CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761275Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	March 1, 2024
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Product Quality Assessment III
Through:	Bazarragchaa Damdinsuren, PhD Product Quality Team Lead OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761275
Applicant:	Fresenius Kabi USA, LLC
Submission Date:	May 31, 2022, and September 5, 2023
Product:	Tyenne (tocilizumab-aazg)
Dosage form(s):	Injection
Strength and Container-Closure:	80 mg/4 mL (20 mg/mL) in single-dose vial 200 mg/10 mL (20 mg/mL) in single-dose vial 400 mg/20 mL (20 mg/mL) in single-dose vial 162 mg/0.9 mL single-dose prefilled syringe 162 mg/0.9 mL single-dose autoinjector
Purpose of assessment:	The Applicant submitted a biologics license application (BLA) to seek approval of Tyenne (tocilizumab-aazg) for the treatment of Rheumatoid Arthritis (RA), Giant Cell Arteritis (GCA), Polyarticular Juveniles Idiopathic Arthritis (PJIA), and Systemic Juvenile Idiopathic Arthritis (SJIA) as a biosimilar to the reference product Actemra (tocilizumab) licensed under BLA 125276 and BLA 125472.
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 and medication guide submitted on March 1, 2024, instructions for use submitted on February 28, 2024, carton labeling submitted on February 20, 2024, and container labels submitted on September 5, 2023, were assessed and found to be acceptable (see Appendix C) from an OPQA III labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on March 21, 2023)
  file:////CDSESUB1/evsprod/BLA761275/0032/m1/us/114-labeling/114a-draft-label

- Medication Guide (submitted on March 21, 2023)
  file:////CDSESUB1/evsprod/BLA761275/0032/m1/us/114-labeling/114a-draft-label

- Instructions for Use (submitted on April 14, 2023, and October 12, 2022)
  file:////CDSESUB1/evsprod/BLA761275/0039/m1/us/114-labeling/114a-draft-label
  file:////CDSESUB1/evsprod/BLA761275/0010/m1/us/114-labeling/114a-draft-label

- Container Labels (submitted on March 21, 2023, and April 6, 2023)

6 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
Comment/Recommendation: The dosage form statement is missing from the principal display panel of some of the container labels. Missing important dosage form information may lead to confusion. Place the dosage form statement, "Injection" directly beneath the proper name and place the proper name in parenthesis. *The applicant revised as requested.*	

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: *The only manufacturer information is the licensed manufacturer and the phrase "Manufactured by" can be omitted. Partial label limited space considerations for the license number. See carton.*	

[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
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ 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

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

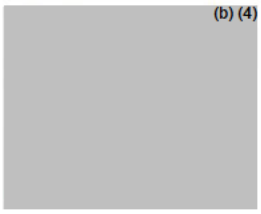
Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: On the container label for prefilled syringe, ensure the statement "Rx Only" appears on the label. *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: Partial label limited space considerations. See carton.	

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 vials. *The applicant confirms that there is no safety information on the ferrule and cap overseal of the vial. A block code is printed on the side of the ferrule, ensuring the traceability of the vial of MSB11456 product.* Figure 1 Example of Block Code Printed on Vial Ferrule (b) (4) 	

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

Comment/Recommendation:
Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.
The applicant confirms that sufficient area of the vial remains uncovered for its full length and for its full circumference to allow for visual inspection when the label is affixed to the container. The space of the full length of (b) (4) ial is approximately 2 mm wide and 2 (b) (4) ial is approximately 4 mm wide.

Figure 2 **Visual Area of inspection for 4 mL Vial (Full Length)**

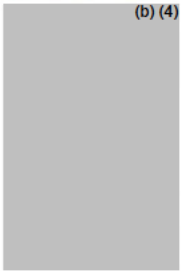


Figure 3 **Visual Area of Inspection for 4 mL Vial (Full Circumference)**

The applicant confirms that sufficient area of the autoinjector containers remains uncovered for its full length to allow for visual inspection when the label is affixed to the device.

Figure 4 **Visual Area of Inspection for the Autoinjector**

The applicant confirms that sufficient area of the PFS (b) (4) container remains uncovered for its full length to allow for visual inspection when the label is affixed to the device.

Figure 5 Visual Area of Inspection for the Prefilled Syringe

(b) (4)

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

Comment/Recommendation:
On the container label for autoinjector, relocate the product strength to appear directly underneath the proper name for consistency with other container labels as follows:

162 mg/0.9 mL
For Subcutaneous Use Only

The applicant revised as requested.

The vial container label route of administration statement differs from the route of administration presented on the carton labeling. Inconsistency of the route of administration across the labels and labeling may lead to wrong route medication errors and confusion. For consistency, revise the route of administration statement to read as follows: "For Intravenous Infusion Only After Dilution."
The applicant revised as requested.

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

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

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: Partial label limited space considerations. See carton.	

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 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Ensure the linear bar code appears on all container label and surrounded by enough white space to facilitate proper scanning.	

The applicant revised as requested.

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: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ 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: Partial label limited space considerations. See carton.	

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	✓ 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: Partial label limited space considerations. See carton.	

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: Partial label limited space considerations. See carton.	

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

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

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

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

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
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
Comment/Recommendation: Add the phrase "No preservative" to appear on the prefilled syringe and autoinjector blister labeling. *The applicant revised as requested.*	

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: On the vial carton labeling, relocate the product strength to appear directly underneath the dosage form and above the route of administration as follows: Tyenne tocilizumab-aazg Injection x mg/ x mL (x mg/mL) For intravenous infusion only after dilution *The applicant revised as requested.*	

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: Revise the storage statement on vial carton labeling from "(b) (4) " to read "Store refrigerated at 36°F to 46°F (2ºC to 8ºC) in the original carton to protect from light. Do not freeze or shake." to delete duplicate statement and avoid clutter. *The applicant revised as requested.* Revise the storage statement on prefilled syringe and autoinjector carton labeling from "(b) (4) " to read "Store refrigerated at 36°F to 46°F (2ºC to 8ºC) in the original carton to protect from light. Do not freeze or shake. Tyenne [syringe/autoinjector] may be stored at room temperature up to a maximum of 77°F (25°C) for up to 14 days." *The applicant revised as requested.* Revise the storage statement on prefilled syringe and autoinjector blister labeling to "Store refrigerated at 36°F to 46°F (2ºC to 8ºC) in the original carton to protect from light. Do not freeze or shake." for consistency. *The applicant revised as requested.*	

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

Comment/Recommendation:
On the vial carton labeling, relocate the product strength to appear directly underneath the dosage form and above the route of administration as follows:

Tyenne
tocilizumab-aazg
Injection
x mg/ x mL
(x mg/mL)
For intravenous infusion only after dilution

The applicant revised as requested.

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	✓ 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:
Add the inactive ingredient list to appear on the blister label.
The applicant added the inactive ingredient names to appear on the blister label.

Add the inactive ingredient quantity to appear on the blister label per 21 CFR 201.100(b)(5).
The applicant revised as requested.

Revise the inactive ingredient list on the blister label and carton labeling to appear in the alphabetical order.
The applicant revised as requested.

Add the pH adjusters used in the inactive ingredient list.
The applicant revised as requested.

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: *Although this statement currently appears on the carton labeling of the reference product, Actemra, 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 Tyenne 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 Tyenne and its reference product.* Remove the statement "No U.S. standard of potency" from the blister labeling. Although this statement appears on the carton labeling of the reference product, Actemra, our current thinking is that 21 CFR 610.61(r) is not applicable, and thus no statement is required for the carton labeling. *The applicant revised as requested.* 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, Actemra, our current thinking is that 21 CFR 610.61(r) is not applicable, and thus no statement is required for the 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
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ 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* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Ensure the linear bar code appears on the blister label and surrounded by enough white space to facilitate proper scanning. *The applicant revised as requested.*	

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *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

Comment/Recommendation:

On the vial carton labeling, revise "(b) (4)" to the appropriate package type term "single-dose vial" on all vial carton labeling.
The applicant revised as requested.

On the vial carton labeling, relocate the statement "Discard unused portion." to appear with the package type term "Single-Dose Vial" on one line as follows: "Single-Dose Vial- Discard Unused Portion"
The applicant revised as requested.

On the prefilled syringe and autoinjector carton labeling, add the statement "Discard unused portion." to appear with the statement "1 single-dose [prefilled syringe/autoinjector]" on the principal display panel.
The applicant revised as requested.

Revise the phrase "(b) (4)." on the back panel of the prefilled syringe and autoinjector carton labeling to read "For one-time use only" for clarity and to mitigate confusion with the package type term no longer used in FDA labeling, "(b) (4)".
The applicant revised as requested.

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: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: On the prefilled syringe and autoinjector carton labeling, add the net quantity "0.9 mL" as a distinct item on the label. *The applicant revised as requested.* On the prefilled syringe and autoinjector blister labeling, add the net quantity "0.9 mL" as a distinct item on the label. *The applicant revised as requested.*	

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 statement to read "Dosage: See prescribing information." to be in alignment with the PLR labeling format.
The DMEPA reviewer suggested to revise the dosage statement to read "Recommended Dosage: See prescribing information." and the applicant revised as requested. This is acceptable from OPQA III labeling perspective.

Add the dosage statement "Dosage: See prescribing information." on the blister label.
The DMEPA reviewer suggested to revise the dosage statement to read "Recommended Dosage: See prescribing information." and the applicant revised as requested. This is acceptable from OPQA III labeling perspective.

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

Comment/Recommendation:
On the blister label, add the medication guide statement "Dispense a Medication Guide to each patient."
The applicant revised as requested.

Other (package labeling)	**Acceptable**
	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Revise the phrase "(b) (4)" to the preferred term "prescribing information."
The applicant revised as requested.

Revise the content statement to read "Contents: 1 single-dose [vial/prefilled syringe/autoinjector] contains: Active Ingredient: Tocilizumab-aazg (x mg)"
The applicant revised as requested.

Delete the statement "(b) (4)" on vial carton labeling underneath the dosage statement since it is redundant and may cause confusion with the package type term.
The applicant revised as requested.

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 products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We deleted unnecessary information and revised the language for clarity. ***Applicant's response February 20, 2024**: Phrase [redacted (b) (4)] retained. Without this statement there is a risk to make these claims.* **OPQA III response**: We deleted the phrase "[redacted (b) (4)]" and added a statement that administration of the diluted solution must be completed within the proposed storage time period. *The applicant revised as requested.* We added specific range for room temperature. *The applicant revised as requested.*	

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: We added concentration per mL in parenthesis. *The applicant revised as requested.*	

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

Comment/Recommendation:
We added a placeholder for the four-letter suffix to the proper name.
The applicant revised as requested.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised 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, arginine, histidine, lactic acid, polysorbate 80 and sodium chloride.
The applicant revised as requested.

We revised the inactive ingredient names to appear in alphabetical order.
The applicant revised as requested.

We added pH adjusters to the inactive ingredient list.
The applicant revised as requested.

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: We revised the statement "(b) (4)" to "not made with natural rubber latex" for consistency. *The applicant revised as requested.*	

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

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

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: We revised the inactive ingredient names to their compendial names to ensure compliance with the Federal Food Drug, and Cosmetic Act (FD&C Act) section 502(e). *The applicant revised as requested.* We added pH adjusters to the inactive ingredient list. *The applicant revised as requested.*	

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: We added the appropriate qualifying phrase "Manufactured by" to the manufacturer information. *The applicant revised as requested.*	

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 Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: On the IFU for autoinjector, add the appropriate dosage form to appear directly underneath the proper name and revise the route of administration for consistency with other labelling as follows: Tyenne Tocilizumab-aazg Injection 162 mg/0.9 mL For Subcutaneous Use Only Single-dose autoinjector *The applicant revised as requested.* On the IFU for prefilled syringe, relocate product strength to appear directly underneath the dosage form as follows: Tyenne tocilizumab-aazg Injection 162 mg/0.9 mL For Subcutaneous Use Only	

Single-dose prefilled syringe *The applicant revised as requested.*

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). 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

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
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). *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: We added the manufacturer information in the instructions for use for the autoinjector. *The applicant revised as requested.*	

APPENDIX C. Acceptable Labels and Labeling

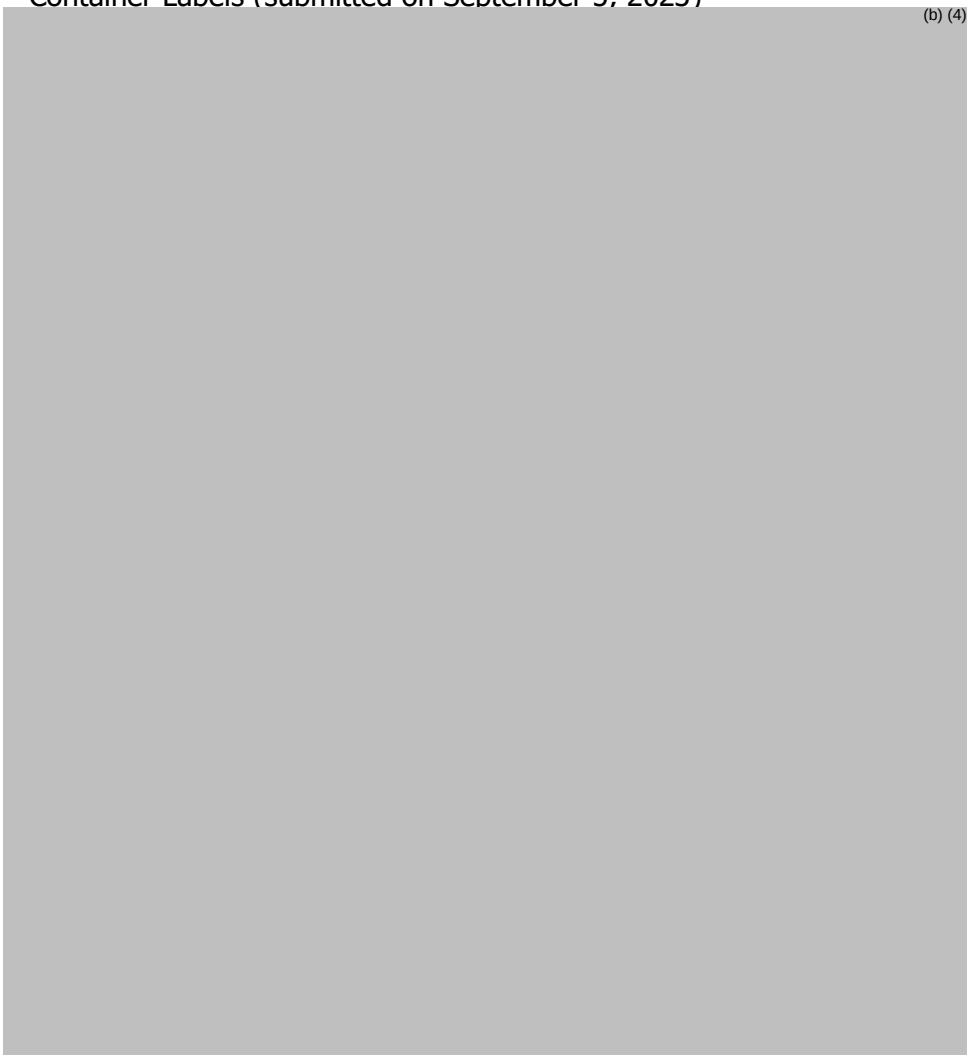
- Prescribing Information (submitted on March 1, 2024)
  \\CDSESUB1\EVSPROD\bla761275\0059\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-sc-and-iv.pdf

- Medication Guide (submitted on March 1, 2024)
  \\CDSESUB1\EVSPROD\bla761275\0059\m1\us\114-labeling\114a-draft-label\draft-labeling-text-medication-guide.pdf

- Instructions for Use (submitted on February 28, 2024)
  \\CDSESUB1\EVSPROD\bla761275\0058\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs.pdf
  \\CDSESUB1\EVSPROD\bla761275\0058\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai.pdf

- Container Labels (submitted on September 5, 2023)

(b) (4)



6 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Jennifer Kim

Digitally signed by Jennifer Kim
Date: 3/01/2024 03:10:33PM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Bazarragchaa Damdinsuren

Digitally signed by Bazarragchaa Damdinsuren
Date: 3/01/2024 03:15:24PM
GUID: 50afa2ce0005f62310093b8bdc00b898

BLA Executive Summary
Assessment Date: February 23, 2024

1. Application/Product Information

BLA number	761275
Submission Type	Resubmission
Regulatory Pathway	Biosimilar 351(k)
Associated IND	129965
Review Designation	Standard review
Applicant	Fresenius Kabi USA, LLC
Indication	Rheumatoid Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis (age ≥ 2 years), Systemic Juvenile Idiopathic Arthritis (age ≥ 2 years)
Rx/OTC dispensed	Rx
Drug Product Name	TYENNE
	tocilizumab-aazg/MSB11456
	MAB HUMANIZED (IGG1) ANTI P08887 (IL6RA_HUMAN) [MSB11456]
Drug Product Description	TYENNE (tocilizumab-aazg) injection is a sterile, clear, colorless to pale yellow, preservative-free solution with a pH of 6 for further dilution prior to intravenous infusion or for subcutaneous use. Each single-dose 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL vial for intravenous infusion contains 20 mg/mL tocilizumab-aazg in (b) (4)Histidine (3.1 mg/mL), (b) (4) Arginine (17.4 mg/mL), (b) (4)Lactic Acid (0.9 mg/mL), polysorbate 80 (0.2 mg/mL), Sodium Chloride (0.6 mg/mL), and Water for Injection, USP. Each single-dose 0.9 mL prefilled syringe (PFS) with a needle safety device or single-dose 0.9 mL autoinjector (AI) contains 180 mg/mL tocilizumab-aazg in (b) (4)Histidine ((b) (4) mg/mL), (b) (4)Arginine ((b) (4) mg/mL), (b) (4)Lactic Acid ((b) (4) mg/mL), Polysorbate 80 (0.2 mg/mL), Sodium Chloride (0.6 mg/mL), and Water for Injection, USP. Hydrochloric acid and sodium hydroxide are added to adjust the pH.

	Tocilizumab-aazg is a recombinant, humanized IgG1 monoclonal antibody directed against human interleukin 6 receptors (IL-6R) and binds to the IL-6 binding site of both soluble IL-6R (sIL-6R) and membrane bound IL-6R (mIL-6R).		
Dosage Form	Injection, solution		
Strength	Vial: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL (20 mg/mL) Prefilled syringe (PFS)/ autoinjector (AI): 162 mg/0.9 mL (180 mg/mL)		
Routes of Administration	Vial: Intravenous (IV) PFS/AI: Subcutaneous (SC)		
Primary Container Closure Systems	Vial PFS		
Device Information	PFS in (b) (4) safety device Prefilled AI		
Co-packaged Product Information	Not applicable		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance (DS)	Ancy Nalli, Deepa Raghu (some methods)	Bazarragchaa Damdinsuren
	Drug product (DP)		
	Immunogenicity Assay	Li Lu	
	CAA	Li Lu	
	Microbiology	Yuan-Chia (Charles) Kuo (DS) Jeanne Fringer (DP)	Maxwell Van Tassell
	Facility		Zhong Li
	RBPM	Anita Brown	
	ATL	Bazarragchaa Damdinsuren	
OPQ Issued Consults	Consult to CDRH for device components. The consult review is performed by Kathleen Fitzgerald and Courtney Evans (Team Lead).		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761275 for Tyenne manufactured by Fresenius Kabi USA, LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of Tyenne is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Tyenne is highly similar to US-licensed Actemra, 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 presentation:
  - Fresenius Kabi Austria GmbH (FEI: 3003708554)
    Hafnerstraβe 36, 8055 Graz, Austria
  - Labeling and secondary packaging: Fresenius Kabi Austria GmbH (FEI: 3003708554)
    Am Gewerbepark 6, 8402 Werndorf, Austria

  PFS/AI presentations:
  - (b) (4)
  - Device assembly, labeling and secondary packaging: Fresenius Kabi Austria GmbH (FEI: 3003708554)
    Am Gewerbepark 6, 8402 Werndorf, Austria

b. Fill size and dosage form:

Injection, solution in single-dose vial: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL
Injection, solution in single-dose PFS in (b) (4) safety device and single-dose prefilled AI: 162 mg/0.9 mL

c. Dating Period:

- **Drug Product:**

Vial presentation: 24 months when stored at 5 ± 3°C
PFS/AI presentations: 36 months when stored at 5 ± 3°C

- **Drug Substance:**
  (b) (4) months when stored at (b) (4) °C
- **For packaged products:** Not packaged
- **Stability Option:**
  - Limited stability data
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
  - For stability protocols:
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: Tyenne 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

1. Re-evaluate the drug substance and drug product lot release and stability acceptance criteria for the degree of coloration after release data from 30 drug substance lots and corresponding drug product lots are available, and with consideration of available stability data. The final report should include the corresponding data, the analysis thereof, and any proposed changes to the drug substance and drug product release or stability specifications resulting from the assessment.
2. Re-evaluate lot release and stability acceptance criteria for the device performance attributes of the pre-filled syringe (b) (4) device (PFS- (b) (4)) and auto-injector device (PFS-AI) after release data from 30 PFS- (b) (4) and PFS-AI lots are available, and with consideration of available stability data. The final report should include the corresponding data, the analysis thereof, and any proposed changes to the drug product release or stability specifications resulting from the assessment.

4. Basis for Recommendation

a. Summary: Tyenne (tocilizumab-aazg, MSB11456) is a proposed biosimilar to US-licensed Actemra (US-Actemra) that is intended to be delivered by the

same routes of administration (IV and SC) for the same indications as the US-Actemra reference product. The comparative analytical assessment (CAA) data submitted support the demonstration that Tyenne is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components and that the analytical portion of the scientific bridge to justify the use of clinical data derived from EU-approved RoActemra was established.

Tocilizumab is a recombinant, humanized IgG1 monoclonal antibody that specifically binds to the IL-6 binding site of both sIL-6R and mIL-6R and blocks the activity of IL-6. This leads to down-regulation of IL-6-driven cellular functions. The biological activity of MSB11456 is evaluated on its capability to inhibit the IL-6-induced cell proliferation in a dose-dependent manner on the DS-1 human cell line.

The pre-license inspections (PLIs) of Fresenius Kabi Austria GmbH (FK-Graz), Austria (FEI 3003708554) and (b) (4) that are responsible for MSB11456 drug product (DP) manufacturing respectively for the single-dose vial and the single-dose PFS/AI resulted in Official Action Indicated (OAI) statuses and recommendations of withhold for both facilities (refer to the OPMA facilities assessment for the deficiency details). An original BLA 761275 was issued a Complete Response Letter on May 31, 2023, due to the facility deficiency. The BLA resubmission (submitted on September 5, 2023) contains responses for the facility deficiency, and for additional product quality and microbiology comments (see technical assessments for facility by OPMA and product quality by OBP uploaded into Panorama). Based on the assessments of manufacturing process and controls in the firms' responses, including adequate corrective and preventative action (CAPA) updates, and additional updates to the submission during the review cycle, the OPQ review team has recommended approval of the MSB11456 DP manufacturing facilities, FK-Graz and (b) (4), and waived re-inspections for both facilities.
The PLIs of (b) (4) manufacture and testing facility of MSB11456 drug substance (DS) and of (b) (4) used for the CAA and testing for MSB11456 recommended approval.

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for DS and DP manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product and the OPMA assessors

are recommending approval for this BLA from a sterility assurance and microbiology product quality perspective.

The DS manufacturing process consists of (b) (4)

The Tyenne DP-IV manufacturing includes (b) (4) The final DP-IV is stored at 5 ± 3°C for long term storage.

The Tyenne DP-SC manufacturing includes (b) (4) The final DP-SC is stored at 5 ± 3°C for long term storage.

The immunogenicity assays to detect and confirm anti-drug antibodies (ADAs) against tocilizumab in the clinical studies to support this BLA were adequately validated and suitable for their intended purpose.
Individual assessments for each discipline are located in separate documents in Panorama.

b. Subdiscipline Recommendation:

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

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for Tyenne (i.e., there is no specific test method described in regulation for Tyenne that establishes an official standard of potency). We next considered whether potency is a factor for Tyenne 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 Tyenne for purposes of § 610.61(r) because lot variability is not a concern for Tyenne as Tyenne'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 for:
         1. Master and working cell bank stability (3.2.S.2.3.2)
         2. Qualification of future working cell banks (3.2.S.2.3.2)
         3. Manufacturing scale (b) (4) validation (3.2.S.2.5)
         4. Manufacturing scale (b) (4) validation (3.2.S.2.5)
         5. (b) (4) at manufacturing scale (3.2.S.2.5)
         6. Qualification of future reference standards (3.2.S.5)
         7. Reference standard re-qualification (3.2.S.5)
         8. On-going stability study (3.2.S.7.1)
         9. Post-approval annual stability and commitment (3.2.S.7.2)
      ii. Residual risk: None
      iii. Future inspection points to consider: None

   c. Drug Products (IV and SC):
      i. Protocols approved for:
         1. On-going stability studies (3.2.P.8.1)
         2. Post-approval annual stability and commitments (3.2.P.8.2)
      ii. Residual risk: No
      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. Analytical Assessment Overview and Conclusions

The Comparative Analytical Assessments (CAAs) between MSB11456, U.S.-licensed Actemra (hereafter referred to as US-Actemra), and E.U.-approved RoActemra (hereafter referred to as EU-RoActemra) were performed separately for tocilizumab products in vial presentation (also referred as DP-IV, i.e., for intravenous (IV) administration) and for tocilizumab products in prefilled syringe (PFS) presentation (also referred as DP-SC, i.e., for subcutaneous (SC) administration). The CAAs included comparisons of 10 vial and 10 PFS MSB11456 batches (manufactured respectively in July 2018 - June 2021 and in Feb 2017 - Oct 2020), 18 vial and 18 PFS US-Actemra batches (with respective expiry dates Sept 2016 - April 2022 and March 2016 - Feb 2022), and 18 vial and 25 PFS EU-RoActemra batches (with respective expiry dates Sept 2015 - April 2022 and April 2016 - Aug 2022). The batches were adequate to capture potential batch-to-batch variability in the US-Actemra and EU-RoActemra products over time.

There were two DP process iterations during the commercial development stage of MSB11456 DP-IV: manufacturing process at (b) (4) (3 batches) and process at FK-Graz (7 batches). The 400 mg/20 mL, 200 mg/10 mL and 80 mg/4 mL MSB11456 DP-IV batches were used in the CAA.
There were two process iterations during the commercial development stage of MSB11456 DP-SC: manufacturing process at (b) (4) (1 batch), and process at (b) (4) (9 batches). The MSB11456 DP-SC batches in PFS presentation (162 mg/0.9 mL) with and without (b) (4) passive safety device, but not in final assembled auto-injector, were used in the CAA. The PFS is the primary container closure system of the auto-injector and (b) (4) device presentations and the assembly process of these devices has no impact on the quality attributes of MSB11456. Therefore, it is acceptable to include MSB11456 PFS batches in the CAA.

The MSB11456 DP batches used in each CAA were derived from independent DS batches and included the process validation batches (i.e., 5 DP-IV and 4 DP-SC batches). Note that MSB11456 DS was manufactured at (b) (4) with minor manufacturing changes during the commercial development stage. In addition, the CAA included all MSB11456 DP, US-Actemra and EU-RoActemra batches used in the comparative clinical studies included in the BLA.

The CAA was comprised of extensive comparative physiochemical and functional assessment of the quality attributes of MSB11456, US-Actemra, and EU-RoActemra. The Applicant used an acceptable risk-based approach for statistical evaluation of analytical results. The critical quality attributes (CQAs) and attributes linked to CQAs that were tested using quantitative assays were evaluated using quality ranges obtained from US-Actemra or EU-RoActemra to account for manufacturing variability and assay variability. In addition, the most sensitive assays for detecting product differences were selected for statistical evaluation using quality ranges. Attributes tested using quantitative assays not amenable to statistical analysis and qualitative assays were evaluated using visual comparisons (referred as descriptive assessment). Results from method validation or qualification studies support the suitability of the methods used in the CAA. The Applicant also provided a comparison of stability under forced degradation conditions of high temperature stress, light stress (photostability), high and low pH stress, oxidative stress, and mechanical stress.

Based on the OBP assessment, the MSB11456 and US-Actemra data supports a demonstration that MSB11456 is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components. MSB11456 has the same strength, dosage form, and routes of administration as US-Actemra. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate CQAs of MSB11456 and US-Actemra to support the demonstration that the products are highly similar. Numbers of batches tested were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While differences were observed in a limited number of attributes, these differences do not preclude a demonstration that MSB11456 is highly similar to US-Actemra (see section D below).

In addition, three-way pairwise comparisons of MSB11456, US-Actemra, and EU-RoActemra were used to establish the analytical component of the three-way scientific bridge between MSB11456, US-Actemra, and EU-RoActemra to support the relevance of the data generated from studies using EU-Actemra as the comparator to the assessment of biosimilarity. Based on the OBP assessment of the data, the Applicant established the analytical portion of the scientific bridge between MSB11456, US-Actemra, and EU-RoActemra, using the same methods and statistical approaches as those to evaluate the similarity between MSB11456 and US-Actemra. The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies with EU-RoActemra as the comparator for the assessment of biosimilarity.

B. Results of Comparative Analytical Assessment

The results of these analytical comparisons support a demonstration that MSB11456 is highly similar to US-Actemra and the establishment of the analytical component of the

scientific bridge between MSB11456, US-Actemra, and EU-RoActemra and the results are summarized in Table A below.

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/ Functional Characteristics	Quality Attribute Assessed (analytical methods)		Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Primary Structure	Amino acid sequence (LC-MS/MS)		Yes	Yes
	Intact Mass (LC-MS)		Yes	Yes
	N-terminal sequence (Edman chemistry)		Yes	Yes
Post-Translational Modifications	Deamidation	(IEX-HPLC)	Yes	Yes
		(peptide mapping by LC-MS/MS)	Yes	Yes
	Oxidation	(RP-UPLC)	Yes	Yes
		(peptide mapping by LC-MS/MS)		
	Glycation (intact mass LC-MS/MS)		Yes	Yes
	N-glyco site occupancy (peptide mapping)		Yes	Yes
	N-terminal Variants (peptide mapping by LC-MS)		Yes	Yes
	C-terminal Variants (peptide mapping by LC-MS/MS)		Yes	Yes
Higher Order Structure	Free Thiol content (Ellman's test)		Yes	Yes
	Secondary and Tertiary Structure	(FTIR)	Yes	Yes
		(CD, near and far UV)	Yes	Yes
		(Fluorescence spectroscopy)	Yes	Yes
	Disulfide linkage (native and reduced peptide mapping by LC-MS/MS)		Yes	Yes
	Disulfide bonds (native and reduced peptide mapping)		Yes	Yes
	Thermal stability (Nano-DSC)		Yes	Yes
Size purity/impurity	Aggregates/ HMW species	(SEC-HPLC)	Yes	Yes
		(AUC)	Yes	Yes
	Fragments/ LMW species	(reduced CE-SDS)	Yes	Yes
		(non-reduced CE-SDS)	Yes	Yes
	Monomer	(SEC-HPLC)	Yes	Yes
		(AUC)	Yes	Yes
	LC+HC	(reduced CE-SDS)	Yes	Yes
	NGHC	(reduced CE-SDS)	Yes	Yes
	Intact IgG	(non-reduced CE-SDS)	Yes	Yes
Charge Variants	pI points (icIEF)		Yes	Yes

Physico-chemical/ Functional Characteristics	Quality Attribute Assessed (analytical methods)	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
	Main Peak (IEC-HPLC, icIEF)	Yes	Yes
	Acidic Species (IEC-HPLC, icIEF)	Yes	Yes
	Basic Species (IEC-HPLC, icIEF)	Yes	Yes
Glycosylation	Total sialylated glycans (HPEAC-PAD, 2-AB glycan mapping)	Yes	Yes
	Galactosylated glycans (2-AB glycan mapping)	Yes	Yes
	Afucosylated glycans (2-AB glycan mapping)	Yes	Yes
	High mannose glycans (2-AB glycan mapping)	Yes	Yes
Content	Protein Concentration (UV280)	Yes	Yes
	Extractable volume (Gravimetric volume determination)	Yes	Yes
Biological activity (Fab binding)	IL-6 neutralization (IL-6 inhibition by in vitro bioassay)	Yes	Yes
	sIL-6R binding (SPR)	Yes	Yes
	mIL-6R binding (Flow cytometry)	Yes	Yes
Biological activity (Fc binding)	FcRn binding affinity (SPR)	Yes	Yes
	FcɣRIIIa (V-type) binding affinity (SPR)	Yes	Yes
	FcɣRIIIa (F-type) binding affinity (SPR)	Yes	Yes
	FcɣRIIIb binding affinity (SPR)	Yes	Yes
	FcɣRIIa binding affinity (SPR)	Yes	Yes
	FcɣRIIb binding affinity (SPR)	Yes	Yes
	FcɣRI binding affinity (SPR)	Yes	Yes
	C1q binding (ELISA)	Yes	Yes
Comparative in vitro activities*	Antibody-dependent cellular cytotoxicity (ADCC-induced cell viability reduction by luminescence)	Yes	Yes
	Complement-dependent cytotoxicity (CDC-induced cell viability reduction by luminescence)	Yes	Yes
	Apoptosis (Apoptosis of THP-1 cells by luminescence)	Yes	Yes
	Flow cytometry (mIL-6R driven STAT3 phosphorylation)	Yes	Yes
Degradation profiles*	High Temperature (50°C)#	Yes	Yes
	Light stress (765 W/m^2·hr)#	Yes	Yes
	Chemical Oxidation (H_2O_2 0.1%)#	Yes	Yes
	Low and high pH (pH 4.0 and 9.0)#	Yes	Yes
	Mechanical stress (shaking at 300 rpm)#	Yes	Yes

* - Additional characterization studies performed with 3-4 lots of each product
# - Conditions for Forced Degradation Study

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

The clinical development of MSB11456 included three clinical studies that compared MSB11456 to US-Actemra and EU-RoActemra:

- Study MS200740-0001: A single-dose comparative pharmacokinetic (PK) study in healthy subjects comparing MSB11456 to US-Actemra and EU-Actemra using the SC route of administration, thus establishing a 3-way clinical bridge between MSB11456, US-Actemra and EU-Actemra
- Study FKS456-001: A multiple-dose comparative efficacy and safety study comparing MSB11456 to EU-RoActemra in patients with rheumatoid arthritis to demonstrate that MSB11456 and EU-RoActemra have similar efficacy, safety, and immunogenicity by the SC route of administration
- Study FKS456-002: A single-dose PK study in healthy subjects comparing MSB11456 and US-Actemra using the IV route of administration, thus demonstrate that MSB11456 and US-Actemra are similar in terms of PK after IV administration.

To support the relevance of the comparative clinical data (Study FKS456-001) generated using EU-RoActemra as a comparator product to the assessment of biosimilarity, the Applicant performed three-way, pairwise comparative analytical assessments using a comprehensive array of analytical methods and a three-way pairwise PK similarity study (MS200740-0001). To support the establishment of the analytical component of the scientific bridge, the Applicant included comparison of MSB11456 to US-Actemra, MSB11456 to EU-RoActemra, and US-Actemra to EU-RoActemra. The same analytical methods used for supporting a demonstration that MSB11456 is highly similar to US-Actemra were used for the pairwise comparisons with EU-RoActemra. The differences observed in the comparative 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 acceptance criteria for the pairwise three-way comparison between MSB11456, US-Actemra and EU-RoActemra were met for all attributes evaluated with the following exceptions:

- Oxidation (by RP-UPLC after IdeS digest):

Total oxidation is higher in MSB11456 DP-SC lots (3.4 - 4.3%) in comparison to US-Actemra lots (2.5 - 3.3%, quality range 2.0 – 3.6%), which was due to Fc/2 oxidized (Fc/2 ox; oxidized single chain of the crystallizable fragment) forms (respectively 2.6 - 3.2% vs 1.3 - 2.1%, quality range 0.9 – 2.4%). Fd oxidized species (oxidized heavy chain portion of the antigen-binding fragment) are similar across the three products. In addition, no difference in oxidized forms was observed for vial presentations. Oxidation is identified as moderate criticality attribute, and the observed difference in SC lots was small (~1.3%), which would not adversely impact efficacy or safety. See also the discussion about the oxidation profiles in degradation studies, below. Therefore, the difference observed in the oxidation of MSB11456 DP-SC does not preclude a demonstration that MSB11456 is highly similar to US-Actemra.

- Glycosylation (by 2-AB Glycan Mapping):

MSB11456 DP-IV and DP-SC lots contained lower levels of G0F (respectively 35.1 - 37.1% and 35.0 - 38.2%) than US-Actemra lots (respectively 39.1 - 47.9% and 41.6 - 47.6%) or EU-RoActemra lots (respectively 38.8 - 51.2% and 41.2 - 50.1%), and a higher of G1F (30.1 - 30.6% and 30.0 - 31.0%) than US-Actemra (22.8 - 29.1% and 25.0 - 28.7%) or EU-RoActemra (22.3 - 28.6% and 20.8 - 28.5%, respectively). however, the content of fucosylated glycans, i.e., sum of G0F, G1F, G1F iso and G2F, (as well as high mannose glycan, and afucosylated glycans) in MSB11456 DPs is within the quality ranges of US-Actemra and EU-RoActemra. MSB11456 DP-IV and DP-SC have a higher level of galactosylated species (53.2 - 54.5% and 53.2 - 54.9%) compared to US-Actemra lots (respectively 40.8 - 50.7% and 44.0 - 50.6%) or EU-RoActemra lots (respectively 39.5 - 50.4% and 36.0 - 50.2%). Individual glycosylated species are classified as low criticality attribute, except high mannose glycans as moderate criticality. Therefore, the minor differences observed for the individual isoforms identified above are not clinically meaningful considering primary mechanism of action of tocilizumab, and do not preclude a demonstration that MSB11456 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

- Glycation:

Levels of glycation of MSB11456 lots (4.5-10.2% for DP-PFS and DP-IV) were found to be higher than US-Actemra and EU-RoActemra (respectively 0.0-2.8% and 0.0-3.0%). Glycation is identified as a low criticality attribute, and the location of the glycation sites is not associated to binding epitopes nor Fc receptor binding regions (i.e., the glycation detected in CDR2 region was <0.2%), and the higher level would not have an adverse effect on safety and efficacy. Therefore, the difference observed in the glycation of MSB11456 does not preclude a demonstration that MSB11456 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

- Size purity (LC+HC):

Marginally higher LC+HC purity by reduced CE-SDS was found for MSB11456 DP-IV (98.3 - 99.0%) than US-Actemra (97.6 - 98.2%) or EU-RoActemra (97.5 - 98.0%). This

small difference would not be expected to have a biological impact on the tocilizumab products and do not preclude a demonstration that MSB11456 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

- Charge heterogeneity (by IEX-HPLC):

MSB11456 DP-IV lots showed a lower percentage of acidic variants than that detected in US-Actemra (19.1 - 21.7% vs. quality range 20.8 - 24.7%, resulting in 60% of DP-IV lots outside of the quality range). The opposite pattern is evident for the basic variants in MSB11456 DP-IV vs US-Actemra and/or EU-RoActemra lots (12.8 - 15.2% vs. respective quality ranges 5.1 - 14.6% and 5.4 - 13.5%). MSB11456 DP-SC lots showed similar contents of charge variants than those detected in US-Actemra or EU-RoActemra. The characterization data show that acidic peaks contain sialylated glycans and fragments (predominantly HHL and HH), and the individual fractions from the acidic peaks showed comparable activity. The basic species contain variants with oxidation at HC M254 or M430, and P447 amidation. The detected minor differences of acidic and basic variants (respectively ~2% and ~4% differences in the mean values) are not anticipated to impact safety, PK or immunogenicity of tocilizumab considering the comparable biological activity of the acidic peaks and the low criticality of the attributes present under the basic peaks. In addition, the difference in levels of acidic and basic variants in the MSB11456 IV and SC presentations is most likely due to the differences in formulation.

IEX-HPLC testing is also applied to tocilizumab products samples with Carboxypeptidase B (CpB) treatment that remove C-terminal heterogeneity (predominantly lysine). Under this condition, MSB11456 DP-IV lots showed a lower percentage of acidic variants than those detected in US-Actemra (20.8 - 22.8% vs quality range 22.3 - 25.5%), while the reverse pattern is seen for the main peak. MSB11456 DP-SC lots showed a lower percentage of basic variants than those detected in US-Actemra or EU-RoActemra (5.9 - 6.4% vs quality ranges 7.4 - 16.3% and 7.9 - 15.6%). The applicant stated that this was most likely due to the lower level of C-terminal proline amidation in MSB11456 DP-SC batches, which was observed by peptide mapping LC-ESI-MS and was unmasked in the presence of CpB. Considering the low criticality of C-terminal proline amidation, the difference observed for basic variants is not anticipated to impact safety or efficacy.

CAA of MSB11456 DPs, US-Actemra and EU-RoActemra using icIEF met the similarity criteria.

Taken together, the charge heterogeneity assessments support that the observed differences in charge variants do not preclude a demonstration that MSB11456 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

- Oxidation profiles in degradation studies:

The stability and degradation studies suggest that the MSB11456 DP-SC and DP-IV are more sensitive and prone to oxidation (including under thermal stress and oxidative stress) when compared to US-Actemra and EU-RoActemra, e.g., Fc/2 ox species increased from 2.6 – 3.0% to 3.5 – 3.7% for MSB11456 DP-SC lots compared to no significant change (from 1.1 - 1.3% to 1.4 – 1.6%) for US-Actemra and EU-RoActemra lots under 30 hours of high temperature stress condition at 50°C. The slightly higher levels of oxidation in MSB11456 can be attributed to the differences in formulations of MSB11456 DP and US-Actemra/EU-RoActemra, specifically, the SC formulation of US-Actemra/EU-RoActemra contains L-methionine (b) (4) while L-methionine is not present in the IV formulation of US-Actemra/EU-RoActemra, or in the MSB11456 DP formulation. The slightly increased susceptibility to oxidation of the MSB11456 does not impact any other product quality attribute, as well as studies in section 3.2.R.1.5.6 showed that up to ~7-10% Fd and Fc oxidation would have no adverse impact on sIL-6R and FcRn binding affinity. Therefore, the differences observed in the oxidation of MSB11456 DP do not preclude a demonstration that MSB11456 is highly similar to US-Actemra.

E. Same Strength

MSB11456 has the same dosage forms and routes of administration as US- licensed Actemra. US-Actemra is available at these strengths: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL (all 20 mg/mL) in vials for further dilution prior to intravenous infusion, and 162 mg/0.9 mL in a prefilled syringe or prefilled autoinjector. The Applicant is seeking approval of 20 mg/mL MSB11456 in 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL vial and 180 mg/mL MSB11456 in 162 mg/0.9 mL prefilled syringe in (b) (4) safety device or autoinjector. Comparative concentration (mg/mL) was assessed as part of the CAA. The extractable volume and fill weight data were also assessed (b) (4) . Based on the comparative concentration data and manufacturing data, the 20 mg/mL MSB11456 in 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL vial and 180 mg/mL MSB11456 in 162 mg/0.9 mL prefilled syringe in (b) (4) safety device or autoinjector 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 the corresponding strengths of US-Actemra. Each strength of MSB11456 vial and prefilled syringe is the same as that of US-Actemra.

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/s/

BAZARRAGCHAA DAMDINSUREN
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BLA Executive Summary
Assessment Date: May 31, 2023

1. Application/Product Information

BLA number	761275
Submission Type	Original Submission
Regulatory Pathway	Biosimilar 351(k)
Associated IND	129965
Review Designation	Standard review
Applicant	Fresenius Kabi USA, LLC
Indication	Rheumatoid Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis (age ≥ 2 years), Systemic Juvenile Idiopathic Arthritis (age ≥ 2 years)
Rx/OTC dispensed	Rx
Drug Product Name	TYENNE
	tocilizumab-aazg/MSB11456
	MAB HUMANIZED (IGG1) ANTI P08887 (IL6RA_HUMAN) [MSB11456]
Drug Product Description	TYENNE (tocilizumab-aazg) injection is a sterile, clear, colorless to pale yellow, preservative-free solution with a pH of 6 for further dilution prior to intravenous infusion or for subcutaneous use. Each single-dose 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL vial for intravenous infusion contains 20 mg/mL tocilizumab-aazg in (b)(4)Histidine (3.1 mg/mL), (b)(4) Arginine (17.4 mg/mL), (b)(4)Lactic Acid (0.9 mg/mL), polysorbate 80 (0.2 mg/mL), Sodium Chloride (0.6 mg/mL), and Water for Injection, USP. Each single-dose 0.9 mL prefilled syringe (PFS) with a needle safety device or single-dose 0.9 mL autoinjector contains 180 mg/mL tocilizumab-aazg in (b)(4)Histidine ((b)(4) mg/mL), (b)(4)Arginine ((b)(4) mg/mL), (b)(4)Lactic Acid ((b)(4) mg/mL), Polysorbate 80 (0.2 mg/mL), Sodium Chloride (0.6 mg/mL), and Water for Injection, USP. Hydrochloric acid and sodium hydroxide are added to adjust the pH.

	Tocilizumab-aazg is a recombinant, humanized IgG1 monoclonal antibody directed against human interleukin 6 receptors (IL-6R) and binds to the IL-6 binding site of both soluble IL-6R (sIL-6R) and membrane bound IL-6R (mIL-6R).		
Dosage Form	Injection, solution		
Strength	Vial: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL (20 mg/mL) Prefilled syringe (PFS)/ autoinjector (AI): 162 mg/0.9 mL (180 mg/mL)		
Route of Administration	Vial: Intravenous PFS/AI: Subcutaneous		
Primary Container Closure System	Vial PFS		
Device Information	PFS in (b) (4) safety device Prefilled AI		
Co-packaged Product Information	Not applicable		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance (DS)	Ancy Nalli, Deepa Raghu (some methods)	Bazarragchaa Damdinsuren
	Drug product (DP)		
	Immunogenicity Assay	Li Lu	
	CAA	Li Lu	
	Microbiology	Yuan-Chia (Charles) Kuo (DS) Jeanne Fringer (DP)	Maxwell Van Tassell
	Facility		Zhong Li
	RBPM	Anita Brown	
	ATL	Bazarragchaa Damdinsuren	
OPQ Issued Consults	Consult to CDRH for device components. The consult review is performed by Kathleen Fitzgerald and Courtney Evans (Team Lead).		

2. Recommendation and Conclusion on Approvability
Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761275 for TYENNE manufactured by Fresenius Kabi USA, LLC. The data submitted in this application are not sufficient to support a conclusion that the manufacture of TYENNE is well-controlled and will lead to a product that is pure and potent. The comparative analytical data support a demonstration that TYENNE is highly similar to US-licensed Actemra. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Fresenius Kabi USA, LLC to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comment (provided by OPMA):

1. Following inspections of Fresenius Kabi Austria GmbH, Graz, Austria (FEI: 3003708554) and (b) (4) listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional Product Quality Comment (provided by OBP):

1. The acceptance criteria for oxidized variants by RP-UPLC, degree of coloration, and device performance attributes for the prefilled syringe (b) (4) and autoinjector in the drug substance and/or drug product specifications are based on a limited number of MSB11456 batches, thus re-evaluation of the acceptance criteria for these attributes is needed after data from sufficient MSB11456 drug substance and/or drug product batches are available. Submit a rationale for the number of batches needed and a statistical plan that will be used to evaluate the results for each assessment.

Additional Microbiology Comment (provided by OPMA):

2. Revise the method for container closure integrity testing of MSB11456 drug product in vial to include a positive control that reflects a breach defect ≤ 20 µm and update the application accordingly.

4. Basis for Recommendation

a. Summary: Tyenne (tocilizumab-aazg, MSB11456) is a proposed biosimilar to US-licensed Actemra (US-Actemra) that is intended to be delivered by the same routes of administration (intravenous and subcutaneous) for the same indications as the US-Actemra reference product. The comparative analytical assessment data submitted support the demonstration that Tyenne is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components and that the analytical portion of the scientific bridge to justify the use of clinical data derived from EU-approved RoActemra was established.

Tocilizumab is a recombinant, humanized IgG1 mAb that specifically binds to the IL-6 binding site of both sIL-6R and mIL-6R and blocks the activity of IL-6. This leads to down-regulation of IL-6-driven cellular functions. The biological activity of MSB11456 is evaluated on its capability to inhibit the IL-6-induced cell proliferation in a dose-dependent manner on the DS-1 human cell line.

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for drug substance and drug product manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product and the OPMA assessors are recommending approval for this BLA from a sterility assurance and microbiology product quality perspective.

The pre-license inspections (PLIs) of (b) (4) manufacture and testing facility of MSB11456 drug substance and of (b) (4) used for the comparative analytical assessment (CAA) and testing for MSB11456 recommended approval.

The PLIs of Fresenius Kabi Austria GmbH (FK-Graz), Austria (FEI 3003708554) and (b) (4) that are responsible for MSB11456 drug product manufacturing respectively for the single-dose vial and the single-dose prefilled syringe/autoinjector concluded with inspection field recommendations of withhold for each facility (refer to the FDA Forms 483 for the observation details). The responses to the FDA Form 483 observations were not adequate and the final inspection conclusions were Official Action Indicated (OAI) and recommendations of withhold for both drug product manufacturing facilities.

The immunogenicity assays to detect and confirm anti-drug antibodies (ADAs) against tocilizumab in the clinical studies to support this BLA were adequately validated and suitable for their intended purpose.
Individual assessments for each discipline are located in separate documents in Panorama.

b. Subdiscipline Recommendation:

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

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations
Not applicable as OPQ does not recommend approval of this application.

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

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

The Comparative Analytical Assessments (CAAs) between MSB11456, U.S.-licensed Actemra (hereafter referred to as US-Actemra), and E.U.-approved RoActemra (hereafter referred to as EU-RoActemra) were performed separately for tocilizumab products in vial presentation (also referred as DP-IV, i.e., for intravenous (IV) administration) and for tocilizumab products in prefilled syringe (PFS) presentation (also referred as DP-SC, i.e., for subcutaneous (SC) administration). The CAAs included comparisons of 10 vial and 10 PFS MSB11456 batches (manufactured respectively in July 2018 - June 2021 and in Feb 2017 - Oct 2020), 18 vial and 18 PFS US-Actemra batches (with respective expiry dates Sept 2016 - April 2022 and March 2016 - Feb

2022), and 18 vial and 25 PFS EU-RoActemra batches (with respective expiry dates Sept 2015 - April 2022 and April 2016 - Aug 2022). The batches were adequate to capture potential batch-to-batch variability in the US-Actemra and EU-RoActemra products over time.

There were two DP process iterations during the commercial development stage of MSB11456 DP-IV: manufacturing process at (b) (4) (3 batches) and process at FK-Graz (7 batches). The 400 mg/20 mL, 200 mg/10 mL and 80 mg/4 mL MSB11456 DP-IV batches were used in the CAA.
There were two process iterations during the commercial development stage of MSB11456 DP-SC: manufacturing process at (b) (4) (1 batch), and process at (b) (4) (9 batches). The MSB11456 DP-SC batches in PFS presentation (162 mg/0.9 mL) with and without (b) (4) passive safety device, but not in final assembled auto-injector, were used in the CAA. The PFS is the primary container closure system of the auto-injector and (b) (4) device presentations and the assembly process of these devices has no impact on the quality attributes of MSB11456. Therefore, it is acceptable to include MSB11456 PFS batches in the CAA.

The MSB11456 DP batches used in each CAA were derived from independent DS batches and included the process validation batches (i.e., 5 DP-IV and 4 DP-SC batches). Note that MSB11456 DS was manufactured at (b) (4) with minor manufacturing changes during the commercial development stage. In addition, the CAA included all MSB11456 DP, US-Actemra and EU-RoActemra batches used in the comparative clinical studies included in the BLA.

The CAA was comprised of extensive comparative physiochemical and functional assessment of the quality attributes of MSB11456, US-Actemra, and EU-RoActemra. The Applicant used an acceptable risk-based approach for statistical evaluation of analytical results. The critical quality attributes (CQAs) and attributes linked to CQAs that were tested using quantitative assays were evaluated using quality ranges obtained from US-Actemra or EU-RoActemra to account for manufacturing variability and assay variability. In addition, the most sensitive assays for detecting product differences were selected for statistical evaluation using quality ranges. Attributes tested using quantitative assays not amenable to statistical analysis and qualitative assays were evaluated using visual comparisons (referred as descriptive assessment). Results from method validation or qualification studies support the suitability of the methods used in the CAA. The Applicant also provided a comparison of stability under forced degradation conditions of high temperature stress, light stress (photostability), high and low pH stress, oxidative stress, and mechanical stress.

Based on the OBP assessment, the MSB11456 and US-Actemra data supports a demonstration that MSB11456 is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components. MSB11456 has the same strength, dosage

form, and routes of administration as US-Actemra. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate CQAs of MSB11456 and US-Actemra to support the demonstration that the products are highly similar. Numbers of batches tested were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While differences were observed in a limited number of attributes, these differences do not preclude a demonstration that MSB11456 is highly similar to US-Actemra (see section D below).

In addition, three-way pairwise comparisons of MSB11456, US-Actemra, and EU-RoActemra were used to establish the analytical component of the three-way scientific bridge between MSB11456, US-Actemra, and EU-RoActemra to support the relevance of the data generated from studies using EU-Actemra as the comparator to the assessment of biosimilarity. Based on the OBP assessment of the data, the Applicant established the analytical portion of the scientific bridge between MSB11456, US-Actemra, and EU-RoActemra, using the same methods and statistical approaches as those to evaluate the similarity between MSB11456 and US-Actemra. The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies with EU-RoActemra as the comparator for the assessment of biosimilarity.

B. Results of Comparative Analytical Assessment

The results of these analytical comparisons support a demonstration that MSB11456 is highly similar to US-Actemra and the establishment of the analytical component of the scientific bridge between MSB11456, US-Actemra, and EU-RoActemra and the results are summarized in Table A below.

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/ Functional Characteristics	Quality Attribute Assessed (analytical methods)		Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Primary Structure	Amino acid sequence (LC-MS/MS)		Yes	Yes
	Intact Mass (LC-MS)		Yes	Yes
	N-terminal sequence (Edman chemistry)		Yes	Yes
Post-Translational Modifications	Deamidation	(IEX-HPLC)	Yes	Yes
		(peptide mapping by LC-MS/MS)	Yes	Yes
	Oxidation	(RP-UPLC)	Yes	Yes
		(peptide mapping by LC-MS/MS)		

Physico-chemical/ Functional Characteristics	Quality Attribute Assessed (analytical methods)		Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
	Glycation (intact mass LC-MS/MS)		Yes	Yes
	N-glyco site occupancy (peptide mapping)		Yes	Yes
	N-terminal Variants (peptide mapping by LC-MS)		Yes	Yes
	C-terminal Variants (peptide mapping by LC-MS/MS)		Yes	Yes
Higher Order Structure	Free Thiol content (Ellman's test)		Yes	Yes
	Secondary and Tertiary Structure	(FTIR)	Yes	Yes
		(CD, near and far UV)	Yes	Yes
		(Fluorescence spectroscopy)	Yes	Yes
	Disulfide linkage (native and reduced peptide mapping by LC-MS/MS)		Yes	Yes
	Disulfide bonds (native and reduced peptide mapping)		Yes	Yes
	Thermal stability (Nano-DSC)		Yes	Yes
Size purity/impurity	Aggregates/ HMW species	(SEC-HPLC)	Yes	Yes
		(AUC)	Yes	Yes
	Fragments/ LMW species	(reduced CE-SDS)	Yes	Yes
		(non-reduced CE-SDS)	Yes	Yes
	Monomer	(SEC-HPLC)	Yes	Yes
		(AUC)	Yes	Yes
	LC+HC	(reduced CE-SDS)	Yes	Yes
	NGHC	(reduced CE-SDS)	Yes	Yes
	Intact IgG	(non-reduced CE-SDS)	Yes	Yes
Charge Variants	pI points (icIEF)		Yes	Yes
	Main Peak (IEC-HPLC, icIEF)		Yes	Yes
	Acidic Species (IEC-HPLC, icIEF)		Yes	Yes
	Basic Species (IEC-HPLC, icIEF)		Yes	Yes
Glycosylation	Total sialylated glycans (HPEAC-PAD, 2-AB glycan mapping)		Yes	Yes
	Galactosylated glycans (2-AB glycan mapping)		Yes	Yes
	Afucosylated glycans (2-AB glycan mapping)		Yes	Yes
	High mannose glycans (2-AB glycan mapping)		Yes	Yes
Content	Protein Concentration (UV280)		Yes	Yes
	Extractable volume (Gravimetric volume determination)		Yes	Yes
Biological activity	IL-6 neutralization (IL-6 inhibition by in vitro bioassay)		Yes	Yes

Physico-chemical/ Functional Characteristics	Quality Attribute Assessed (analytical methods)	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
(Fab binding)	sIL-6R binding (SPR)	Yes	Yes
	mIL-6R binding (Flow cytometry)	Yes	Yes
Biological activity (Fc binding)	FcRn binding affinity (SPR)	Yes	Yes
	FcγRIIIa (V-type) binding affinity (SPR)	Yes	Yes
	FcγRIIIa (F-type) binding affinity (SPR)	Yes	Yes
	FcγRIIIb binding affinity (SPR)	Yes	Yes
	FcγRIIa binding affinity (SPR)	Yes	Yes
	FcγRIIb binding affinity (SPR)	Yes	Yes
	FcγRI binding affinity (SPR)	Yes	Yes
	C1q binding (ELISA)	Yes	Yes
Comparative in vitro activities*	Antibody-dependent cellular cytotoxicity (ADCC-induced cell viability reduction by luminescence)	Yes	Yes
	Complement-dependent cytotoxicity (CDC-induced cell viability reduction by luminescence)	Yes	Yes
	Apoptosis (Apoptosis of THP-1 cells by luminescence)	Yes	Yes
	Flow cytometry (mIL-6R driven STAT3 phosphorylation)	Yes	Yes
Degradation profiles*	High Temperature (50°C)#	Yes	Yes
	Light stress (765 W/m^2·hr)#	Yes	Yes
	Chemical Oxidation (H_2O_2 0.1%)#	Yes	Yes
	Low and high pH (pH 4.0 and 9.0)#	Yes	Yes
	Mechanical stress (shaking at 300 rpm)#	Yes	Yes

* - Additional characterization studies performed with 3-4 lots of each product
# - Conditions for Forced Degradation Study

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

The clinical development of MSB11456 included three clinical studies that compared MSB11456 to US-Actemra and EU-RoActemra:

- Study MS200740-0001: A single-dose comparative pharmacokinetic (PK) study in healthy subjects comparing MSB11456 to US-Actemra and EU-Actemra using the SC route of administration, thus establishing a 3-way clinical bridge between MSB11456, US-Actemra and EU-Actemra
- Study FKS456-001: A multiple-dose comparative efficacy and safety study comparing MSB11456 to EU-RoActemra in patients with rheumatoid arthritis to

demonstrate that MSB11456 and EU-RoActemra have similar efficacy, safety and immunogenicity by the SC route of administration

- Study FKS456-002: A single-dose PK study in healthy subjects comparing MSB11456 and US-Actemra using the IV route of administration, thus demonstrate that MSB11456 and US-Actemra are similar in terms of PK after IV administration.

To support the relevance of the comparative clinical data (Study FKS456-001) generated using EU-RoActemra as a comparator product to the assessment of biosimilarity, the Applicant performed three-way, pairwise comparative analytical assessments using a comprehensive array of analytical methods and a three-way pairwise PK similarity study (MS200740-0001). To support the establishment of the analytical component of the scientific bridge, the Applicant included comparison of MSB11456 to US-Actemra, MSB11456 to EU-RoActemra, and US-Actemra to EU-RoActemra. The same analytical methods used for supporting a demonstration that MSB11456 is highly similar to US-Actemra were used for the pairwise comparisons with EU-RoActemra. The differences observed in the comparative 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 acceptance criteria for the pairwise three-way comparison between MSB11456, US-Actemra and EU-RoActemra were met for all attributes evaluated with the following exceptions:

- Oxidation (by RP-UPLC after IdeS digest):

Total oxidation is higher in MSB11456 DP-SC lots (3.4 - 4.3%) in comparison to US-Actemra lots (2.5 - 3.3%, quality range 2.0 – 3.6%), which was due to Fc/2 oxidized (Fc/2 ox; oxidized single chain of the crystallizable fragment) forms (respectively 2.6 - 3.2% vs 1.3 - 2.1%, quality range 0.9 – 2.4%). Fd oxidized species (oxidized heavy chain portion of the antigen-binding fragment) are similar across the three products. In addition, no difference in oxidized forms was observed for vial presentations. Oxidation is identified as moderate criticality attribute, and the observed difference in SC lots was small (~1.3%), which would not adversely impact efficacy or safety. See also the discussion about the oxidation profiles in degradation studies, below. Therefore, the difference observed in the oxidation of MSB11456 DP-SC does not preclude a demonstration that MSB11456 is highly similar to US-Actemra.

- Glycosylation (by 2-AB Glycan Mapping):

MSB11456 DP-IV and DP-SC lots contained lower levels of G0F (respectively 35.1 - 37.1% and 35.0 - 38.2%) than US-Actemra lots (respectively 39.1 - 47.9% and 41.6 -

47.6%) or EU-RoActemra lots (respectively 38.8 - 51.2% and 41.2 - 50.1%), and a higher of G1F (30.1 - 30.6% and 30.0 - 31.0%) than US-Actemra (22.8 - 29.1% and 25.0 - 28.7%) or EU-RoActemra (22.3 - 28.6% and 20.8 - 28.5%, respectively). however, the content of fucosylated glycans, i.e., sum of G0F, G1F, G1F iso and G2F, (as well as high mannose glycan, and afucosylated glycans) in MSB11456 DPs is within the quality ranges of US-Actemra and EU-RoActemra. MSB11456 DP-IV and DP-SC have a higher level of galactosylated species (53.2 - 54.5% and 53.2 - 54.9%) compared to US-Actemra lots (respectively 40.8 - 50.7% and 44.0 - 50.6%) or EU-RoActemra lots (respectively 39.5 - 50.4% and 36.0 - 50.2%). Individual glycosylated species are classified as low criticality attribute, except high mannose glycans as moderate criticality. Therefore, the minor differences observed for the individual isoforms identified above are not clinically meaningful considering primary mechanism of action of tocilizumab, and do not preclude a demonstration that MSB11456 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

- Glycation:

Levels of glycation of MSB11456 lots (4.5-10.2% for DP-PFS and DP-IV) were found to be higher than US-Actemra and EU-RoActemra (respectively 0.0-2.8% and 0.0-3.0%). Glycation is identified as a low criticality attribute, and the location of the glycation sites is not associated to binding epitopes nor Fc receptor binding regions (i.e., the glycation detected in CDR2 region was <0.2%), and the higher level would not have an adverse effect on safety and efficacy. Therefore, the difference observed in the glycation of MSB11456 does not preclude a demonstration that MSB11456 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

- Size purity (LC+HC):

Marginally higher LC+HC purity by reduced CE-SDS was found for MSB11456 DP-IV (98.3 - 99.0%) than US-Actemra (97.6 - 98.2%) or EU-RoActemra (97.5 - 98.0%). This small difference would not be expected to have a biological impact on the tocilizumab products and do not preclude a demonstration that MSB11456 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

- Charge heterogeneity (by IEX-HPLC):

MSB11456 DP-IV lots showed a lower percentage of acidic variants than that detected in US-Actemra (19.1 - 21.7% vs. quality range 20.8 - 24.7%, resulting in 60% of DP-IV lots outside of the quality range). The opposite pattern is evident for the basic variants in MSB11456 DP-IV vs US-Actemra and/or EU-RoActemra lots (12.8 - 15.2% vs. respective quality ranges 5.1 - 14.6% and 5.4 - 13.5%). MSB11456 DP-SC lots showed similar contents of charge variants than those detected in US-Actemra or EU-RoActemra. The characterization data show that acidic peaks contain sialylated glycans and fragments (predominantly HHL and HH), and the individual fractions from the acidic peaks showed comparable activity. The basic species contain variants with oxidation at

HC M254 or M430, and P447 amidation. The detected minor differences of acidic and basic variants (respectively ~2% and ~4% differences in the mean values) are not anticipated to impact safety, PK or immunogenicity of tocilizumab considering the comparable biological activity of the acidic peaks and the low criticality of the attributes present under the basic peaks. In addition, the difference in levels of acidic and basic variants in the MSB11456 IV and SC presentations is most likely due to the differences in formulation.

IEX-HPLC testing is also applied to tocilizumab products samples with Carboxypeptidase B (CpB) treatment that remove C-terminal heterogeneity (predominantly lysine). Under this condition, MSB11456 DP-IV lots showed a lower percentage of acidic variants than those detected in US-Actemra (20.8 - 22.8% vs quality range 22.3 - 25.5%), while the reverse pattern is seen for the main peak. MSB11456 DP-SC lots showed a lower percentage of basic variants than those detected in US-Actemra or EU-RoActemra (5.9 - 6.4% vs quality ranges 7.4 - 16.3% and 7.9 - 15.6%). The applicant stated that this was most likely due to the lower level of C-terminal proline amidation in MSB11456 DP-SC batches, which was observed by peptide mapping LC-ESI-MS and was unmasked in the presence of CpB. Considering the low criticality of C-terminal proline amidation, the difference observed for basic variants is not anticipated to impact safety or efficacy.

CAA of MSB11456 DPs, US-Actemra and EU-RoActemra using icIEF met the similarity criteria.

Taken together, the charge heterogeneity assessments support that the observed differences in charge variants do not preclude a demonstration that MSB11456 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

- Oxidation profiles in degradation studies:

The stability and degradation studies suggest that the MSB11456 DP-SC and DP-IV are more sensitive and prone to oxidation (including under thermal stress and oxidative stress) when compared to US-Actemra and EU-RoActemra, e.g., Fc/2 ox species increased from 2.6 – 3.0% to 3.5 – 3.7% for MSB11456 DP-SC lots compared to no significant change (from 1.1 - 1.3% to 1.4 – 1.6%) for US-Actemra and EU-RoActemra lots under 30 hours of high temperature stress condition at 50°C. The slightly higher levels of oxidation in MSB11456 can be attributed to the differences in formulations of MSB11456 DP and US-Actemra/EU-RoActemra, specifically, the SC formulation of US-Actemra/EU-RoActemra contains L-methionine (b) (4), while L-methionine is not present in the IV formulation of US-Actemra/EU-RoActemra, or in the MSB11456 DP formulation. The slightly increased susceptibility to oxidation of the MSB11456 does not impact any other product quality attribute, as well as studies in section 3.2.R.1.5.6 showed that up to ~7-10% Fd and Fc oxidation would have no

adverse impact on sIL-6R and FcRn binding affinity. Therefore, the differences observed in the oxidation of MSB11456 DP do not preclude a demonstration that MSB11456 is highly similar to US-Actemra.

E. Same Strength

MSB11456 has the same dosage forms and routes of administration as US- licensed Actemra. US-Actemra is available at these strengths: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL (all 20 mg/mL) in vials for further dilution prior to intravenous infusion, and 162 mg/0.9 mL in a prefilled syringe or prefilled autoinjector. The Applicant is seeking approval of 20 mg/mL MSB11456 in 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL vial and 180 mg/mL MSB11456 in 162 mg/0.9 mL prefilled syringe in (b) (4) safety device or autoinjector. Comparative concentration (mg/mL) was assessed as part of the CAA. The extractable volume and fill weight data were also assessed (b) (4) . Based on the comparative concentration data and manufacturing data, the 20 mg/mL MSB11456 in 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL vial and 180 mg/mL MSB11456 in 162 mg/0.9 mL prefilled syringe in (b) (4) safety device or autoinjector 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 the corresponding strengths of US-Actemra. Each strength of MSB11456 vial and prefilled syringe is the same as that of US-Actemra.

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