62.7 – 71.0%). However, when terminal unsialylated galactose is considered, CT-P43 contains a slightly higher level of terminal galactosylated glycans at 44.10 – 53.18% than U.S.-Stelara (40.94 – 43.71%) and E.U.-Stelara (41.32 – 43.16%). Terminal galactose in mAbs is associated with C1q binding and CDC activity (Boyd et al., 1995, Hodoniczky et al., 2005). However, there was no difference in C1q binding of the three products. In an agalactosylation study conducted by the Applicant, a reduction in total galactose content (mole of total galactose content to mole of total glycan) correlated to a reduction in Fc binding affinity to FcγRIIIa-V, FcγRIIIb, FcγRIIb and FcγRI (SPR), but had no impact on Fab functionality or binding affinity to FcRn (SPR), hIL-12 binding inhibition activity (CELISA) or hIL-12-mediated signaling inhibition activity (inhibition reporter assay). However, ustekinumab does not mediate effector function such as ADCC or CDC (Benson et al., 2011). Thus, the observed difference in galactosylated glycans is not expected to have an adverse effect on potency in vivo. In addition, recent studies¹ indicate that galactosylation may play a role in antibody clearance. Antibodies containing lower galactosylation are cleared more rapidly than those containing more galactosylation. There is currently no known bioactivity assay that can assess the impact of differences in galactosylation on the PK of mAbs. The results from the PK similarity study CT-P43 1.2, considered in the context of other information submitted by the Applicant and the publicly available literature, have provided a framework for evaluating the acceptable range of the differences observed in the comparative analytical assessment. On that basis, the observed differences in galactosylation

¹ Literature reference is made to the following two articles:

- i. David Falck et al. Glycoform-resolved pharmacokinetic studies in a rat model employing glycoengineered variants of a therapeutic monoclonal antibody. MABS 2020, VOL. 13, NO. 1, e1865596.
- ii. David Falck et al. Clearance of therapeutic antibody glycoforms after subcutaneous and intravenous injection in a porcine model. MABS 2022, VOL. 14, NO. 1, e2145929.

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	between CT-P43 and US-Stelara do not preclude a demonstration of highly similar or the establishment of the analytical component of the scientific bridge. Thus, CT-P43 is highly similar to US-Stelara.
α-galactosylation	Due to differences in the cell line used, CT-P43 does not have α-galactosylation, which is present in U.S.-Stelara and E.U.-Stelara. α-gal has been associated with increased safety risk such as immunogenicity. Lack of α-galactosylation in CT-P43 is not expected to impact safety risks as lack of α-galactosylation in CT-P43 is not expected to increase immunogenicity. Therefore, the difference in α-galactosylation in this case does not preclude a demonstration that CT-P43 is highly similar to U.S.-Stelara or establishment of the analytical component of the scientific bridge.
FcγRIIIa binding	CT-P43 has lower relative FcγRIIIa (V158) binding activity (min-max: 84 -99%) compared to U.S.-Stelara (min-max: 111 -131 %) and E.U.-Stelara (min-max: 113 -136 %). The results for all CT-P43 lots are below the lower bound of the U.S.- and E.U.- Stelara. Lower FcγRIIIa (V158) binding activity is not attributed to the level of afucosylated glycans in CT-P43 which is higher than both US-Stelara and EU-Stelara. The Applicant suggests the lower FcγRIIIa-V binding affinity of CT-P43 may be due to the lower level of total galactose content shown by oligosaccharide profiling based on an agalactosylation study conducted by the Applicant. FcγRIIIa binding could impact ADCC activity. Lack of ADCC and ADCP activity was demonstrated for CT-P43, U.S.-Stelara, and E.U.-Stelara. In addition, the Applicant provided data showing that CT-P43 and ustekinumab are unable to bind to IL-12 or IL-23 that is already bound to its receptor complexes, supporting that they are not likely to mediate Fc effector functions. Therefore, the lower FcγRIIIa (V158) binding activity for CT-P43 is not expected to have an increased risk for unexpected effector functions and therefore the difference is not expected to be clinically significant and does not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.
FcγRIIIb binding	CT-P43 shows slightly lower binding affinity to FcγRIIIb (min-max: 92 - 101%) compared to U.S.-Stelara (min-max:103 – 117%) and E.U.-Stelara (min-max:100 – 119%). This is consistent with the results for FcγRIIIa binding and was also justified to be due to differences in galatose content based on the Applicant's agalactosylation study. However, as discussed above, this lower binding affinity is not considered clinically meaningful because effector function has not been demonstrated to play a role in the efficacy or safety of ustekinumab and lack of ADCC and ADCP activity was demonstrated for CT-P43, U.S.-Stelara, and E.U.-Stelara. Therefore, the noted differences do not

Critical Quality Attributes with Differences	Related Critical Quality Attributes
Post-translational modifications (PTMs)	preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge. The peptide map analysis shows significantly lower C-terminal Lysine levels in CT-P43 (16.7 -32.9%) compared to U.S.-Stelara (44.2 – 52.1%), and E.U.-Stelara (39.9 – 50.8%). However, lower levels of C-terminal lysine are not considered clinically significant because they did not impact potency, which is similar for CT-P43, U.S.-Stelara, and E.U.-Stelara. In addition, C-lysine truncation occurs readily in vivo; therefore, the differences are not expected to impact PK and safety. For other PTMs that do not meet the min-max range similarity criteria, the differences between CT-P43 and U.S.-Stelara, CT-P43 and E.U.-Stelara, and or U.S Stelara and E.U.-Stelara are small (~≤1%) and the level of these PTMs in all three products is low (<1 – 5%). Therefore, the differences in C-terminal lysine and other PTMs do not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.
Charge Variants	The IEC-HPLC results for CT-P43, U.S.-Stelara, and E.U.-Stelara before enzymatic treatments show lower levels of acidic species and lower levels of basic species for CT-P43. CT-P43 contained ~ 9 – 17% lower level of acidic peaks, 12 – 32% higher level of main peak, and 0 – 23% lower level of basic species compared to U.S.-Stelara and E.U.-Stelara. The IEC-HPLC profiles for the three products following enzyme treatment using carboxypeptidase B (CPB) and α2-3,6,8 neuraminidase (sialidase) suggests the difference in charge variant profile and the ratio of acidic and basic variants between CT-P43 and U.S-Stelara and E.U.-Stelara are predominantly due to the lower level of variants with C-terminal lysine in CT-P43 which results in lower levels of basic peaks, and the high level of sialic acids residues in US-Stelara and EU- Stelara which result in higher levels of acidic peaks for US-Stelara and EU-Stelara. Characterization of enriched charge variant fractions supports the following: Enriched IEC-HPLC fractions of acidic peaks, main peak, and basic peaks from the three products contain the same PTMs (oxidation, isomerization, deamidation, Lysine C, etc.) at the same amino acid residues and similar levels, except for unprocessed C-terminal lysine and deamidation at HC Asn327 (<1%), which are addressed above. The observed differences do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	• Acidic peaks in all three products are enriched with sialylated glycan-containing species with biological activity similar to that of unfractionated material. The observed differences do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge as discussed above. This is also consistent with the results of the study CT-P43 1.2, in which PK similarity is demonstrated between CT-P43, U.S.-Stelara, and E.U.-Stelara (see BMER). • The basic peaks in all three products are enriched with unprocessed HC C-terminal lysine and high mannose glycan-containing species and show biological activity that is similar to the unfractionated material. As discussed above, the observed differences do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge. Overall, the data support that the differences in charge variants are not expected to have a clinically meaningful impact and therefore do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.
Size variants by SEC-HPLC, reduced CE-SDS and non-reduced CE-SDS	<u>Reduced CE-SDS:</u> Purity (HC+LC) of most CT-P43 lots trends slightly lower and HMW species and NGHC higher (by <1%) than U.S.-Stelara and E.U.-Stelara of similar age. However, the levels of impurities in all products are low (<1.3%). Overall, the data support similar levels and types of the different size variants in CT-P43, U.S.-Stelara, and E.U.-Stelara. Minor differences in purity (HC+LC), NGHC and HMW species levels, between CT-P43 and U.S.-Stelara, and between CT-P43 and E.U.-Stelara do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.

E. Same Strength(s)

CT-P43 has the same dosage form and routes of administration as US-Stelara. Celltrion is seeking approval of 90 mg/ mL and 45 mg/0.5 mL CT-P43 in a single-dose prefilled syringe (PFS) for the subcutaneous route of administration, and 130 mg/26 mL CT-P43 in a single dose vial for the intravenous route of administration as an interchangeable biosimilar to US-Stelara. US-Stelara is available in these strengths². Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical

² "U.S. Prescribing Information, US-licensed Stelara. Accessed June 26, 2024 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125261s163lbl.pdf"

assessment. The deliverable volume (mL) and fill weight data were assessed (b) (4)
(b) (4) Based on the comparative analytical assessment and manufacturing data, the proposed strengths of CT-P43 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US- Stelara. The strengths of CT-P43 90 mg/1.0 mL and 45 mg/0.5 mL in the PFS, and 130 mg/26 mL in the single dose vial are the same as those of US-Stelara.

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