

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761379Orig1s000

PRODUCT QUALITY REVIEW(S)

LABELS AND LABELING ASSESSMENT

Date of Assessment:	September 24, 2024
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Eric Hales, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIII
Application:	BLA 761379
Applicant:	Fresenius Kabi USA, LLC <i>Per Official Acceptance of the Transfer of BLA Applicant Responsibilities from Formycon AG to Fresenius Kabi USA, LLC dated April 23, 2024</i>
Submission Date:	September 28, 2023
Product:	Otulfi (ustekinumab-aauz)
Dosage form(s):	Injection
Strength and Container-Closure:	45 mg/0.5 mL or 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 a biologics license application for the proposed biosimilar product, ustekinumab injection 45 mg/0.5 mL and 90 mg/1 mL prefilled syringes and 130 mg/26 mL vial.
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

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 September 6, 2024, the container labels and carton labeling submitted on September 24, 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 September 28, 2023)

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Container Labels

Submitted April 23, 2024 with manufacturer name change

(b) (4)

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: Revise the manufacturer's information to

"Mfd by: Fresenius Kabi USA, LLC

Lake Zurich, IL 60047, U.S.A

US License Number 2146"

If space does not permit on the container label, then the city, state and country may be omitted

The Applicant revised as requested

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: Revise the strength from "90 mg/1 mL" 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 ☐ N/A
<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>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Considering removing any bolding of Rx Only to allow for prominence of other critical information on the PDP.
The Applicant revised as requested

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

Comment/Recommendation: 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).

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
<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.
Applicant confirms that there will be no text on the ferrule and cap overseal of the vials.

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 there will be sufficient area (around 5 mm) on the vial containers that allows for visual inspection. With regard to the visual inspection of the pre-filled syringe container, the applicant is fully aware of the need for a viewing window with regard to visual inspection and hereby confirms to affix a label that allows for sufficient visual inspection.

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

Comment/Recommendation: Add the NDC numbers or revise to "NDC pending".
The Applicant revised as requested.

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: Revise the package type term to include the hyphen as follows "Single-dose ..." *The Applicant revised as requested*

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
<i>Recommended labeling practices references: Guidance for Industry Bar Code Label Requirements Questions and Answers (August 2011)</i> <i>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: For the 130 mg/26 mL vial label, Revise Statement of Dosage to read "Dosage: See Prescribing Information." to be in alignment with PLR labeling format. *The Applicant revised as requested*

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

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: Add the degree symbol, the unit of temperature, and revise from a hyphen to "to" to the storage statement as follows: "Store in a refrigerator at 2°C to 8°C (36°F to 46 F°) in original carton to protect from light."
The Applicant's revision is acceptable

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

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.

	☐ No ☐ N/A
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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: Revise the strength from "90 mg/1 mL" 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

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: 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 for the 130 mg/26 mL vial 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 hydrochloride monohydrate, methionine, Polysorbate 80, and sucrose. <i>The Applicant revised as requested</i>	
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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 for the prefilled syringes 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, histidine, Polysorbate 80, and sucrose. *The Applicant revised as requested*

Revise the quantity for histidine for the 45 mg and 90 mg prefilled syringe based on the information provided in 3.2.P.1 so that the 45 mg PFS shows histidine as 0.512 mg and the 90 mg PFS shows histidine as 1.024 mg. *The Applicant revised as requested*

Consider revising the presentation of the ingredient information to match your prescribing information as follows:

Each 0.5 mL prefilled syringe delivers 45 mg ustekinumab-[xxxx], histidine (0.512 mg), Polysorbate 80 (0.02 mg), sucrose (38 mg) and hydrochloric acid (to adjust pH).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab-[xxxx], histidine (1.024 mg), Polysorbate 80 (0.04 mg), sucrose (76 mg) and hydrochloric acid (to adjust pH).

Each 26 mL vial delivers 130 mg ustekinumab-[xxxx], edetate disodium ((b) (4) mg), histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg).

The Applicant retained their proposed format.

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 Otulfi

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.

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 Otulfi carton labeling. *The Applicant revised as requested*

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

Comment/Recommendation: Considering removing any bolding of Rx Only to allow for prominence of other critical information on the PDP. *The Applicant revised as requested*

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

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

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

Comment/Recommendation: Add NDC numbers or revise to "NDC pending". <i>The Applicant revised as requested.</i>
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<u>Preparation instructions (package labeling)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☒ 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

<u>Package type term (package labeling)</u>	<u>Acceptable</u>
<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

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

<u>Prominence of required label statements (package labeling)</u>	<u>Acceptable</u>
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
<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: Revise Statement of Dosage to read "Dosage: See Prescribing Information." to be in alignment with PLR labeling format. *The Applicant revised as requested*

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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>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 products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components</i> <i>Draft Guidance Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2023)</i>	☒ Yes ☐ No ☐ 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).
(b) (4)
<i>Revisions and recommendations were not sent to the Applicant. During internal labeling</i>

negotiation, the clinical team declined to use the verbatim statement as recommended by OPQA III Labeling.

PQR confirmed compatibility for the infusion set (as polypropylene or PVC) with an in-line, sterile, non-pyrogenic, low protein-binding filter with a pore size of 0.2 micrometer.

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 (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The clarity is missing. Please confirm the clarity is correct.

(b) (4)

Applicant revised 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
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: 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 for the prefilled syringes 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, histidine, Polysorbate 80, and sucrose.

(b) (4)

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 for the 130 mg/26 mL vial 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 hydrochloride monohydrate, methionine, Polysorbate 80, and sucrose.

(b) (4)

The Applicant revised (b) (4) to "edetate disodium" but did not revise "L-histidine" and "L-methionine".

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 for the 130 mg/26 mL vial 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 hydrochloride monohydrate, methionine, Polysorbate 80, and sucrose. Please revise "L-histidine" to "histidine" and "L-methionine" to "methionine".

Applicant revised as recommended.

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 for the 130 mg/26 mL vial 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 hydrochloride monohydrate, methionine, Polysorbate 80, and sucrose. Please revise "L-histidine" to "histidine" and "L-methionine" to "methionine". Update

the Description and Composition Table in Section 3.2.P.1 so that "histidine" and "methionine" are in the established names.

Histidine amounts were revised for the 45 mg and 90 mg strengths based on the information provided in 3.2.P.1.

(b) (4)

Cell line was updated.

(b) (4)

Applicant revised 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

<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A
--	--

Comment/Recommendation: The clarity is missing. Please confirm the clarity is correct. 16 HOW SUPPLIED/STORAGE AND HANDLING (b) (4) Add NDC numbers. <i>Applicant revised as recommended.</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

Comment/Recommendation: <i>Per Official Acceptance of the Transfer of BLA Applicant Responsibilities from Formycon AG to Fresenius Kabi USA, LLC dated April 23, 2024.</i> <i>These revision comments were sent to the applicant prior to the transfer from Formycon AG to Fresenius Kabi USA, LLC.</i> FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, for biologic products, the applicant as listed in field 2 Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer. Ensure that the manufacturer name and address appears exactly as intended for the US license holder. If necessary, correct this on your form FDA 356h.
--

The licensed manufacturer should appear as:

Manufactured by: Applicant name as listed in field 2 of Form FDA 356h
Address as listed on line 5 of form FDA 356h
US License No. XXXX

Per your Official Acceptance of the Transfer of BLA Applicant Responsibilities from Formycon AG to Fresenius Kabi USA, LLC submission dated April 23, 2024, revise to:
Fresenius Kabi USA, LLC
Lake Zurich, IL 60047, U.S.A
US License Number 2146

The Applicant listed two separate manufacturers for the prefilled syringe and the vial. The separate manufacturers are not required.

(b) (4)

The Applicant accepted the revisions to the manufacturer as recommended.

Medication Guide Evaluation

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

MEDICATION GUIDE	
<u>STORAGE AND HANDLING</u>	<u>Acceptable</u>
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☒ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
<u>INGREDIENTS</u>	<u>Acceptable</u>

<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: 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 for the prefilled syringes 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, histidine, Polysorbate 80, and sucrose. 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 for the 130 mg/26 mL vial 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 hydrochloride monohydrate, methionine, Polysorbate 80, and sucrose.	
(b) (4)	
<i>The Applicant revised (b) (4) to "edetate disodium" but did not revise "L-histidine" and "L-methionine".</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 for the 130 mg/26 mL vial 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 hydrochloride monohydrate, methionine, Polysorbate 80, and sucrose. Please revise "L-histidine" to "histidine" and "L-methionine" to "methionine". <i>Applicant revised as recommended.</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

Comment/Recommendation: The proprietary name was revised to uppercase letters. Please add in the pronunciation spelling in brackets. Per Instructions for Use – Patient Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry (July 2022)



The Applicant revised as requested.

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:

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)	

Comment/Recommendation:

Per Official Acceptance of the Transfer of BLA Applicant Responsibilities from Formycon AG to Fresenius Kabi USA, LLC dated April 23, 2024.

These revision comments were sent to the applicant prior to the transfer from Formycon AG to Fresenius Kabi USA, LLC.

FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, for biologic products, the applicant as listed in field 2 Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer.

(b) (4)

The Applicant revised as requested.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information, Medication Guide, and Instructions for Use (submitted on September 6, 2024)
<\\CDSESUB1\EVSPROD\bla761379\0036\m1\us\114-labeling\draft\labeling\prescribing-information-otulfi-clean-word.docx>
- Container Labels (submitted on September 24, 2024)

(b) (4)



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



Diana
Pei

Digitally signed by Diana Pei

Date: 9/25/2024 01:56:15PM

GUID: 6352da2c009ad0777a2c3b47ec094b9a



Eric
Hales

Digitally signed by Eric Hales

Date: 9/25/2024 03:03:29PM

GUID: 57d6a5ef01b1162fe9ae3a025d49565e

BLA Executive Summary

Assessment Date: September 4, 2024

1. Application/Product Information

BLA number	761379
Submission Type	Original Submission
Regulatory Pathway	351(k) BLA
Associated IND/BLA	PIND 141478
Review Designation	Standard
Applicant	Fresenius Kabi USA, LLC
Indication	Adult patients with: • Moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy • Active psoriatic arthritis (PsA) • Moderately to severely active Crohn's disease (CD) • Moderately to severely active ulcerative colitis Pediatric patients 6 years and older [who weigh 60 kg or more] with: • Moderate to severe plaque psoriasis (Ps), who are candidates for phototherapy or systemic therapy • Active psoriatic arthritis (PsA)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Otulfi
	Non-proprietary Name/Code Name ustekinumab-aauz
	OBP Naming MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [FYB202]

Drug Product Description	Otufi (FYB202, ustekinumab-aauz) drug product is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly brown-yellow solution with a pH of 5.7-6.3 for subcutaneous (SC) injection or intravenous (IV) infusion. - Otufi SC injection is supplied in a single-dose prefilled syringe (PFS) containing 45 mg/0.5 mL or 90 mg/1 mL of ustekinumab-aauz. Each 0.5 mL PFS contains 45 mg ustekinumab-aauz, histidine (0.512 mg), polysorbate 80 (0.02 mg), and sucrose (38 mg). Each 1 mL PFS contains 90 mg ustekinumab-aauz, histidine (1.024 mg), polysorbate 80 (0.04 mg), and sucrose (76 mg). - Oltufi IV infusion is supplied in a single-dose vial containing 130 mg/26 mL of ustekinumab-aauz, with edetate disodium (0.47 mg), L-histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), polysorbate 80 (10.4 mg) and sucrose (2210 mg). Ustekinumab-aauz is a human immunoglobulin G1 kappa monoclonal antibody produced in CHO cells consisting of 1326 amino acids and an estimated molecular mass that ranges from 148,079-149,690 Daltons.
Dosage Form	Liquid
Strength	SC injection: 90 mg/1 mL and 45 mg/0.5 mL (90 mg/mL) in a PFS IV infusion: 130 mg/26 mL (5 mg/mL) in a vial
Route of Administration	SC injection and IV infusion

Primary Container Closure System	90 mg/mL SC injection: The container closure system is a (b) (4) glass syringe with a staked-in stainless steel (b) (4) needle (b) (4) with a rigid needle shield and a (b) (4) rubber stopper (b) (4). 130 mg/26 mL IV infusion: A (b) (4) Type 1 clear (b) (4) glass vial with a (b) (4) stopper and an aluminum seal with a plastic flip-off cap.		
Device Information	The PFS has a plunger rod (b) (4) screwed into the plunger stopper and a needle safety device (b) (4).		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance and Immunogenicity Assay	Christina Farris	Kristen Nickens
	Drug product and Comparative analytical assessment	Eric Hales	
	Facility	DS: Ekaterina Allen DP: Hyung Lee	Zhong Li
	Microbiology	DS: Ekaterina Allen DP: Hyung Lee	Maxwell Van Tassell

	RBPM	Andrew Shiber
	ATL	Kristen Nickens
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.	

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761379 for Otulfi manufactured by Fresenius Kabi USA, LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of Otulfi is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Otulfi 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:
 - o PFS: (b) (4)
 - Syringe labelling, assembly, and secondary packaging: (b) (4)
 - o Vial: (b) (4)
 - Vial Labeling and secondary packaging: (b) (4)

- b. Fill size and dosage form:
 - 90 mg/1 mL and 45 mg/0.5 mL in a PFS
 - 130 mg/26 mL in a vial
- c. Dating Period:
 - Drug Product:
 - o 90 mg/1 mL and 45 mg/0.5 mL PFS: 36 months at 5°C ± 3°C, protected from light
 - o 130 mg/26 mL vial: 24 months at 5°C ± 3°C, protected from light
 - Drug Substance: (b) (4) months at (b) (4) °C
 - For packaged products: Not packaged
 - Stability Option:
 - o 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 drug product stored in pre-filled syringes and vials under 21 CFR 601.12.
- d. Exempt from lot release:
 - Yes
 - Rationale, if exempted: Otulfi is exempted from lot release per FR 95-29960.
- e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable

PMC #1: Perform a real-world shipping validation study to confirm the suitability of shipping container and transportation method with respect to maintaining intended product temperature, package integrity, and product quality of the Otulfi drug product, stored in a vial (5 mg/mL) and pre-filled syringe (90 mg/mL), based on the worst case scenario. The study design and results will be provided in the final study report to the BLA.

Final report submission date: September 2025

PMC #2: Perform an additional study(ies) to support the control limits for (b) (4) FYB202 90 mg/mL pre-filled syringe drug product batch. The study should be designed to support worst-case (b) (4) e) using FYB202 DS batches (b) (4) Submit the results in a final study report to the BLA.

Final report submission date: September 2025

PMC #3: Implement pressure monitoring during sterilizing filtration of FYB 202 5 mg/mL vial drug product (DP) and update Sections 3.2.P.3.3 and 3.2.P.3.4 of the BLA (b) (4)
validated by a bacterial retention study.

Final report submission date: June 2025

PMC #4: Validate and implement a container closure integrity test (CCIT) method (b) (4)

Final report submission date: December 2024

PMC #5: Conduct a minimum load sterilization validation study with three runs (b) (4)

Final report submission date: December 2024

PMC #6: Validate and implement an alternative quantitative bacterial endotoxin method not subject to low endotoxin recovery to replace the USP <151> pyrogen test for FYB 202 5 mg/mL vial DP release.

Final report submission date: September 2025

PMC #7: Revalidate the blue dye ingress CCIT method to demonstrate the CCIT method is reliable for use (i.e., all positive controls show positive results) for FYB202 drug product pre-filled syringe (PFS) 45 mg in 0.5 mL and FYB202 DP PFS 90 mg in 1.0 mL.

Final report submission date: December 2024

4. Basis for Recommendation

a. Summary:

FYB202 is a proposed biosimilar and proposed interchangeable to US-Stelara for the same routes of administration, dosage forms and strengths as US-Stelara, except the 45 mg/0.5 mL vial presentation. As such, the proposed presentations of FYB202 only support the dosing regimens for adults (Ps, PsA, CD, UC) and pediatric patients 6 years of age and older weighing at least 60 kg (Ps, PsA) in the proposed indications, as applicable.

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 FYB202 is controlled via a cell-based reporter gene assay using the DT40 cell line stably transfected to express the IL-23 receptor and IL-12 receptor beta 1. Neutralization of the p40 subunit of IL-12 and IL-23 by ustekinumab is measured as inhibition of IL-23 induced firefly luciferase activation. Potency is expressed relative to reference standard.

The totality of evidence from the comparative analytical assessment supports that FYB202 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. Fresenius Kabi USA, LLC, adequately established a three-way scientific bridge between FYB202, US-Stelara, and EU-Stelara to support the relevance of the data generated from studies using EU-Stelara as the comparator to the assessment of biosimilarity. Refer to Appendix for detailed summary of the comparative analytical assessment.

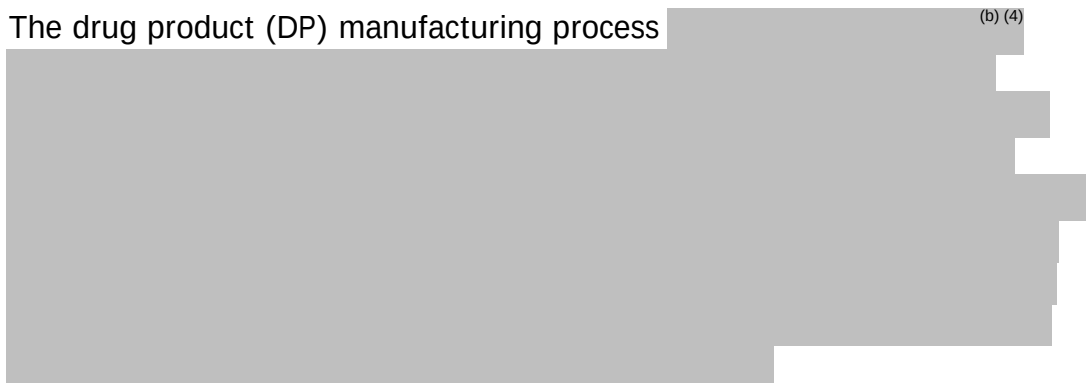
The FYB202 drug substance (DS) manufacturing process consists of

(b) (4)



The drug product (DP) manufacturing process

(b) (4)



The overall FYB202 control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing processes, adventitious agents, microbial contamination, sterility of the DP, and release and stability of DS and DP. The DP is filled (b) (4)

(b) (4) Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategies were provided for DS manufacturing site (b) (4) DP manufacturing sites (b) (4) and

(b) (4) and device facility (b) (4)

All proposed manufacturing and testing facilities are acceptable based on their current cGMP compliance status and recent relevant inspectional coverage. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for intended purposes. A total of 7 PMCs (detailed in Section 3) will be issued to resolve residual concerns that are of low risk in nature. The additional data committed by the Applicant to resolve the described residual risks, with justification in parenthesis, are as follows: real-world vial and PFS DP shipping data (simulation studies were provided, real world data should be provided to confirm shipping validation and quality); confirmation of DP

(b) (4) data were provided at target, data under worst case will confirm control strategy); sterilizing filter

(b) (4) pressure control (b) (4)

(b) (4) will mitigate the risk (b) (4)

during sterile filtration); vial capping and crimping validation

(b) (4) validation will provide additional

assurance of consistent capping and crimping control); (b) (4)

validation (b) (4)

(b) (4) bacterial endotoxin method optimization (the rabbit pyrogen test is currently implemented, development and implementation of an alternative method not using rabbits will increase efficiency); and revalidation of container closure integrity test (CCIT) method to confirm reliability (some positive controls failed to show leakage during the CCIT validation study, additional studies will confirm reliability of the CCIT method). The BLA is recommended for approval from product quality, facility, microbiology and sterility assurance, and device perspectives.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate with PMCs/PMRs
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 ustekinumab (i.e., there is no specific test method described in regulation for ustekinumab that establishes an official standard of potency). We next considered whether potency is a factor for ustekinumab 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 Otulfi for purposes of § 610.61(r) because lot variability is not a concern for Otulfi as Otulfi’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

b. Drug Substance:

i. Protocols approved:

1. Protocol for future Working Cell Bank (WCB) qualification
2. Protocol for Master Cell Bank and WCB stability testing
3. Protocol for concurrent validation of [REDACTED] (b) (4)
4. Protocol for validation of [REDACTED] filter (b) (4)
5. Protocol for qualification of future Primary Reference Standard (PRS) and Working Reference Standard (WRS)
6. Protocol for requalification of PRS and WRS
7. Post-approval stability protocol and stability commitment
8. Post-approval protocol for shelf-life extension of DS

ii. Residual risk: N/A

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:

1. Post-approval stability protocol and stability commitment (PFS and Vial)
2. Post-approval protocol for shelf-life extension of DP (PFS and Vial)
- ii. Residual risk: Refer to PMCs in Section 3.
 1. Confirmation that the quality, temperature, and package integrity of the DP vial and PFS presentations are maintained when shipped in the commercial shipping configuration under real-world shipping conditions.
 2. Confirmation of commercial DP process control limits for (b) (4)
 3. Potential risk of (b) (4) sterilizing filters.
 4. Validation of a container closure integrity test (CCIT) to ensure vials are capped and the crimping process is in place.
 5. Confirmation that (b) (4) validated.
 6. Suboptimal bacterial endotoxin method design currently using rabbits.
 7. Revalidation of CCIT method to confirm results for control groups and reliability of the method.
- 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. Comparative Analytical Assessment Summary

A. Overview and Conclusions

Fresenius Kabi USA, LLC (referred to hereafter as Fresenius Kabi) is seeking licensure of FYB202 as an interchangeable biosimilar to US-licensed Stelara (referred to hereafter as US-Stelara). US-Stelara is available in the following strengths: 45 mg/0.5 mL (90 mg/mL) and 90 mg/1.0 mL (90 mg/mL) in a single-dose prefilled syringe (PFS), and 45 mg/0.5 mL (90 mg/mL) and 130 mg/26 mL (5 mg/mL) in a single-dose vial. Fresenius Kabi is seeking licensure for the same strengths currently available for US-Stelara with the same dosage form, and routes of administration as US-Stelara, with the exception of the 45 mg/0.5 mL (90 mg/mL) in a single-dose vial for which licensure is not being sought. FYB202 has the same formulation as US-Stelara.

To support a demonstration that FYB202 is highly similar to US-Stelara and establish the analytical component of the scientific bridge, Fresenius Kabi performed a three-way comparative analytical assessment (CAA). The following numbers and types of lots were included in the CAA for the PFS: 8 independent lots of FYB202 drug product (DP; 6 lots of 45 mg/0.5 mL, 2 lots of 90 mg/mL; 3 non-independent PPQ 90 mg/mL lots were included for information purposes only; 3 additional commercial drug substance lots were provided to support the protein concentration CAA), 18 lots of US-Stelara (14 lots of 45 mg/0.5 mL, 4 lots of 90 mg/mL) with expiration dates ranging from 03/2015-04/2024, and 20 lots of EU-licensed Stelara, referred to hereafter as EU-Stelara, (7 lots of 45 mg/0.5 mL and 13 lots of 90 mg/mL) with expiration dates ranging from 02-2014-12-2024. The following numbers and types of lots were included in the CAA for the vial: 6 lots of FYB202 130 mg/26 mL, 10 lots of US-Stelara 130 mg/26 mL with expiration dates ranging from 06/2018-06/2024, and 10 lots of EU-Stelara 130 mg/26 mL with expiration dates ranging from 10/2021-01/2025. The ages of the US-Stelara and EU-Stelara lots at the time of testing appear adequate to capture potential differences or variability over time for US-Stelara and EU-Stelara. Only 45 mg/0.5 mL PFS lots of US-Stelara, EU-Stelara and FYB202 DP were used in clinical studies, all lots were included in the CAA. Analytical comparability data were provided between the PFS presentations as well as between the 45 mg/0.5 mL PFS and the 130 mg/26 mL vial presentation to enable leveraging clinical data from the 45 mg/0.5 mL presentation to support licensure. Data were provided to support the stability of the US-Stelara and EU-Stelara lots stored frozen over the course of the CAA.

PFS and vial CAA studies were performed separately and included extensive comparative physiochemical and functional assessments of quality attributes, as well as comparative assessments of the degradation profiles under forced degradation conditions. The product quality attributes assessed in the CAA, as well as the comparative forced degradation studies were appropriate. Orthogonal assessments were used to evaluate most quality attributes. Data from analytical method qualification/validation studies, and the totality of data in the CAA, support the suitability of the methods used in the CAA.

A risk-based approach for the statistical evaluation of the analytical results was implemented in which high risk-ranked attributes were assessed against quantitative criteria using the mean $\pm$ x standard deviation (SD) approach. The multiplier x was set to 2.5 for attributes with very high criticality relevant to the mode of action, to 2.75 for highly critical attributes with an abundance $\geq 1\%$ and for all critical attributes not measured by abundance and a 3 for all remaining attributes. The pre-defined acceptance criteria require that at least $\geq 90\%$ of lots are within the appropriate quality range (QR). A pre-defined limit approach was applied for data which are not directly quantifiable and primarily depend on method variability. Low risk-ranked attributes or

attributes tested using qualitative assays were evaluated using side-by-side visual comparisons. The Applicant excluded results from FYB202 DP lots derived from non-independent DS lots in the statistical analysis, where applicable. The risk-based approach to assess whether FYB202 is highly similar to US-Stelara and to justify the analytical component of the scientific bridge is acceptable.

Our assessment of FYB202 and US-Stelara data supports the determination that FYB202 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. FYB202 has the same strengths, dosage form, and routes of administration as US-Stelara, as applicable. The Applicant used a comprehensive set of analytical methods that were suitable to evaluate the critical quality attributes of FYB202 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 quality attributes do not preclude a determination that FYB202 and US-Stelara are highly similar.

In addition, the Applicant used three-way pairwise comparisons of FYB202, US-Stelara, and EU-Stelara to establish the analytical component of the scientific bridge between FYB202, 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 FYB202, US-Stelara and EU-Stelara, using the same methods and statistical approaches used to evaluate the FYB202 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

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
	Intact mass, deglycosylated	Yes	Yes
Post Translational Modifications	Isoaspartate	Yes	Yes
	C-terminal lysine	Yes	Yes
	Deamidation Fab and Fc domain	Yes	Yes
	Oxidation Fab and Fc domain	Yes	Yes
	C-terminal proline	Yes	Yes
	Pyroglutamate	Yes	Yes
	Glycation	Yes	Yes
Higher Order Structure	Secondary structure	Yes	Yes
	Tertiary structure	Yes	Yes
	Free thiols	Yes	Yes
	Disulfide bonds	Yes	Yes
	Thermal Stability	Yes	Yes
Biological Activity – Fab mediated	IL-12 binding by ELISA	Yes	Yes
	IL-12 relative binding affinity by SPR	Yes	Yes
	IL-23 binding by ELISA	Yes	Yes
	IL-23 relative binding by SPR	Yes	Yes
	IL-12 neutralization by NK92 cell-based assay	Yes	Yes
	IL-23 neutralization by iLite IL-23 cell-based assay	Yes	Yes
	Inhibition of cytokine (IL-17F) release	Yes	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Biological Activity – Fc mediated	IL-12/IL-23 inhibition (STAT 3/4 signaling)	Yes	Yes
	Lack of IL-6R binding	Yes	Yes
	FcRn binding by BLI	Yes	Yes
	FcyRI binding by SPR	Yes	Yes
	FcyRIIIa (V) binding by SPR	Yes	Yes
	C1q binding by ELISA	Yes	Yes
	ADCC	Yes	Yes
Purity and impurities	CDC	Yes	Yes
	Size variants by CE-SDS non-reduced	Yes	Yes
	Non-glycosylated HC by CE-SDS reduced	Yes	Yes
	Size variants by SE-HPLC	Yes	Yes
	Size variants by AUC	Yes	Yes
Glycosylation	Charge variants by iCIEF (native and deglycosylated)	Yes	Yes
	Afucosylation	Yes	Yes
	High mannose	Yes	Yes
	Total Galactosylation	Yes	Yes
	Sialylation	Yes	Yes
Drug Product Attributes	Alpha-galactose	Yes	Yes
	Protein concentration	Yes	Yes
Comparative Forced	Isoelectric point	Yes	Yes
	Freeze/thaw	Yes	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Degradation	Thermal stress	Yes	Yes
	Agitation	Yes	Yes
	Light stress	Yes	Yes
	Glycation	Yes	Yes
	pH	Yes	Yes
	Oxidation	Yes	Yes

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

The comparative clinical study, FYB202-03-01, supporting this application compared FYB202 to EU-Stelara. To support the relevance of these comparative clinical data to the assessment of biosimilarity, the applicant performed three-way pairwise analytical and PK comparisons between FYB202, US-Stelara and EU-Stelara. The same analytical methods used for supporting a demonstration that FYB202 is highly similar to US-Stelara were used for the pairwise analytical comparisons with EU-Stelara (see discussion in Section A). The differences observed in the analytical studies do not preclude the establishment of the analytical component of the scientific bridge. See section D below. The results support the establishment of the analytical component of the scientific bridge.

D. Assessment of Comparative Analytical Study Results

Comparative analytical assessment criteria were met for all attributes within the quality ranges with the following exceptions discussed in Table B below:

Table B: Resolution of Residual Uncertainties for Individual Critical Quality Attributes

Critical Quality Attributes with Differences	Related Critical Quality Attributes
Post-translational modifications (PTM)	C-terminal lysine: The c-terminal lysine levels in all FYB202 PFS and vial lots (min-max: <0.9- 10.1%) are lower and outside the US-Stelara QR (PFS: 24.9-61.8%, vial: 35.1-53.1%) and EU-Stelara QR (PFS: 24.4-61.0%, vial: 31.3-57.5%). This is also

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	reflected by differences in the peak profile by intact mass analysis where peaks corresponding to C-terminal lysine were absent from the FYB202 deconvoluted LC-MS spectra. The difference is likely attributed to the use of different production cell lines (i.e., CHO-K1 cell line for production of FYB202 and Sp2/0 mouse cell line for production of US-Stelara). C-terminal lysine is a critical quality attribute for therapeutic antibody products developed for subcutaneous (SC) administration because of its potential impact on antibody SC bioavailability and pharmacokinetics (PK). Correlative relevance of potential impact of C-terminal lysine from a product quality perspective can generally be assessed through an evaluation of shifts in charged isoelectric point (pI). With that, despite the lower amount of C-terminal lysine observed in FYB202 lots, the overall pI for the same FYB202 lots were all within the US-Stelara QR and EU-Stelara QR. Additionally, no differences in other PQAs known to impact SC absorption and PK (e.g., FcRn binding activity) were observed. Relevant to the vial presentation, because C-terminal Lys is rapidly cleaved in the systemic circulation, the difference in the C-terminal lysine levels is low risk for an impact to clinical safety, immunogenicity, potency, PK, and/or efficacy of FYB202. Further, the difference did not impact potency, which is similar for FYB202, US-Stelara, and EU-Stelara. Therefore, the difference in C-terminal lysine does not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge. This is consistent with the results of the PK similarity study in which PK similarity was demonstrated between FYB202, US-Stelara, and EU-Stelara (see BMER). Oxidation of Fab and Fc domains: <u>HC Met70</u>: The HC Met70 levels of the FYB202 lots (PFS min-max: 1.2-1.9%; vial min-max: 0.6-1.0%) are slightly higher than the US-Stelara QR (PFS QR: ≤1.0%; vial QR: ≤0.7%) and EU-Stelara QR (PFS QR: ≤1.2%; vial QR: ≤0.7%). The differences in the means between FYB202, US-Stelara and EU-Stelara are small (~<1.0 %) and the level of these PTMs in all three products is low. No impact on biological activity attributes is observed. <u>LC Met4</u>: The LC Met4 levels of FYB202 lots (PFS min-max 0.5-1.4%; vial min-max: 0.3-0.6%) are slightly higher and/or at the US-Stelara QR (PFS QR: ≤0.9%; vial QR: ≤0.6%) and EU-Stelara

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	QR (PFS QR: $\leq 1.0\%$; vial QR: $\leq 0.4\%$). The differences in the means between FYB202, US-Stelara and EU-Stelara are small ($\sim < 0.5\%$) and the level of these PTMs in all three products is low. No impact on potency attributes is observed. <u>LC Trp32/35</u>: The LC Trp32/35 levels of FYB202 lots (PFS min-max: 0.3-1.4%, vial min-max: 0.1-0.4%) generally within the US-Stelara QR (PFS QR: $\leq 0.8\%$, vial QR: $\leq 0.5\%$) and EU-Stelara QR (PFS QR: $\leq 0.8\%$, vial QR: $\leq 0.3\%$), with minor differences impacting the ability to meeting the CAA acceptance criteria. The differences in the means between FYB202, US-Stelara and EU-Stelara are small ($\sim < 0.3\%$) and the level of these PTMs in all three products is low. No impact on potency attributes is observed. <u>HC Met254</u>: The HC Met254 levels of FYB202 lots (PFS min-max: 3.2-4.6%, vial min-max: 2.0-2.7%) are higher than the US-Stelara QR (PFS QR: $\leq 2.7\%$, vial QR: 0.5%-1.2%) and EU-Stelara QR (PFS QR: $\leq 3.2\%$, vial QR: 0.4-1.2%). The differences in the means and maximum amounts of oxidation between FYB202, US-Stelara and EU-Stelara are small ($\sim < 2\%$) and the level of these PTMs in all three products is low. No impact on potency attributes is observed. <u>HC Trp419/Met430</u>: The HC Trp419/Met430 levels of FYB202 lots (PFS min-max: 0.5-1.6%) are higher than the US-Stelara QR (PFS QR: 0.2-0.5%) and the EU-Stelara QR (PFS QR: 0.1-0.8%). The total amount of the PTM ($\sim < 1.6\%$) and the difference in the means ($\sim < 0.6$) is small. Trp419/Met430 oxidation was not detected in the FYB202 vial lots owing to the already low levels observed in the PFS lots. No impact on potency attributes is observed or FcRn binding. Overall, the differences in these PTMs are small in magnitude, do not correlate with any other changes in attributes related to potency, and are not expected to impact PK, safety, or efficacy. These differences do not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	C-terminal proline: The C-terminal proline levels (HC Pro447) of FYB202 lots (PFS min-max: 0.4-1.0%, vial min-max: 0.3-1.3%) are higher than the levels in US-Stelara and EU-Stelara in which the PTM is not detectable (N/D). However, the maximum amount of this PTM in FYB202 is 1.3%, which is low. The presence of proline amide formation is a correlative consequence of the lower levels of C-terminal Lys in FYB202. Ultimately, the levels of are low amongst all three products (ranging from not detectable to 1.3%). The magnitude of the difference is small, there was no impact on potency attributes observed, and this difference is not expected to impact PK, safety, or efficacy. Therefore, the differences in C-terminal proline do not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge. Glycation: The glycation levels in FYB202 lots (PFS min-max: 0.22-0.73%, vial min-max: 0.21-0.71%) are slightly higher than most of the US-Stelara (PFS min-max: N/D-0.08%, vial min-max: N/D-0.08%) and EU-Stelara lots (PFS min-max: 0.01-0.13%, vial min-max: 0.06-0.18%) ranges. Overall, the levels of glycation are low amongst all three products and forced degradation studies show that even high levels of glycation ~15% have no impact on bioactivity. The magnitude of the differences are small and these differences are not expected to impact PK, safety, or efficacy. The differences in glycation do not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.
High order structure	Free thiol: The free thiol levels in the FYB202 lots (PFS min-max: 0.302-0.362 mol/mol, vial min-max: 0.269-0.368 mol/mol) have higher free thiol content and are outside of the US-Stelara QR (PFS QR: 0.149-0.292 mol/mol, vial QR: 0.117-0.297 mol/mol) and EU-Stelara QR (PFS QR: 0.170-0.270 mol/mol, vial QR: 0.132-0.288 mol/mol). The results show a positive linear correlation between free thiol content in the FYB202 lots with higher levels of LMW9 species in the FYB202 lots. LMW9 species corresponds to FYB202 product-related species missing one LC (i.e., HHL species); note that its presence was confirmed by LC-MS. The magnitude of the differences observed between FYB202, US-Stelara, and EU-Stelara and overall levels of free thiol content is low in magnitude and risk for an impact to safety, potency, immunogenicity, and efficacy. The differences in free thiol do not

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.
Biological activity	IL-23 neutralization by NK92 cell-based assay: The IL-23 neutralization results show that one FYB202 vial lot (min-max: 94-115%) is higher than the EU-Stelara QR (vial QR: 89-112%) and that two US-Stelara lots (vial min-max: 88-113%; vial QR: 80-120%) are outside of the EU-Stelara QR. The differences are very minor (<3%), also all of the FYB202 lots are within the US-Stelara QR and follow similar data trends. The observed difference is attributed to method variability, further, no differences were observed by IL-12 binding ELISA. The minor difference in the IL-23 neutralization NK92 cell-based assay results do not preclude establishment of the analytical component of the scientific bridge. FcyRI: The FcyRI levels in all FYB202 lots (PFS min-max: 94.5-101.7%, vial min-max: 100.0-102.8%) are all lower and outside of the US-Stelara QR (PFS QR: 124.2-134.1%, vial QR: 119.4-145.1%) and EU-Stelara QR (PFS QR: 116.8-128.9%, vial QR: 125.2-132.5%). FcyRI is a high affinity receptor for monomeric IgG and most of the FcyRI is expected to be heavily occupied by serum IgG and unavailable for binding to therapeutic antibodies. Therefore, the differences noted in FcyRI binding affinity are not expected to have a significant impact on clinical PK and safety of FYB202. The differences in FcyRI binding do not preclude a demonstration that FYB202 is highly similar or establishment of the analytical component of the scientific bridge. FcyRIIIa V: The FcyRIIIa(V) levels in all FYB202 lots (PFS min-max: 84.0-102.5%, vial min-max: 90.3-103.4%) are lower and outside of the US-Stelara (PFS QR: 127.8-153.3%, vial QR: 130.1-141.3%) and EU-Stelara (PFS QR: 131.5-150.1%, vial QR: 130.7-143.1%) QRs. Lower FcyRIIIa(V) binding activity can be attributed to the lower level of afucosylated glycans in FYB202 compared to US-Stelara and EU-Stelara. FcyRIIIa binding could impact ADCC activity. Lack of ADCC activity was demonstrated for all three product. Also, based on the demonstrated binding of the products to soluble ligands (i.e., IL-12 and IL-23 cytokines) the likelihood that FYB202 would mediate Fc effector function is low. Therefore, the lower FcyRIIIa(V) binding activity for FYB202 is not expected to have an increased risk for unexpected effector

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	function; 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. C1q: The C1q levels in the FYB202 lots (PFS min-max: 74-106%, vial min-max: 93-97%) partially overlaps with the range of the US-Stelara (PFS min-max: 82-114%, vial min-max: 87-144%) and EU-Stelara lots (PFS min-max: 82-111%, vial min-max: 122-124%). The difference is minor considering the expected method variability and overlap of the results. Further, FYB202, US-Stelara and EU-Stelara were demonstrated to not mediate CDC activity. The difference does not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.
Size variants	CE-SDS non-reduced: The FYB202 lots have lower purity (PFS min-max: 96.84-97.95%, vial min-max: 97.11-97.98%) and higher % LMW species (PFS min-max: 2.05-3.16%, vial min-max: 2.02-2.89%) and are outside of the US-Stelara QR (purity - PFS QR: 97.88-98.45%, vial QR: 97.95-98.45%; LMWS -PFS QR: 1.55-2.12%, vial QR: 1.55-2.05%) and EU-Stelara QR (purity - PFS QR: 97.93-98.47%, vial QR: 97.88-98.51%; LMWS -PFS QR: 1.53-2.07%, vial QR: 1.49-2.12%). The slightly higher levels of LMW species by CE-SDS non-reduced were mainly attributed to higher levels of LMW9 species in the FYB202 lots as compared to lower levels observed in US-Stelara and EU-Stelara. The magnitude of the differences observed in purity and LMWS, both ~<1%, are minor between FYB202, US-Stelara, and EU-Stelara. No impact on biological activity was observed. The difference does not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge. CE-SDS reduced [non-glycosylated (NG-HC)]: The levels of NG-HC in all FYB202 lots (PFS min-max: 0.63-0.73%, vial min-max: 0.57-0.77%) are higher outside of the US-Stelara QR (PFS QR: 0.12-0.31%, vial QR: 0.15-0.30%) and EU-Stelara QR (PFS QR: 0.14-0.32%, vial QR: 0.15-0.27%). However, the differences are minor in magnitude and the attribute is low in overall abundance attribute, which is low risk for impact on PK, potency, and safety of FYB202. The difference does not preclude

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	a demonstration of highly similar or establishment of the analytical component of the scientific bridge. SE-HPLC: The amount of HMW species in the FYB202 lots (PFS min-max: 0.31-0.51%, vial min-max: 0.23-0.39%) are higher and/or overlap with the US-Stelara QR (PFS QR: 0.15-0.29%, vial QR: 0.06-0.33%) and EU-Stelara QR (PFS QR: 0.15-0.29%, vial QR: 0.02-0.39%). The differences in HMW species are very minor with a maximum amount detected of 0.51%, which is a level expected not to have an impact on clinical safety, immunogenicity, potency, PK, and/or efficacy. Further, differences in HMW species did not have significant impact on monomeric purity by SE-HPLC and AUC. These differences do not impact biological activity. The difference does not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.
Charge variants	icIEF (native and deglycosylated): The amount of main charged species in all FYB202 lots (PFS min-max: 62.45-71.05%, vial min max: 62.06-71.21%) is higher than and outside of the US-Stelara QR (PFS QR: 20.87-46.53%, vial QR: 27.10-36.72%) and EU-Stelara QR (PFS QR: 28.05-39.69%, vial QR: 27.11-36.57%). The amount of acidic charged species in the FYB202 lots (PFS min-max: 22.72-26.59%, vial min max: 23.90-25.80%) are either within or slightly lower than and outside of the US-Stelara QR (PFS QR: 19.95-35.85%, vial QR: 26.39-31.74%) and EU-Stelara QR (PFS QR: 24.15-34.46%, vial QR: 25.27-33.00%). The amount of basic charged species in the FYB202 lots (PFS min-max: 3.90-14.34%, vial min max: 3.81-13.88%) are lower than and outside of the US-Stelara QR (PFS QR: 30.76-46.04%, vial QR: 34.75-43.29%) and EU-Stelara QR (PFS QR: 28.82-44.84%, vial QR: 31.36-46.69%). Upon deglycosylation, the amount of main charged species in all FYB202 lots (PFS min-max: 73.53-77.89%, vial min max: 72.73-75.59%) is lower than and outside of the US-Stelara QR (PFS QR: 78.90-83.50%, vial QR: 76.67-84.25%) and EU-Stelara QR (PFS QR: 78.68-84.01%, vial QR: 79.47-81.73%). The amount of acidic charged species in the FYB202 lots (PFS min-max: 19.01-22.98%, vial min max: 21.39-23.65) are higher than and outside of the US-Stelara QR (PFS QR: 14.60-18.75%, vial QR: 14.13-20.58%) and EU-Stelara QR (PFS QR: 14.05-19.02%, vial QR: 14.05-19.02%).

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	16.29-18.23%). The amount of basic charged species in the FYB202 lots (PFS min-max: 2.91-3.61%, vial min max: 2.85-3.62%) overlap or are higher than and outside of the US-Stelara QR (PFS QR: 1.69-2.56%, vial QR:1.35-3.02%) and EU-Stelara QR (PFS QR: 1.78-2.46%, vial QR: 1.74-2.54%). These primary differences noted in charge species are in main and basic species, which were attributed to lower abundance of specific basic species [e.g., C-terminal Lys (Lys449)]. The minor differences in acidic species were attributed to the correlative differences in sialylation. Deglycosylation pre-treatment reduced the complexity in the charge pattern and resulted in similar electropherograms for FYB202, US-Stelara, and EU-Stelara with exception of an additional basic variant peak (BV3 correlative with c-terminal proline) found only in the FYB202 samples. This also resulted in a shift in the charge variants with higher levels of acidic and basic species and lower levels of main peak in the FYB202 PFS and vial samples relative to US-Stelara and EU-Stelara. The higher levels of acidic modifications were attributed to LMW and demonstrated linear correlation. Overall, the differences in the charge profiles are attributed to differences in C-terminal Lys, sialylation, Fc oxidation, Proline amidation, and LMW species between FYB202, US-Stelara, and EU-Stelara. The differences noted are not expected to impact PK, safety, or efficacy and do not preclude a demonstration of highly similar or the establishment of the analytical component of the scientific bridge.
Glycosylation	Afucosylation: The levels of afucosylation in FYB202 lots (PFS min-max: 3.0-4.7%, vial min-max: 3.1-4.5%) are generally lower than the US-Stelara QR (PFS QR: 4.0-7.6%, vial QR: 4.5-7.1%) and EU-Stelara QR (PFS QR: 3.9-8.0%, vial QR: 4.5-7.2%). Afucosylated species may impact binding to Fcy receptors, such as FcyRIIIa, which can lead to ADCC activity, and the lower levels are consistent with the differences seen in FcyRIIIa binding. The noted differences are not expected to have a clinically meaningful impact because all three products were shown to have no effector functions. High mannose: The levels of high mannose in FYB202 lots (PFS min-max: 0.5-0.9%, vial min-max: 0.6-0.9%) are lower than or overlap with the US-Stelara QR (PFS QR: 0.2-2.0%, vial QR: 0.8-

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	1.0%) and EU-Stelara QR (PFS QR: 0.5-1.4%, vial QR: 0.6-1.2%). High mannose may impact PK and have the potential to impact ADCC activity. The difference, where noted are very minor (< 0.5%) and not expected to have a clinically meaningful impact because the biological activities of the products are similar, and lack of ADCC activity is demonstrated. The differences noted do not preclude a demonstration of highly similar or the establishment of the analytical component of the scientific bridge.
	Total-Galactosylation: Minor differences in total galactosylation were noted between US-Stelara PFS (min-max: 16.1-47.3%, PFS QR: 8.0-71.6%) and EU-Stelara QR (PFS QR: 40.4-49.0%) where three lots of the US-Stelara lots are outside of the EU-Stelara QR. The three US-Stelara lots that are outside of the EU-Stelara QR also have lower levels of total sialylation and higher levels of high mannose consistent with the lower levels of total galactosylation observed (refer to applicable discussions). As FYB202, US-Stelara, and EU-Stelara are shown not to mediate CDC and ADCC activity, and the small magnitude of the differences, the variability in galactosylation is not expected to have a clinically meaningful impact. The differences noted do not preclude a demonstration of highly similar or the establishment of the analytical component of the scientific bridge.
	Sialylation and alpha-galactosylation: The amounts of sialylation and alpha-galactosylation (alpha-gal) in FYB202 lots (sialylation -PFS min-max: 1.4-2.4%, vial min-max: 1.6-2.2%; alpha-gal – PFS min-max: N/D, vial min-max: N/D) are all lower and outside of the US-Stelara QR (sialylation- PFS QR: 5.1-35.3%, vial QR: 15.7-32.0; alpha-gal – PFS QR: 1.0-9.0%, vial QR: 1.4-9.3%) and EU-Stelara QR (sialylation- PFS QR: 13.8-29.2%, vial QR 16.3-30.5%; alpha-gal – PFS QR: 1.4-9.1%, vial QR: 2.6-8.2%). Significant amounts 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. In addition, sialylated glycan levels may impact PK and immunogenicity. However, the differences observed did not impact biological activity. Further, the composition of the sialylated and alpha-gal glycans are expected to differ due to differences in the production cell lines between the US-Stelara

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	and EU-Stelara lots and the FYB202 lots. Lower levels of sialylation (NANA predominate expected form in FYB202) and alpha-gal in FYB202 are expected to result in lower risk for immunogenicity reactions to FYB202. Overall, the differences noted are not expected to impact safety risks, and are not expected to be clinically meaningful. Therefore, the differences do not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge. This is consistent with the conclusions from the clinical study results where PK similarity was demonstrated between FYB202, US-Stelara, and EU-Stelara, and there were no meaningful differences in immunogenicity between the three products (see BMER).
Forced Degradation	PFS: • <u>Freeze/Thaw</u>: Differences are noted in the data trends for main peak and acidic species by icIEF DC between FYB202, US-Stelara, and EU-Stelara. Acidic species decreased by 2.63-5.08% and main peak increased by 2.17-4.75% (owing to a slight increase in basic species by 0.18-0.46% among the three products) in the FYB202 lots relative to time zero. No significant changes were observed in main peak or acidic species for US-Stelara and EU-Stelara lots. The direction and magnitude of the change in main peak and acidic species observed in the FYB202 lots is relatively minor and results in potentially increased purity, which is unexpected in response to stress based on the direction of the change. • <u>Heat Stress</u>: Differences are noted in the data trends for HMW species by SE-HPLC, purity and LMW species by CE-SDS non-reduced, basic species by icIEF DC, and PTMs (i.e., isomerization by IsoAsp, LC Trp32/35 oxidation, HC Asn317 and Asn386/391 succinimide by peptide mapping, and Fd subunit glycation by subunit analysis). The magnitude of the differences in HMW species is generally consistent with the 2-fold greater starting level in the FYB202 lots at time zero as similar difference in final levels observed and not a difference in degradation rates. The differences in the PTMs noted above are likely related to the method variability when considering that the range of

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	the FYB202 lots partially overlaps the range of the US-Stelara and/or EU-Stelara lots for these attributes and the method performance. Differences were observed in the data trends for purity/LMW species by CE-SDS non-reduced and basic species by icIEF DC. However, the data demonstrates the same overall degradation pathway and only slight differences are observed in the overall magnitude of the data trends. • <u>Photo Stress</u>: Higher levels of oxidation were observed among all oxidation sites studied in the FYB202 lots, as compared to the US-Stelara and EU-Stelara lots with photo stress. The potency appeared lower in the FYB202 lots after photo stress relative to the levels observed at time zero to the US-Stelara and EU-Stelara lots. A slightly slower degradation rate in basic species is also observed in the FYB202 lots relative to the US-Stelara and EU-Stelara lots where faster degradation rates are observed. The differences in the magnitude of the trends (e.g., HMW species, oxidation) are generally proportional with the higher starting levels observed in the FYB202 lots relative to the US-Stelara and EU-Stelara lots. The differences in potency appear to be related to sample and/or method variability. • <u>Basic pH Stress</u>: A slight decrease in glycation is observed in both FYB202 lots compared to the US-Stelara and EU-Stelara lots. The magnitude of the trends among the lots is minor (<2-fold difference), and opposite trends of similar magnitude are observed between the two US-Stelara lots based on assessment of the individual lot trends. Glycation is an acidic modification, and no significant differences were observed in the degradation trends in acidic species between FYB202, US-Stelara, and EU-Stelara. <u>Oxidation Stress</u>: LMW species and acidic species increased in the US-Stelara and EU-Stelara lots with corresponding changes in main peak levels; however, no changes were observed in the FYB202 lots in response to

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	the stress condition. Reduced sensitivity of FYB202 to chemical oxidation stress is not a similarity concern because final purity is within the upper limit of the range of the reference products on stability. All three products demonstrate similar degradation trends in the other attributes, including potency, indicating that the increased fragmentation does not have an impact on higher order structure. Vial • <u>Freeze/Thaw</u>: Differences are noted in the data trends for Met51 oxidation and potency. No changes are observed in Met51 oxidation in the FYB202 lots; however, the US-Stelara and EU-Stelara lots both demonstrate decreasing trends in Met51 oxidation; the magnitude of the change is minor (i.e., 0.2-0.5% relative to time zero). The FYB202 and US-Stelara lots had similar potency trends; however, the EU-Stelara lots demonstrated an opposite trend (Figure 9). The magnitude of the changes in potency (i.e., 2-8% relative to time zero) are relatively minor. • <u>Heat Stress</u>: Differences are noted in the data trends for Fc glycation where the FYB202 lots demonstrated opposite trends from the US-Stelara and EU-Stelara lots. The FYB202 lots increased by 1.28-1.31% relative to time zero while the US-Stelara and EU-Stelara lots demonstrated only a slight decrease. The trend in Fc glycation of the FYB202 lots is relatively minor, and the levels observed after heat stress only differ from the US-Stelara and EU-Stelara lots by ~1%. • <u>Basic pH Stress</u>: Differences are noted in the data trends for Trp47 oxidation and Fc glycation. No changes in Trp47 oxidation are observed for FYB202; however, both US-Stelara and EU-Stelara lots demonstrate an increasing trend with slightly higher levels (US: 0.8-1.1%, EU: 0.9-1.2%, and FYB202: 0.4-0.5%) after 1 months of exposure to the stress condition. The data trends for Fc glycation are similar between FYB202 and US-Stelara; however, the EU-Stelara lots demonstrate a different trend. However, the ending levels are similar among the lots (US: <2.89%,

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	EU: 2.36-2.64%, and FYB202: 2.31-2.74%). The direction and/or magnitude of the trends in Trp47 oxidation and Fc glycation are relatively minor. The trends for Gln65/67 deamidation, Met51 oxidation, and Fd glycation are most likely explained by the method variability based on the wide variation observed in the data and/or inconsistent trends • <u>Oxidation Stress</u>: Differences are noted in the data trends for purity and LMW species by CE-SDS non-reduced (Figures 116-117). The FYB202 lots demonstrate a slightly greater rate in formation of LMW species relative to US-Stelara and EU-Stelara. The estimated fold change in LMW species for the FYB202 lots is ~2-fold and ~1.7 for the US-Stelara and EU-Stelara lots. This indicates that the rates in formation of LMW species is not significantly different between FYB202, US-Stelara, and EU-Stelara. However, the difference in the final levels of LMW species (US: 2.80-2.99%, EU: 2.88-3.04%, and FYB202: 4.46-4.55%) and impact on purity (US: 97.01-97.20%, EU: 96.96-97.12%, and FYB202: 95.45-95.54%) is low risk with respect to similarity. Overall, the data trends and raw data profiles are generally similar between FYB202, US-Stelara, and EU-Stelara after exposure to the forced degradation conditions with only minor differences in the results. The differences noted do not preclude a demonstration of highly similar or the establishment of the analytical component of the scientific bridge.

E. Same Strength(s)

FYB202 has the same dosage form and routes of administration as US-Stelara. Fresenius Kabi USA, LLC is seeking approval for the 45 mg/0.5 mL (90 mg/mL) and 90 mg/1.0 mL (90 mg/mL) in a single-dose PFS, and the 130 mg/26 mL (5 mg/mL) single-dose vial. US-Stelara is available at these strengths and in these presentations. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment, and deliverable volume and fill weight data assessed (b) (4)

Based on the comparative analytical assessment and

manufacturing data, the proposed strengths of FYB202 have the same total content of drug substance in units of mass per volume as US-Stelara. The strengths of 45 mg/0.5 mL and 90 mg/1.0 mL in the PFS, and 130 mg/26 mL in the single-dose vials are the same as those of US-Stelara.

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