DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Food and Drug Administration
Center for Drug Evaluation and Research
OND / OII / DRTM
10903 New Hampshire Ave.
Silver Spring, MD 20993

CDTL AND DIVISION SUMMARY MEMO TO FILE

BLA:	761275
SD:	012
Reviewer:	Eric J. Gapud, M.D., Ph.D., CDER/OND/OII/DRTM
CDTL:	Rachel L. Glaser, M.D., CDER/OND/OII/DRTM
Division Signatory:	Rachel L. Glaser, M.D.
Submitted:	September 5, 2023
Reviewed:	March 4, 2024
BsUFA Goal:	March 5, 2024
Product:	Tyenne/ tocilizumab-aazg (MSB11456)[1]
Dosage Forms/Strength:	80 mg/4 mL single-dose vial for further dilution prior to intravenous (IV) infusion 200 mg/10 mL single-dose vial for further dilution prior to IV infusion 400 mg/20 mL single-dose vial for further dilution prior to IV infusion 162 mg/0.9 mL single-dose prefilled syringe (PFS) 162 mg/0.9 mL single-dose prefilled autoinjector (AI)
Route of Administration:	Intravenous (80 mg/4mL, 200 mg/10 mL, 400 mg/20 mL single-dose vials) Subcutaneous (PFS, AI)
Indications:	Rheumatoid Arthritis (RA), Giant Cell Arteritis (GCA), Polyarticular Juvenile Idiopathic Arthritis (PJIA) in patients ≥ 2 years of age, Systemic Juvenile Idiopathic Arthritis (SJIA) in patients ≥ 2 years of age
Applicant:	Fresenius Kabi USA, LLC
Submission:	Resubmission

Review:
Fresenius Kabi USA, LLC (also referred to as "Applicant" in this review) submitted a biologics license application (BLA) under section 351 (k) of the Public Health Service Act (PHS Act) for MSB11456 as a proposed biosimilar to US-licensed Actemra (tocilizumab) on May 30, 2022. The application received a complete response (CR) letter (CRL) on May 31, 2023, due to manufacturing facilities deficiencies. A response to CR submission containing information to address the

[1] In this document, the Applicant's proposed product is referred to by the descriptor "MSB11456," which was the name used to refer to this product during development. Both "Tyenne", the proposed proprietary name, and "tocilizumab-aazg", the proposed nonproprietary name, are conditionally accepted until the application is approved.

manufacturing facilities deficiencies and to address additional comments in the CRL, was received on September 5, 2023.

Initial BLA Submission

During review of the initial BLA submission, the Agency determined that:

- MSB11456 is highly similar to US-licensed Actemra (US-Actemra), notwithstanding minor differences in clinically inactive components. Each strength of MSB11456 in single-dose vials, PFS, and AI is the same as that of US-Actemra, and the dosage form and routes of administration are the same as for US-Actemra. In addition, the three pairwise comparisons of MSB11456, US-Actemra, and EU-approved RoActemra (EU-RoActemra) established the analytical component of the scientific bridge used to support the relevance of data generated from studies using EU-RoActemra as the comparator to the assessment of biosimilarity.

- The submitted clinical pharmacology studies were adequate to (1) establish the pharmacokinetic (PK) similarity between MSB11456 and US-Actemra, and (2) establish the PK component of the scientific bridge to support the relevance of the comparative data generated using EU-RoActemra to the assessment of biosimilarity.

- The submitted clinical studies demonstrated that there are no clinically meaningful differences between MSB11456 and US-Actemra in terms of safety, purity, and potency in the indication studied (RA).

- In addition, the Applicant provided information and an extensive data package to address the scientific considerations for extrapolation of data and information to support licensure of MSB11456 under section 351(k) of the Public Health Service (PHS) Act as a biosimilar for each of the indications for which US-Actemra is currently licensed and for which Fresenius Kabi USA, LLC is seeking licensure of MSB11456, including GCA, PJIA in patients 2 years and older, and SJIA in patients 2 years and older.

However, data submitted in the original BLA were not sufficient to support a conclusion that the manufacture of MSB11456 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. The Office of Pharmaceutical Manufacturing Assessment (OPMA) identified the following manufacturing facilities deficiencies during the initial BLA review:

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

The OPMA and Office of Product Quality Assessment III (OPQA III) also provided the following product quality comments/recommendations that were not approvability issues:

1. 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.

2. 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.

See the Biosimilar Multidisciplinary Evaluation Review (BMER) and CRL dated May 31, 2023, for full details of the original BLA review.

Current Submission

A response to the CRL containing manufacturing facilities information to address the deficiencies was received on September 5, 2023. In the response, the Applicant included product quality information to address the comments on the acceptance criteria and commitment to revise the method for container closure integrity testing as outlined in the CRL. The Applicant also provided a safety update with submission of the Week 63 addendum to the clinical study report for Study FKS456-001, the comparative clinical study conducted in subjects with moderate to severely active rheumatoid arthritis.

OPMA recommends approval of the MSB11456 drug product manufacturing facilities Fresenius Kabi Austria GmbH and (b) (4) and waives re-inspections for both facilities based on the firms' responses, adequate corrective and preventative action (CAPA) updates, and additional updates to the submission during the review cycle. OPMA and OPQA III recommend approval of the BLA from the product quality, manufacturing process controls and facility assessments and the sterility assurance perspective. Refer to the OPMA and OPQA III reviews, respectively, for detailed discussions of the responses for the deficiencies and other non-CR issues. The OPQ review teams conclude that the data submitted in this application are adequate to support a conclusion that the manufacture of MSB11456 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life.

In the current submission, the Applicant provided the Week 63 addendum to Study FKS456-001. Clinical data from Weeks 1 to 55 of the comparative clinical study were reviewed during the original BLA review (refer to the BMER dated May 31, 2023). The addendum includes post-treatment data from the Safety Follow-Up Period (Weeks 55 to 63). The last study drug administration occurred at Week 51; no study drug was administered during the Safety Follow-Up period. During the Safety Follow-Up period, no new deaths were reported; a fatal myocardial infarction in the EU-RoActemra/MSB11456 arm previously reported in the Extended Period was clarified as having occurred post-treatment in the Safety Follow Up Period (Week 61). Post-treatment proportions of treatment-emergent serious adverse events (MSB11456: 1.1%, EU-RoActemra: 1.5%, EU-RoActemra/MSB11456: 3.6%) and treatment-emergent adverse events (MSB11456: 9.4%, EU-RoActemra 11.8%, EU-RoActemra/MSB11456: 11.5%) were low and generally balanced across treatment arms. The event types were generally consistent with those reported from Weeks 1 to 55, and no new safety signals were identified. Review of the safety data in the Week 63 addendum does not alter the determination made during the original BLA review that there are no meaningful differences in safety between the MSB11456 and EU-RoActemra treatment arms in Study FKS456-001.

Conclusions

Review of the data submitted by the Applicant in the initial BLA submission showed that MSB11456 is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between MSB11456 and US-Actemra in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrated that MSB11456 is biosimilar to US-Actemra for each of the following indications for which US-Actemra has been previously approved and for which the Applicant is seeking licensure of MSB11456: RA, GCA, PJIA in patients 2 years and older, and SJIA in patients 2 years and older. However, data submitted in the original application was not sufficient to support a conclusion that the manufacture of MSB11456 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life.

In the response to the CRL, the Applicant has provided information to confirm that the manufacturing facilities deficiencies have been adequately addressed. The Applicant has provided adequate data to support a conclusion that the manufacture of MSB11456 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. Additional clinical information in the resubmission does not change the previous clinical conclusions that (1) there are no clinically meaningful differences between MSB11456 and US-Actemra in terms of safety, purity, and potency in the indication studied and that (2) MSB11456 is biosimilar to US-Actemra for each of the following indications for which US-Actemra has been previously approved and for which the Applicant is seeking licensure of MSB11456: RA, GCA, PJIA in patients 2 years and older, and SJIA in patients 2 years and older.

The OPMA and OPQA III review teams recommend approval of BLA 761275 with post-marketing commitments. We agree with the conclusions and the recommendations by the OPMA and OPQA III review teams. Therefore, the recommended regulatory action is Approval with post-marketing commitments outlined below.

Labeling

- **Nonproprietary Name**

The Applicant's proposed nonproprietary name, tocilizumab-aazg, was found to be conditionally acceptable by the Agency. See the DMEPA review dated December 14, 2023, for full details.

- **Proprietary Name**

The proposed proprietary name for MSB11456, Tyenne, was reviewed by the Division of Medication Error and Prevention Analysis 1 (DMEPA), and determined to be conditionally acceptable. See the DMEPA review dated December 21, 2023, for full details.

- **Other Labeling Recommendations**

MSB11456 is proposed as a biosimilar to US-Actemra. The Applicant is seeking licensure for the following indications, for which US-Actemra has been previously approved: rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, and systemic juvenile idiopathic arthritis in patients 2 years of age and older.

The Applicant is not seeking licensure for the following indications for which US-Actemra has been previously approved: systemic sclerosis-associated interstitial lung disease (SSc-ILD) in adults and cytokine release syndrome (CRS) in adults and pediatric patients 2 years of age and older, due to existing orphan exclusivity for the reference product for these indications, nor is the Applicant seeking licensure for Coronavirus Disease 2019 (COVID-19). The Applicant's proposed labeling does not include information related to indications for SSc-ILD, CRS, or COVID-19.

The proposed MSB11456 prescribing information incorporated relevant data and information from the US-Actemra prescribing information, with appropriate modifications.

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

Additional modifications to the labeling for MSB11456 include the following:

- References to ACTEMRA were changed to TYENNE or tocilizumab/tocilizumab products, consistent with biosimilar labeling practice
- Information on the Actemra pregnancy registry which has been closed was removed from the USPI
- Inactive ingredients were updated for IV infusion and SC injection
- Storage and stability information was updated

Aligning changes were made to the Medication Guide and Instructions For Use (IFU). The container labels and carton labeling were revised such that they are adequately differentiated in order to minimize selection errors between the PFS and AI presentations. Additional minor editorial revisions were made.

Labeling consultants, including OPQA III-labeling, DMEPA, the Office of Prescription Drug Promotion (OPDP), and the Division of Medical Policy Programs (DMPP), have reviewed the submitted labeling and found the proposed revisions acceptable. All labeling changes were agreed upon with the Applicant.

Postmarketing Recommendations

- **Risk Evaluation and Mitigation Strategies**

None

- **Postmarketing Requirement (PMR)**

None

- **Postmarketing Commitments (PMC)**

<u>Product Quality:</u>

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.

Recommended Action: Approval

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

/s/

ERIC J GAPUD
03/04/2024 02:38:17 PM

RACHEL GLASER
03/04/2024 02:39:26 PM