CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761373Orig2s000
761425Orig2s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 06/04/2024

1. Application/Product Information

BLA number	761425
Submission Type	Original Submission
Regulatory Pathway	351(k)
Associated IND/BLA	IND136959
Review Designation	Standard
Applicant	Samsung Bioepis Co., Ltd.
Indication	Pyzchiva (ustekinumab-ttwe) injection is indicated for adult and pediatric patients 6 years and older with moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy, adult and pediatric patients 6 years and older with active psoriatic arthritis (PsA), adult patients with moderately to severely active Crohn's disease (CD), and adult patients with moderately to severely active ulcerative colitis.
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** Pyzchiva
	Non-proprietary Name/Code Name: Ustekinumab-ttwe injection/SB17
	OBP Naming: BsMAB: MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [SB17]
Drug Product Description	SB17 is a fully human immunoglobulin G1 (IgG1) kappa monoclonal antibody (mAb) produced in a mammalian cell line (b) (4) SB17 is a human interleukin (IL)-12 and IL-23 antagonist that binds to the shared p40 subunit of human cytokines IL-12 and IL-23 and prevents

	IL-12 and IL-23 from binding to their receptor. Samsung Bioepis proposed SB17 injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable with US-licensed Stelara injection 130 mg/26 mL single -dose vial for intravenous use. SB17 drug product (DP) is a preservative-free solution formulated at pH (b) (4) and provided as solution in a single-dose vial (130mg/26mL) for intravenous (IV) administration after dilution in 0.9% or 0.45% saline. The formulation contains 130 mg SB17, 20(b) (4) mg histidine, 27(b) (4) mg histidine hydrochloride monohydrate, 10.4 mg methionine, (b) (4), 10.4 mg polysorbate 80, and 2210 mg sucrose (b) (4)
Dosage Form	Liquid
Strength	130mg/26 mL concentrate in a single-dose vial for use after dilution in commercially available 0.9% or 0.45% saline.
Route of Administration	Intravenous infusion
Primary Container Closure System	30mL Type I clear glass vial with 20 mm (b) (4) rubber stoppers and a 20 mm aluminum seal with a flip-off cap.
Device Information	None
Co-packaged Product Information	None

	Discipline	**Primary**	**Secondary**
	Drug substance Drug product Immunogenicity Assay	Gunther Boekhoudt (OPQ/OBP/DBRR IV)	Samuel Mindaye (OPQ/OBP/DBRR IV)

OPQ Review Team	Facility	Chani Broner (Drug product) Ekaterina Allen (Drug substance)	Zhong Li (CDER/OPQ/OPMA/DBM)
	Microbiology	Chani Broner (Drug product) Ekaterina Allen (Drug substance)	Maxwell Van Tassel (CDER/OPQ/OPMA),
	RBPM	Kristine Leahy (OPQ/OPRO)	
	ATL	Samuel Mindaye (OPQ/OBP/DBRR IV)	
OPQ Issued Consults	None		

Submissions Assessed:

Submission	**Date received**	**Assessment Completed (yes or no):**
761425/EDR0001 Original	January 29, 2024	Original
761425/EDR0008 Response IR1	May 09, 2024	OPQAIII and OPMA
761425/EDR0010 Response IR2	May 28, 2023	OPMA

Regulatory history: In BLA 761425, Samsung is seeking licensure for Pyzchiva (ustekinumab-ttwe) injection 130 mg/26 mL single-dose vial for intravenous use as interchangeable with Stelara (ustekinumab) injection 130 mg/26 mL single-dose vial for intravenous use in accordance with Section 351(k) pathway of the Public Health Service (PHS) Act. Samsung initially submitted BLA 761373 on Mar 30, 2023 for licensure of Pyzchiva (45 mg/0.5 mL PFS, 90 mg/mL PFS, and 130 mg/26mL vial presentations). Later, the applicant submitted BLA 761425 to separate the 130mg vial DP information from the initial BLA 761373 submission. In the current BLA 761425, Samsung submitted the same information provided in Section 3.2.P and Section 3.2.R of the initial BLA 761373. As the vial and PFS DP are developed from the common drug substance, cross-reference to the BLA761373 package is made and no DS information is provided in

BLA761425. Furthermore, since all the chemistry, manufacturing, and control (CMC) information provided in BLA 761373 package (PFS and vial presentations) had been reviewed by the Agency (Executive Summary uploaded in DARRTS on January 12, 2024 and CMC Assessment memorandum uploaded to Panorama on November 30, 2023), the current memo references the previous Executive Summary and memorandum for additional details on the DS and DP manufacturing processes, manufacturing process controls, comparative analytical assessment (CAA), and immunogenicity assays.

2. Recommendation and Conclusion on Approvability

Recommendation: Approval

The Office of Pharmaceutical Quality recommends approval of BLA 761425 for Pyzchiva manufactured by Samsung Bioepis Co., Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of Pyzchiva is well-controlled and leads to a product that is safe, pure, and potent. The comparative analytical data support a demonstration that Pyzchiva 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:** (b) (4)
- **Drug Product:** (b) (4)

b. Fill size and dosage form: Pyzchiva is provided in a single-dose vial 130mg/26mL for IV injection after dilution in commercially available 0.9% or 0.45% normal saline.

c. Dating Period:

- **SB17 Drug Product:** 18 months for the Pyzchiva vial presentation when stored at 2°C - 8°C protected from light.
- **Drug Substance:** (b) (4) months at (b) (4) °C
- **For packaged products:** None

- **Stability Option:**
  - For stability protocols: We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and/or drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: Pyzchiva 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. Recommendation on Phase 4 (Post-Marketing) Commitments,

PMC 4651-1: Develop an endotoxin testing method for the 5 mg/mL drug product that mitigates the low endotoxin recovery (LER) effect, submit method qualification results with 3 lots of 5 mg/mL drug product, and provide results of a LER study performed with the updated method using 3 lots of drug product. The USP <151> pyrogen test will be replaced by a suitable in vitro endotoxin method upon approval of the supplement.

Final Report Submission 01/31/2026

4. Basis for Recommendation

a) **Summary of Quality assessments:** Refer to the previous BLA 761373 Executive Summary Memorandum referenced above for the basis of recommendation of approval for the drug substance, drug product, comparative analytical assessment (CAA), immunogenicity assays, and microbiology aspects. Specifically, the original ***BLA 761373 IQA Executive Summary 01122024*** ATL memorandum (uploaded in DARRTS on January 12, 2023) details the basis for the subdiscipline approval including the facility approval recommendation. The BLA is recommended for approval from product quality, facility, microbiology and sterility assurance perspectives with the PMC indicated above to improve detection of potential impurities (i.e. endotoxin).

b) Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Adequate**
Microbiology	**-**	**Adequate with PMCs/PMRs**

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 Pyzchiva (i.e., there is no specific test method described in regulation for SB17 that establishes an official standard of potency). We next considered whether potency is a factor for SB17 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 Pyzchiva for purposes of § 610.61(r) because lot variability is not a concern for Pyzchiva as the 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

b. Drug Substance: Refer to the BLA 761373 IQA Executive Summary 01122024 ATL memorandum (uploaded in DARRTS on January 12, 2023) for list of approved protocols.

c. Drug Product:

i. Protocols approved:
   1. 3.2.P.2.4 Long-term Leachable stability study protocol for DP container closure system of the 130 mg vial presentations.
   2. 3.2.P.8.2 DP Post-approval annual stability protocol and commitment

ii. Residual risk: See PMC

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.

Appendix

II. Evaluation of the Comparative Analytical Assessment

Refer to the BLA 761373 IQA Executive Summary 01122024 ATL memorandum (uploaded in DARRTS on January 12, 2023) for full discussion and summary of the evaluation of the Comparative Analytical Assessment (CAA).

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/s/

SAMUEL MINDAYE
06/11/2024 11:02:55 PM

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	May 23, 2024
Assessor:	Diana Pei, PharmD Vicky Borders-Hemphill, PharmD Labeling Assessors Office of Product Quality Assessment III (OPQA III)
Through:	Gunther Boekhoudt, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761373 (for PFS) and 761425 (for vial)
Applicant:	Samsung Bioepis Co., Ltd.
Submission Date:	March 30, 2023
Product:	Pyzchiva (ustekinumab-ttwe)
Dosage form(s):	Injection
Strength and Container-Closure:	45 mg/0.5 mL solution in a single-dose prefilled syringe 90 mg/mL solution in a single-dose prefilled syringe 130 mg/26 mL (5 mg/mL) solution in a single-dose vial
Purpose of assessment:	The Applicant submitted biologics license applications (351(k), a proposed biosimilar product to U.S.-licensed Stelara (ustekinumab).
Recommendations:	The prescribing information, medication guide, and instructions for use (submitted on May 17, 2024), PFS container labels and carton labeling (submitted on March 19, 2024, and May 22, 2024), and vial container labels and carton labeling (submitted on March 20, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III BLA 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

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, medication guide, and instructions for use (submitted on May 17, 2024), PFS container labels and carton labeling (submitted on March 19, 2024, and May 22, 2024), and vial container labels and carton labeling (submitted on March 20, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III BLA Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information, Medication Guide, and Instructions for Use (submitted on March 30, 2023 **\\CDSESUB1\EVSPROD\bla761373\0001\m1\us\114-labeling\114a-draft-label\draft-label-text-redline.docx**)

Container Labels (submitted on March 30, 2023)

(b) (4)

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

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] 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
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

[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.

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
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: A "Mfd for:" statement is not required and can be deleted. *The Applicant has kept "Mfd for" on the container labels and added Sandoz Inc..*

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
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)	✓ Yes ☐ No ☐ N/A

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

[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."

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
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*	✓ Yes ☐ No ☐ N/A

For the 130 mg/26 mL (5 mg/mL) vial, the principal display panel (PDP) is displaying duplicate strength presentations. When the container labels are crowded, text size and prominence are generally decreased, and important information may be difficult to read or easily overlooked. We recommend removing the product strength statement from the top right portion of the PDP. Incorporate boxing or highlighting to increase the prominence of the product strength statement that appears under the dosage formulation, injection. *The Applicant made the revised recommendation.*

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

Comment/Recommendation: The prefilled syringe labels are small and could be considered a partial label. A "Rx only" statement is not required per 21 CFR 610.60(c), and thus a "Rx only" statement does not appear on the prefilled syringe label. An "Rx only" statement appears on the vial label.

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

Comment/Recommendation: The prefilled syringe and vial labels are small and would be considered a partial label. Thus, a Medication Guide statement is not required per 21 CFR 610.60(a)(7).

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	✓ Yes ☐ No ☐ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	✓ Yes ☐ No ☐ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vial. *The Applicant confirmed there is no text on the ferrule and cap overseal of the vial.*

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

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
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Include an actual NDC on all labels and labeling. *The Applicant has made revisions as recommended.*

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

Comment/Recommendation: The prefilled syringe labels do not need a preparation instruction statement, because the presentation is ready to use. The vial label is small and could be considered a partial label. Thus, preparation instruction statement is not required per 21 CFR 610.60(c).

Package type term (container label)	**Acceptable**
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) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The prefilled syringe labels could be considered a partial label and does not have space for a package type term. The vial label displays 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

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
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)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Display and or confirm the proposed bar code on the labels and labeling complies with 21 CFR 201.25, and 21 CFR 610.67. *The Applicant has confirmed that the barcode on the label and labeling have been displayed and added the proposed bar code to the labels and labeling.*

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
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015)	✓ Yes ☐ No ☐ N/A

USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).	

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: The label is small and could be considered a partial label. Thus, a dosage statement is not required.

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The prefilled syringe label is small and could be considered a partial label. Thus, a storage statement is not required. The vial label displays a storage statement.

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

Package[6] 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
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ 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
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: (b) (4)
Relocate the logo "**SAMSUNG** BIOEPIS" from above the manufacturer's name in the manufactured by statement. The logo "**SAMSUNG** BIOEPIS" can appear as a stand-alone statement elsewhere on the carton labeling. *The applicant has made the revised recommendation.*

Include the postal code, 21987, as part of the address in the "Manufactured by:" statement. *The applicant has made the revised recommendation.*

Note a "Manufactured for:" statement is not required and can be deleted. *The Applicant has kept the "Manufactured for:" statement on the cartons and included Sandoz Inc.*

Revise the abbreviation "US" to appear as "U.S." on the labels and labeling. *The applicant has made the revised recommendation.*

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ 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.

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

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ 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
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Prefilled Syringes: Replace the statements "[redacted]" and "[redacted]" with the statements "If needed, prefilled syringe may be stored at room temperature up to 30°C (86°F) for up to 60 days in the original carton to protect from light", "If not used within 60 days of room temperature storage, discard the prefilled syringe. The prefilled syringe may be returned to the refrigerator 1 time only for a maximum of 3 days", and "If not used within 3 days, discard the prefilled syringe". "Record the date when the prefilled syringe is removed from and returned to the refrigerator."
Also include statements to write the date removed and returned to the refrigerator, similar to:

Date removed from the refrigerator:
_____/_____/_____

Date returned to refrigerator:
_____/_____/_____

The Applicant made the revised recommendations.

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
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ 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

Comment/Recommendation: The drug product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the ingredient statements. Each ingredient and quantity added to the formulation should be listed. Thus, quantities were included for the ingredients, histidine and histidine hydrochloride monohydrate. The ingredient (b) (4) (b) (4) has an official USP monograph, and the official name should appear as edetate disodium. Revise the active ingredient, ustekinumab, to include the 4-letter suffix.
Prefilled Syringe 45 mg/0.5 mL- revise to read:

Each 0.5 mL prefilled syringe delivers 45 mg ustekinumab-xxxx, histidine (0.095 mg), histidine hydrochloride monohydrate (0.405 mg), polysorbate 80 (0.02 mg), and sucrose (42.5 mg).

Prefilled Syringe 90 mg/mL- revise to read:
Each 1 mL prefilled syringe delivers 90 mg ustekinumab-xxxx, histidine (0.19 mg), histidine hydrochloride monohydrate (0.81 mg), polysorbate 80 (0.04 mg), and sucrose (85 mg).

The Applicant made revisions as recommended.

Vial 130 mg/26 mL: Correct the spelling of the word "containing". The ingredient " (b) (4) (b) (4)" has an official USP monograph under the name Edetate Disodium. Thus, the ingredient should be listed as "edetate disodium".

Revise to read: Each vial contains 26 mL of solution containing 130 mg ustekinumab-xxxx, edetate disodium (0.52 mg), histidine (20 mg), histidine hydrochloride monohydrate (27 mg), methionine (10.4 mg), polysorbate 80 (10.4 mg) and sucrose (2,210 mg).

The Applicant made revisions as recommended.

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP 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.

Although this statement currently appears on the carton labeling of the reference product, Stelara this inclusion predated the Agency's renewed attention to the labeling requirement in § 610.61(r) as part of FDA's implementation of section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009. The absence of the statement for the current product should not be interpreted to mean that the Agency reached different conclusions about whether potency is a factor (within the meaning of § 610.61(r)) for the current product and its reference product.

Remove the statement "No U.S. standard of potency" from the carton labeling. Although this statement appears on the carton labeling of the reference product, Stelara, our current thinking is that 21 CFR 610.61(r) is not applicable, and thus no statement is required for your product's carton labeling. *The Applicant revised as recommended.*

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

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A

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 *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)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Display and or confirm the proposed bar code on the labels and labeling complies with 21 CFR 201.25, and 21 CFR 610.67. *The Applicant has confirmed the display of the bar code on the labels and labeling.*

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 *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
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) *USP chapter <659> Packaging and Storage Requirements*	✓ 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

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

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

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

Comment/Recommendation: Vial: Revise the statement "Single-dose vial" to incorporate the quantity of 1 unit to read "One single-dose vial" or "1 single-dose vial". *The Applicant made revisions as recommended.*

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the dosage statements to read "Recommended Dosage: See Prescribing Information". *The Applicant revised as recommended.*

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
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	✓ Yes ☐ No ☐ N/A

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

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv) *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."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted	✓ Yes ☐ No

products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	☐ N/A

Comment/Recommendation: The identifying characteristics were updated based upon your submission dated Oct 12, 2023.

(b) (4)

The Applicant made revisions as recommended.

A protect from light statement was inserted, because the diluted solution with the drug product should be protected from light.

(b) (4)

The Applicant made revisions as recommended.

The (b) (4) information distracts the healthcare providers attention from the important administration information and should be presented in the (b) (4) subsection below. Thus, the statements were deleted.

(b) (4)

The Applicant made revisions as recommended.

The storage times and duration were revised based upon your microbiology and product quality submissions. Please confirm.
The Applicant made revisions as recommended.

A "Protect from light" statement was inserted, because the diluted solution with the drug product should be protected from light during storage and administration of the diluted solution.

(b) (4)

The Applicant made revisions as recommended.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
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*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The identifying characteristics were updated based upon your submission dated Oct 12, 2023.

(b) (4)

The Applicant made revisions as recommended.

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
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised the cell line reference to match your manufacturing process.

(b) (4)

The Applicant revised the cell line from (b) (4) to "Chinese hamster ovary cell line." The Applicant did not include (b) (4) which is acceptable.

The identifying characteristics were updated based upon your submission dated Oct 12, 2023.

(b) (4)

The Applicant made revisions as recommended.

Each ingredient and quantity added to the formulation should be listed. Thus, quantities were included for the ingredients histidine and histidine hydrochloride monohydrate. The ingredient (b) (4) has an official USP monograph, and the official name should appear as edetate disodium. The ingredient names and quantities were revised. Please confirm.

(b) (4)

The Applicant made revisions as recommended.

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
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The identifying characteristics were updated based upon your submission dated Oct 12, 2023.

(b) (4)

The Applicant made revisions as recommended.

The phrasing was revised to reflect the recommended wording found in the FDA Guidance document titled: "Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex".

(b) (4)

The Applicant made revisions as recommended.

The (b) (4) phrase is not needed and thus the phrase was deleted. The phrase (b) (4) (b) (4)" was revised to read "60 days" to help patients determine the exact time period at RT and if needed under refrigeration.

(b) (4)

The Applicant made revisions as recommended.

The labeling was revised to reflect an additional 3 days of refrigerated storage for the syringe after room temperature storage. The stability data provided only supports 3 days of additional refrigerated storage.

(b) (4)

The Applicant made revisions as recommended.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
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)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: A "Manufactured for" statement is not required and can be deleted. *The Applicant has kept the "Manufactured for" statement and included Sandoz Inc..*

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: The alternate storage information was revised to match the messaging in the USPI, section 16. *The Applicant made revisions as recommended.*

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the active ingredient, ustekinumab, to include the 4-letter suffix, and revise "(b) (4)" to appear as "edetate disodium", the official USP monograph name for the ingredient. The ingredient names should be

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
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)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: A "Manufactured for" statement is not required and can be deleted. *The Applicant has kept the "Manufactured for" statement and included Sandoz Inc..*

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: The alternate storage information was revised to match the messaging in the USPI, section 16. *The Applicant made revisions as recommended.*

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the active ingredient, ustekinumab, to include the 4-letter suffix, and revise "(b) (4)" to appear as "edetate disodium", the official USP monograph name for the ingredient. The ingredient names should be

consistent with the names in Section 11 of the Prescribing Information. *The Applicant made revisions as recommended.*

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

Comment/Recommendation: A "Manufactured for" statement is not required. *The Applicant has kept the "Manufactured for" statement and included Sandoz Inc.."*

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
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).*	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
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)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: *The Applicant has updated the storage instructions to match the messaging in the USPI, Section 16.*

INSTRUCTIONS FOR USE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	☐ 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 *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*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

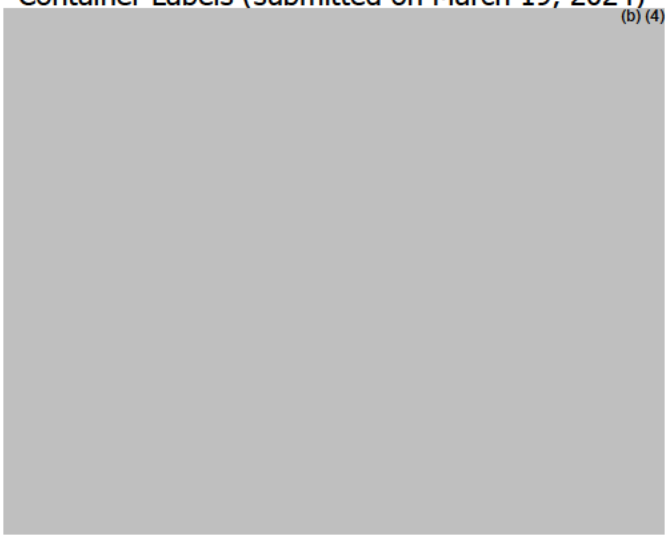
Comment/Recommendation: A Manufactured for statement is not required and can be deleted. *The Applicant has kept the "Manufactured for" statement and include Sandoz Inc.."*

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information, Medication Guide, and Instructions for Use (submitted on May 17, 2024 \\CDSESUB1\EVSPROD\bla761373\0044\m1\us\114-labeling\114a-draft-label\uspi-clean.docx and \\CDSESUB1\EVSPROD\bla761425\0009\m1\us\114-labeling\114a-draft-label\uspi-clean.docx)

Container Labels (submitted on March 19, 2024)

(b) (4)



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

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 5/23/2024 09:57:37AM
GUID: 50814c7000007a3d59329f660d8ddf02

Gunther Boekhoudt

Digitally signed by Gunther Boekhoudt
Date: 5/24/2024 11:39:59AM
GUID: 508da6d7000262c4c5e3578cc0a15fbf

BLA Executive Summary
Assessment Date: 01/11/2024

1. Application/Product Information

BLA number	761373
Submission Type	Original Submission
Regulatory Pathway	351(k)
Associated IND/BLA	IND136959
Review Designation	Standard
Applicant	Samsung Bioepis Co., Ltd.
Indication	• Moderate to severe plaque psoriasis (PsO) in adult patients and pediatric patients 6 years of age and older. • 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. The use in PsO, PsA pediatric subjects (6 years or older) is proposed to be restricted to patients with a body weight of 60 kg or more who can administer whole dose of SB17 PFS.
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** To be determined
	Non-proprietary Name/Code Name: Ustekinumab-xxxx (to be determined)/SB17
	OBP Naming: BsMAB: MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [SB17]

Drug Product Description	SB17 is a fully human immunoglobulin G1 (IgG1) kappa monoclonal antibody (mAb) produced in a mammalian cell line (b) (4) SB17 is a human interleukin (IL)-12 and IL-23 antagonist that binds to the shared p40 subunit of human cytokines IL-12 and IL-23 and prevents IL-12 and IL-23 from binding to their receptor. Samsung Bioepis proposed SB17 as a biosimilar to the reference US-licensed Stelara. SB17 drug product (DP) is a preservative-free solution formulated at pH (b) (4) and provided in multiple presentations as summarized below. • Solution for subcutaneous (SC) administration provided in a single-dose prefilled syringe (PFS) with a 29-gauge fixed ½ inch needle equipped with a passive safety device and a needle cover. There are two strengths: ○ 45 mg SB17 in 0.5 mL (containing 45 mg SB17, 0.095 mg histidine, 0.405 mg histidine hydrochloride monohydrate, 0.02 mg polysorbate 80, 42.5 mg sucrose (b) (4)) ○ 90 mg SB17 in 1 mL (containing 90 mg SB17, 0.190 mg histidine, 0.810 mg histidine hydrochloride monohydrate, 0.04 mg polysorbate 80, 85 mg sucrose (b) (4) (b) (4)) • Solution in a single-dose vial (130mg/26mL) for intravenous (IV) administration after dilution in 0.9% or 0.45% saline. The vial formulation contains 130 mg SB17, 20(b) (4) mg histidine, 27(b) (4) mg histidine hydrochloride monohydrate, 10.4 mg methionine, (b) (4) (b) (4), 10.4 mg polysorbate 80, and 2210 mg sucrose (b) (4)
Dosage Form	Liquid
Strength	SC injection: 45 mg/0.5 mL in a single-dose PFS and 90 mg/1 mL PFS for administration without dilution IV injection: 130mg/26 mL in a single-dose vial for use after dilution in commercially available 0.9% or 0.45% saline.

Route of Administration	• Subcutaneous injection • Intravenous infusion		
Primary Container Closure System	• PFS presentations (45 mg/0.5 mL and 90 mg/1 mL): 1 mL Type I glass syringe with a staked-in-place stainless steel needle and a rubber plunger-stopper equipped with a passive safety device. • Vial presentation (130 mg/26 mL): 30mL Type I clear glass vial with 20 mm (b) (4) rubber stoppers and a 20 mm aluminum seal with a flip-off cap.		
Device Information	The PFS has a staked-in-place stainless steel needle and is assembled with an elastomeric needle shield, a rubber plunger-stopper, and a passive safety device		
Co-packaged Product Information	None		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance Drug product Immunogenicity Assay	Gunther Boekhoudt (OPQ/OBP/DBRR IV)	Samuel Mindaye (OPQ/OBP/DBRR IV)
	Facility	Chani Broner (Drug product) Ekaterina Allen (Drug substance)	Zhong Li (CDER/OPQ/OPMA/DBM)
	Microbiology	Chani Broner (Drug product) Ekaterina Allen (Drug substance)	Maxwell Van Tassel (CDER/OPQ/OPMA),
	RBPM	Kristine Leahy (OPQ/OPRO)	

	ATL	Samuel Mindaye (OPQ/OBP/DBRR IV)
OPQ Issued Consults	The final recommendation from CDRH is that the device constituent parts of the combination product are acceptable. There are no PMC/PMR or CR deficiencies from CDRH.	

Submissions Assessed:

Submission	Date received	Assessment Completed (yes or no):
761373/EDR0003 Response IR1	May 18, 2023	OPMA
761373/EDR0011 Response IR1	September 15, 2023	OPMA
761373/EDR0011 Response IR2	October 12, 2023	OBP
761373/EDR0014 Response IR3	October 12, 2023	OPMA
761373/EDR0016 Response IR4	October 27, 2023	OPMA
761373/EDR0017 Response IR5	November 3, 2023	OBP
761373/EDR0018 Response IR6	November 6, 2023	OPMA
761373/EDR0021 Response IR7	November 17, 2023	OBP
761373/EDR0022 Response IR8	November 22, 2023	OBP
761373/EDR0023 Response IR9	November 27, 2023	OBP
761373/EDR0024 Response IR10	December 01, 2023	OPMA
761373/EDR0025 Response IR11	December 11, 2023	CDRH
761373/EDR0026 Response IR12	December 13, 2023	OPMA
761373/EDR0029 Response IR13	December 22, 2023	OBP
761373/EDR0031 Response IR14	December 28, 2023	OPMA
761373/EDR0033 Response IR15	January 9, 2024	OPMA

Related/Supporting Documents: DMFs

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	As adequate information is provided in the application, no
			Yes	

(b) (4)	Yes	further reviews were performed

2. Recommendation and Conclusion on Approvability

Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761373 for SB17 manufactured by Samsung Bioepis Co., Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of SB17 is well-controlled and leads to a product that is safe, pure, and potent. The comparative analytical data support a demonstration that SB17 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:**

(b) (4)

- **Drug Product:** Vial and PFS presentations:

(b) (4)

b. Fill size and dosage form: SB17 is provided in a single-dose as 45 mg/0.5 mL PFS and 90 mg/1 mL PFS for SC injection and in a single-dose vial 130mg/26mL for IV injection after dilution in commercially 0.9% or 0.45% normal saline.

c. Dating Period:

- **SB17 Drug Product:** 24 months at 2°C - 8°C protected from light for PFS and 18 months for the vial presentation when stored at 2°C - 8°C protected from light.
- **Drug Substance:** (b) (4) months at (b) (4) °C
- **For packaged products:** None
- **Stability Option:**

- For stability protocols: We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and/or drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: SB17 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. Benefit/Risk Management Steps

The assessment of manufacturing information provided in the application concluded that the methodologies and processes used for SB17 DS, and DP manufacturing, release, and stability testing are robust and sufficiently controlled to produce product with consistent quality and safety profile. The manufacturing process is robust for inactivation and removal of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

In lieu of pre-license inspection (PLI) for the DP manufacturing facility, (b) (4) (b) (4), a review of the manufacturing site records was conducted under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act. The review team identified several observations during the evaluation of the records as described in the review memo in Panorama. The DP manufacturing facility at (b) (4) was waived from the PLI inspection. The facility was determined to have sufficient inspection history, with the most recent inspection performed (b) (4) (b) (4) in support of (b) (4). Overall, the facilities were found acceptable for the proposed operations.

f. Recommendation on Phase 4 (Post-Marketing) Commitments,

4572-2: Develop an endotoxin testing method for the 5 mg/mL drug product that mitigates the low endotoxin recovery (LER) effect, submit method qualification results with 3 lots of 5 mg/mL drug product, and provide results of a LER study performed with the updated method using 3 lots of drug product. The USP <151> pyrogen test will be replaced by a suitable in vitro endotoxin method upon approval of the supplement.

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4. Basis for Recommendation

a) Summary of Quality assessments:

SB17 is a humanized immunoglobulin IgG1 monoclonal antibody consists of two identical heavy chains (HC) and two identical light chains (LC) belonging to the kappa subclass. The biological activity of SB17 involves binding to human IL-12p40, the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. By blocking the p40 protein from binding to the IL-12Rβ1, SB17 can inhibit the bioactivity of human IL-12 and IL-23 and potentially interrupt the T helper 1 (Th1) and T helper 17 (Th17) cytokine pathways. It is a proposed biosimilar to and interchangeable with the US-Stelara for the same indications as US-Stelara. The approved US- and EU-Stelara comes in three presentations (0.5 mL 45 mg PFS, 1 mL 90 mg PFS, and 26 mL 130 mg vial) which are also pursued by Samsung. Potency of SB17 is controlled (b) (4) SB17 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 comparative analytical assessment (CAA) involves multitude of orthogonal analytical techniques to assess a three-way similarity (SB17, US- Stelara, and EU-Stelara) and assessment was performed based on quality attributes (QAs) ranked on their potential impact on activity, PK/PD, safety, and immunogenicity. The totality of the evidence from the CAA supports that SB17is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. Furthermore, a three-way scientific bridge between SB17, US-, and EU-Stelara has been adequately established to support the relevance of the data generated from studies using EU-Stelara as the comparator to the assessment of biosimilarity. Further discussion on the CAA summary is provided in the Appendix.

SB17 DS is manufactured (b) (4) The DP manufacturing process for

(b) (4)

The overall SB17 control strategy (b) (4) The DP is filled (b) (4) (b) (4). The manufacturing processes and overall control strategies for SB17 as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for DS manufacturing at (b) (4) and DP manufacturing at (b) (4). All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status, recent relevant inspectional coverage, or manufacturing site records review conducted under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is recommended for approval from product quality, facility, microbiology and sterility assurance perspectives with the PMC indicated above to improve detection of potential impurities (i.e. endotoxin).

CDRH final recommendation is that the device constituent parts of this combination product are approvable. There is no PMC/PMR from CDRH.

b) Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Adequate**
Microbiology	**-**	**Adequate with PMCs/PMRs**

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 SB17 (i.e., there is no specific test method described in regulation for SB17 that establishes an official standard of potency). We next considered whether potency is a factor for SB17 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 SB17 for purposes of § 610.61(r) because lot variability is not a concern for SB17 as the 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

b. Drug Substance:

i. Protocols approved:

1. (b) (4)
2.
3.
4. 3.2.S.7.2 Post-approval Stability Commitment

ii. Residual risk: None

iii. Future inspection points to consider: See manufacturing site records review memo for (b) (4) in Panorama

c. Drug Product:

i. Protocols approved:

1. 3.2.P.2.4 Long-term Leachable stability study protocol for DP container closure system of the 45 mg and 90 mg PFS, and 130 mg vial presentations.
2. 3.2.P.8.2 DP Post-approval annual stability protocol and commitment

ii. Residual risk: See PMC

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.

Appendix

II. Evaluation of the Comparative Analytical Assessment

A. Overview and Conclusions

Samsung is seeking licensure of SB17 as an interchangeable biosimilar to U.S.-licensed Stelara (referred to hereafter as US-Stelara) for these strengths: 90 mg/ 1.0 mL (90 mg/mL) and 45 mg/0.5 (90 mg/mL) mL in a single-dose prefilled syringe (PFS), and 130 mg/26 mL (5 mg/mL) in a single dose vial. These are the same strengths currently available for US-Stelara. Samsung provided results of the comparative analytical assessment (CAA) to support the demonstration that SB17 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components and to establish the analytical component of the scientific bridge. The study design was in accordance with the recommendations of FDA and ICH guidance documents. Also, the feedback provided to Samsung during formal Biological Product Development (BPD) meetings Type 3 and Type 2 were incorporated in the development. The CAA was performed based on quality attributes (QAs) ranked on their potential impact on activity, PK/PD, safety, and immunogenicity, using risk assessment principles set forth in the FDA Guidance for Industry. Similarity is established when at least 90% of data fall within the quality range defined as $\overline{XR} \pm xSR$, where $\overline{XR}$ is a sample mean of the reference product lots, SR is a sample standard deviation of the reference product lots, and x is the standard deviation (SD) multiplier. The multiplier x = 2.6 was used for the high-risk quality attributes and x = 3 for the moderate risk quality attributes. For the lowest risk quality attributes, raw data/graphical comparison was employed.

The CAA included comparison of physicochemical and functional quality attributes of SB17, US-Stelara and EU-Stelara. A total of 39 US-Stelara lots for reference product, 38 EU-Stelara lots for comparator, (all lots were of 45 mg/0.5 mL PFS) and a total of 6 lots of SB17 were included in the CAA. For vial presentation (130 mg/26 mL), a total of 13 US-Stelara for similarity range establishment, 3 US-Stelara and 3 Eu-Stelara for side-by-side characterization study, and 6 SB17 lots were used for the CAA. Furthermore, all US-Stelara and EU-Stelara lots used in the clinical studies were included in the CAA. All reference standard and comparator lots had expiry dates between December 2016 and October 2024, allowing the impact of DP age to be a component of the CAA. The CAA included the 45mg/0.5 mL PFS and 130 mg/26 mL vial presentations. Justification for performing the CAA on the 45mg/0.5 mL PFS and not on the 90 mg/1.0 mL PFS was provided, and it was based on risk assessment and was acceptable.

Our assessment of the SB17 and US-Stelara data supports the determination that SB17 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. SB17 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 SB17 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 adjusted 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 SB17 and US-Stelara are highly similar.

In addition, Samsung used three-way pairwise comparisons of SB17, US-Stelara, and EU-Stelara to establish the analytical component of the scientific bridge between SB17, 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 SB17, US-Stelara, and EU-Stelara, using the same methods and statistical approaches used to evaluate that SB17 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 1. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physicochemical/Functional Characteristics	Quality attributes	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Primary structure and post translational modification.	Intact molecular weight	Yes	Yes
	Amino acid sequence	Yes	Yes
	Peptide mapping	Yes	Yes
	N-terminal sequence	Yes	Yes
	C-terminal sequence	Yes	Yes
	Extinction coefficient	Yes	Yes
	Oxidation	Yes	Yes
	Deamidation	Yes	Yes
Glycan profiles	Glycan map	Yes	Yes
	Afucosylation	Yes	Yes
	High mannose	Yes	Yes
	α-Galactosylation	Yes	Yes
	Charged glycan	Yes	Yes
	Total sialic acid contents	Yes	Yes
	Other glycans G0F, G1F, G2F	Yes	Yes
Purity and Impurities	HMW (SE-HPLC)	Yes	Yes
	Monomer (SE-HPLC)	Yes	Yes
	LMW (SE-HPLC)	Yes	Yes
	2H1L (CE-SDS (non-reduced)	Yes	Yes
	IgG (CE-SDS (non-reduced)	Yes	Yes
	LC+HC (CE-SDS (reduced)	Yes	Yes
	NGHC (CE-SDS (reduced)	Yes	Yes
Charge heterogeneity	Acidic (CEX-HPLC and icIEF)	Yes	Yes
	Main (CEX-HPLC and icIEF)	Yes	Yes
	Basic (CEX-HPLC and icIEF)	Yes	Yes
	pI of Main (icIEF)	Yes	Yes
Higher order structure	Disulfide bond	Yes	Yes
	Free sulfhydryl group	Yes	Yes
	Higher order structure	Yes	Yes
Biological properties	IL-23 neutralization assay	Yes	Yes
	IL-12 neutralization assay	Yes	Yes
	IL-23 binding assay	Yes	Yes

Physicochemical/Functional Characteristics	Quality attributes	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
	IL-12 binding assay	Yes	Yes
	FcRn binding assay	Yes	Yes
Additional biological properties	FcγRIa binding assay	Yes	Yes
	FcγRIIa binding assay	Yes	Yes
	FcγRIIb binding assay	Yes	Yes
	FcγRIIIa binding assay	Yes	Yes
	C1q binding assay	Yes	Yes
	Lack of Antibody-dependent cell-mediated cytotoxicity (ADCC)	Yes	Yes
	Lack of Complement dependent cytotoxicity (CDC)	Yes	Yes
Drug product attributes	Protein concentration (mg/mL)	Yes	Yes
Forced degradation studies	Thermal stress	Yes	Yes
	Photo degradation	Yes	Yes
	pH	Yes	Yes
	Oxidative stress	Yes	Yes

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

Two clinical studies were conducted that compared SB17 to US-Stelara and/or EU-Stelara.

- **Clinical Study – SB17-1001:** randomized, double-blind, three-arm, parallel group, single-dose, PK similarity study to compare the PK, safety, tolerability, and immunogenicity of SB17, US-Stelara, and EU-Stelara in healthy subjects.
- **Clinical Study – SB17-3001**: randomized, double-blind, multicenter, active-controlled comparative clinical study to evaluate the efficacy, safety, tolerability, PK, and immunogenicity of SB17 compared to EU-Stelara in patients with moderate to severe plaque psoriasis.

Based on the data provided to support analytical similarity of SB17 to US-Stelara, SB17 to EU-Stelara, and US-Stelara to EU-Stelara from comparative structural, physicochemical, and biological studies, an adequate analytical component of the scientific bridge between SB17, US-Stelara, and EU-Stelara was established, which

justifies the relevance of the clinical data generated using EU-Stelara as the comparator product. For the CAA studies, the same analytical methods used for the assessment of highly similar between SB17 and US-Stelara were used for comparison of SB17 and EU-Stelara and EU-Stelara and US-Stelara. The differences observed in a subset of quality attributes in the CAA (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

Primary structure and post translational modification (PTM): differences were observed in the C-terminal amino acid of the heavy chain of SB17 compared to US-Stelara and EU-Stelara. SB17 had higher (95.7%-98.1%) Lys-removed species compared to US-Stelara and EU-Stelara (31.0%-39.8%). Conversely, Lys-preserved form is more abundant in the US-Stelara and EU-Stelara (60.2% - 69.0%). Furthermore, SB17 had low levels of α-amidated proline (0.6%-1.6%), which is not observed in US-Stelara and EU-Stelara. Based on structure activity relationship study on SB17, it was shown that C-terminal Lys variants have no effect on ligand binding and neutralization. Further, levels of C-terminal Lys variants are not considered clinically significant because they did not impact potency, which is similar for SB17, 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. Therefore, the differences in the C-terminus Lys variants and other PTMs do not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.

Glycan profiles: the glycosylation profile of SB17, US-Stelara, and EU-Stelara was assessed using LC-ESI-MS and the results revealed some qualitative and quantitative differences between lots. The major qualitative differences include N-acetylneuraminic acid (NANA) and M6 species were detected only in SB17. In contrast, N-glycolylneuraminic acid (NGNA), M3G1, and G1F + Gal were detected only in US-Stelara and EU-Stelara. These differences were attributed to the production cell line differences between SB17 (mammalian cell line CHO) and US-Stelara and EU-Stelara (murine cell line (b) (4)). In further investigation, HILIC-UPLC analysis was performed on the seven N-glycan groups including G0F, G1F, G2F, afucose, charged glycan, high mannose (HM), and α-Gal as part of the CAA. Overall, there were some minor differences between SB17, US-Stelara and EU-Stelara lots in the individual glycan profiles. For example, SB17 has higher G0F (57%-65%) compared to US-Stelara (28.4%-29.5%) and EU-Stelara (35.7%-36.5%) or lower G1F (2.9%-4.6%) compared to US-Stelara (6.6%-7.2%) and EU-Stelara (6.1%-7.6%). But in all cases, the similarity ranges (US-

Stelara and EU-Stelara) were met owing to a higher heterogeneity in the glycan profile in the US-Stelara, making the similarity range wider. The high mannose levels were similar between SB17 (0.7-1.0) and US-Stelara (0.8-0.9), and EU-Stelara (0.9-1.2). For afucose glycan species, all SB17 lots fell below the lowest similarity ranges set for US-Stelara (1.5%-5.0%) and EU-Stelara (2.0%-5.0%). Afucosylated species may impact binding to Fcγ receptors, such as FcγRIIIa, which can lead to ADCC activity, and the lower levels are consistent with the differences seen in FcγRIIIa binding. However, the noted differences are not expected to have a clinically meaningful impact because all three products were shown to have no effector functions. α-Gal species were not detected in SB17 while both US-Stelara (1.9%-2.4%) and EU-Stelara (1.8%-2.6%) had measurable levels of α-Gal. α-gal has been associated with increased safety risk such as immunogenicity. Lack of α-galactosylation in SB17 is not expected to impact safety risks as lack of α-galactosylation in SB17 is not expected to increase immunogenicity.

Overall, there were qualitative and quantitative differences in the N-glycan profiles between SB17 and EU-Stelara and US-Stelara, but the differences did not seem to affect functional activity and are unlikely to present safety and efficacy risk for SB17. This is consistent with the results of the comparative PK study (SB17-1001), in which PK similarity is demonstrated between SB17, US-Stelara, and EU-Stelara (see BMER). To further investigate the risk of variation in the glycosylation patterns, Samsung performed regression analysis in the N-glycan profiles of both US-Stelara and EU-Stelara against selected biological activities. The results revealed that differences in glycosylation do not seem to have any measurable impact on the biological tests (IL-23 neutralization, IL-12 neutralization, IL-23 binding, IL-12 binding, and FcRn binding assays). Taken together, the residual uncertainties were adequately explored, and risk-based assessment was performed. The results and discussion confirmed that the observed variation in glycosylation between SB17, US-Stelara and EU-Stelara have no clinically meaningful impact on safety, PK, and efficacy and thus do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.

Total sialic acid contents: the total sialic acid (TSA) was assessed using ion-exclusion chromatography (IEX) and the results revealed SB17 TSA content is lower (0.0%-0.1%) compared to US-Stelara (0.2 - 0.3%) and EU-Stelara (0.1%-0.3%). Nevertheless, all the SB17 lots were within the US-Stelara similarity ranges (0.0%-0.4%). For the EU-Stelara, 5 out of 6 SB17 lots were below the similarity range (0.1%-0.4%). NANA was identified in SB17 but not in US-Stelara and EU-Stelara, while NGNA was identified in US-Stelara and EU-Stelara but not in SB17. Significant levels of sialylated species in mAbs have the potential to impact other antibody functional

domains and could result in differences in bioactivity related to the Fab arm functionality. In addition, sialylated glycan levels may impact PK. However, the observed differences in sialylated species did not result in differences in biological activity. Therefore, the noted differences are not expected to have a significant impact on product quality, safety, or biological activity and do not preclude a demonstration that SB17 is highly similar to US-Stelara or the establishment of the analytical component of the bridge. This is consistent with the results of the comparative PK study, in which PK similarity is demonstrated between SB17, US-Stelara, and EU-Stelara (see BMER).

Charge Heterogeneity: Comparative assessment was performed on SB17, US-Stelara and EU-Stelara samples treated with enzymes (PNGase F and carboxypeptidase B enzyme) as well as without enzymatic treatment using CEX-HPLC and IEF. Some differences in the relative levels of the main, acidic, and basic peaks of SB17 DP were observed compared to US-Stelara and EU-Stelara (with and without enzymatic treatment). In un-treated samples, the difference is more pronounced. Specifically, SB17 had significantly lower contents of acidic (8.2 – 11.8%) and basic variants (4.3 – 6.4%), and higher contents of the main peak (83.8 – 86.3%) compared to US (21.2 - 25.5% for acidic, 41.1 -46.5% for basic, and 32.4 – 33.4% for main) and EU-Stelara (21.3 -25.2% for acidic, 39.3 - 42.8% for basic, and 34.8 – 35.9% for main). The causes and impact of charge heterogeneity on biological activity was investigated by collecting individual charge variant fractions from SB17, US-Stelara and EU-Stelara. Peptide mapping, SE-HPLC, CE-SDS (non-reduced), and biological assays (IL-23 neutralization assay, IL-23 binding assay, and FcRn binding assay) of individual fractions revealed that sialic acid (NANA and NGNA), C-terminal lysine, and α-amidation are the major causes of size heterogeneity. Furthermore, biological activities (IL-12/-23 neutralizing activity and IL-12/-23 binding activity), FcRn binding, Fc-gamma receptor binding, Cq1, binding, ADCC activity, CDC activity, and stress stability profile (except oxidative condition) were similar between SB17, and US-Stelara, and EU-Stelara lots. The minor charge heterogeneity appears to be mainly contributed by the differences in production cell line. Structure activity relationship study also revealed that potency of the acidic, main, and basic fractions was comparable between SB17 and US-Stelara. Moreover, the acidic and basic fractions had comparable potency with the unfractionated lots confirming that, the difference in relative contents of acidic or basic variants between SB17 and US-Stelara and EU-Stelara is unlikely to have clinically meaningful impact and thus do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge. This is consistent with the results of the comparative PK study, in which PK similarity is demonstrated between SB17, US-Stelara, and EU-Stelara (see BMER).

Impurities: Size heterogeneity of SB17 DP, US- Stelara, and EU-Stelara was evaluated by reduced-CE-SDS. All the levels of LC+HC in SB17 DP (98.8%-99.3%) were within the similarity ranges derived from US- Stelara (≥ 95.8) and the EU-Stelara (≥ 97.8). However, the level of NGHC in SB17 DP (0.3% - 0.4%) was only within the similarity ranges of US-Stelara (≤ 0.4), but not EU-Stelara (≤ 0.3). Specifically, 4 out of 6 lots were slightly above the EU-Stelara similarity range. Minor differences in NGHC levels, between SB17 and EU-Stelara 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.

Forced degradation study: Comparative forced degradation studies were performed with SB17, US-Stelara and EU-Stelara samples under stressed conditions (40 ± 2ºC/75 ± 5% RH) for 3 months, basic (pH 9.5 at 25ºC) for 7 days, acidic (pH 3.0 at 25ºC) for 3 days, oxidative at 5 ± 3ºC for 6 hours, and photostability (cool fluorescent lamp and ultraviolet lamp light at 25 ± 2ºC). While similar stability profiles were observed for SB17, US-Stelara, and EU-Stelara under various stress conditions, some differences under oxidative stress conditions were observed. For example, difference in the trends of the oxidation level of Met254 in HC and FcRn binding observed between SB17 and US-Stelara and EU-Stelara when exposed to enhanced oxidative stress. US-Stelara and EU-Stelara appear to be more susceptible to oxidative stress than SB17. Difference in the oxidation level of Met254 between SB17 and US-Stelara and EU-Stelara was traced to polysorbate 80 (PS80) used in the formulation of the products. PS80 accounts for (b) (4) % of the formulation across all presentations of SB17 and Stelara. However, analysis of PS80 isolated from SB17, US-Stelara, and EU-Stelara by precipitation and assessed using HPLC-CAD revealed different chromatograms of PS80. Furthermore, PS80 as the primary contributor to differences in Met254 oxidation was confirmed by purifying SB17, US-Stelara and EU-Stelara using Protein A chromatography and diluted with SB17 (b) (4) Under oxidative stress, similar degradation trends in all tested attributes including oxidation level were demonstrated in buffer exchanged SB17, US-Stelara and EU-Stelara. This finding confirms that the differences in oxidative stress stability results were attributed to the difference (b) (4) between the products and not due to any differences in the characteristics of SB17. Given the extent of oxidative stress induced in this study is far beyond what SB17 will be exposed to during normal use, the observed differences under enhanced oxidative stress does not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.

Taken together, the totality of the CAA supports the following conclusion:

- SB17 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components.
- For attributes where minor differences were observed between SB17 and US-Stelara and EU-Stelara, the sources of differences were adequately explored, and residual uncertainties were risk-assessed. None of these minor differences were reflected in cell-based functional assays such as binding, neutralization, ADCC, and CDC assays or were shown to have any clinically meaningful impact on safety, PK, and efficacy. Overall, the totality of the analytical data supports that the function, activity, and forced degradation profiles of SB17 and US-Stelara are similar. Therefore, the observed differences between SB17, EU-Stelara and US-Stelara do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.

E. Same Strength(s)

SB17 has the same dosage form and routes of administration as US-Stelara. Samsung is seeking approval of 90 mg/ mL and 45 mg/0.5 mL SB17 in a single-dose prefilled syringe for subcutaneous administration, and 130 mg/26 mL SB17 in a single dose vial for intravenous route of administration as an interchangeable biosimilar to US-Stelara. Comparative protein concentration (mg/mL) was assessed as part of the CAA. The (b) (4) and (b) (4) were assessed as part of manufacturing process controls. Based on the CAA and manufacturing data, the proposed strengths of SB17 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 SB17 in 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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