CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761354Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 9/12/2023

1. Application/Product Information

BLA number	761354
Submission Type	Original Submission
Regulatory Pathway	Biosimilar 351(k) A proposed biosimilar to US-licensed Actemra (tocilizumab)
Associated IND/BLA	IND 142381
Review Designation	Standard Review
Applicant	Biogen MA Inc.
Indication	Rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and systemic juvenile idiopathic arthritis (sJIA) (Note: Due to data and market protection, Biogen is not seeking approval for giant cell arthritis (GCA), systemic sclerosis-associated interstitial lung disease (SSc-ILD), and cytokine release syndrome (CRS), three additional indications approved for US-licensed Actemra.)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Tofidence
	Non-proprietary Name/Code Name: tocilizumab-bavi / BIIB800
	OBP Naming: MAB HUMANIZED (IGG1) ANTI P08887 (IL6RA_HUMAN) [BIIB800]
Drug Product Description	Tofidence (tocilizumab-bavi) injection is a sterile, clear to opalescent, colorless to light yellow, preservative-free solution, with a concentration of 20 mg/mL and a pH of

	approximately 6.2, for further dilution prior to intravenous (IV) infusion. Single-dose vials are available containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of Tofidence (tocilizumab-bavi). Each mL of solution contains 0.81mg L-histidine, 1.01 mg L-histidine hydrochloride monohydrate, 10.53 mg arginine hydrochloride, 20 mg sucrose, 0.5 mg polysorbate 80, and water for injection. (Note: Biogen is only seeking approval for the vial presentations for IV administration listed below. They are not seeking approval for the 162 mg/0.9 mL strength, currently available for US-licensed Actemra as single-dose prefilled syringes or single-dose prefilled autoinjectors for subcutaneous administration.) Tocilizumab-bavi 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). The antibody is produced in a Chinese Hamster Ovary (CHO) cell line.
Dosage Form	Solution for injection
Strength	80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), and 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to IV infusion
Route of Administration	IV infusion
Primary Container Closure System	6 mL, 15 mL, and 25 mL (b) (4) clear glass vials, closed with a (b) (4) rubber and sealed with an aluminum crimp seal with (b) (4) flip off button.
Device Information	Not applicable

Co-packaged Product Information	Not applicable		
OPQ Review Team	Discipline	Primary	Secondary
	Drug Substance (DS), Drug Product (DP)	Dilip Devineni	Nailing Zhang
	Immunogenicity Assay, Comparative Analytical Assessment (CAA)	Mercy Oyugi	
	Facility	Jiangsong Jiang (DS), Yi (Eva) Wang (DP)	Michael Shanks
	Microbiology		Virginia Carroll (DS), Madushini Dharmasena (DP)
	RBPM	Shazma Aftab	
	ATL	Nailing Zhang	
	Review Chief	Maria-Teresa Gutierrez-Lugo	
OPQ Issued Consults	None		

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

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761354 for Tofidence (tocilizumab-bavi) manufactured by Biogen MA Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Tofidence (tocilizumab-bavi) is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Tofidence (tocilizumab-bavi) is highly similar to US-licensed Actemra (tocilizumab), 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:** [redacted] (b) (4)
- **Drug Product:** Same as DS.

b. Fill size and dosage form:

80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion

c. Dating Period:

- **Drug Product:** 24 months at 2°C - 8°C, protected from light
- **Drug Substance:** (b) (4) months at (b) (4) °C
- **Stability Option:**
  - For stability protocols:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Tofidence 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

Two OPMA PMCs (to be submitted by 03/31/2024) are listed below:

- To implement the [redacted] (b) (4) of the sterile filter during sterile filtration.
- To implement revised procedure with target flushing volume of ≥ (b) (4) L for post-use filter integrity test

4. Basis for Recommendation

a. Summary:

Tofidence (tocilizumab-bavi) is a proposed biosimilar to US-licensed Actemra (tocilizumab) for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and systemic juvenile idiopathic arthritis (sJIA). Tocilizumab is a recombinant humanized IgG1 monoclonal antibody

that binds to both sIL-6R and mIL-6R, preventing them from binding to IL-6 and thereby inhibiting IL-6 mediated biological activities including B-cell and helper T-cell differentiation and pro-inflammatory responses.

Two assays are used to control the potency for Tofidence (tocilizumab-bavi). The first is an ELISA assay to measure its binding affinity to sIL-6R. The second is a cell-based assay to measure its ability to inhibit IL-6 induced proliferation of TF-1 cells, a human erythroleukemia cell line that expresses mIL-6R. All potency results are reported as percentage relative to a qualified reference material.

The totality of the comparative analytical evidence supports that Tofidence (tocilizumab-bavi) is highly similar to US-licensed Actemra (tocilizumab), notwithstanding minor differences in clinically inactive components. The strengths of 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), and 400 mg/20 mL (20 mg/mL) in single-dose vials demonstrated the same strengths as that of US-licensed Actemra. Refer to Appendix for detailed summary on comparative analytical assessment.

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

No approvability issues were identified from a sterility assurance or microbiology product quality perspective. Two PMCs will be issued for (b) (4) during sterile filtration, and establishment of target flushing volume for post-use filter integrity test. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations. An on-site pre-license inspection (PLI) for the DS and DP manufacturing facility, (b) (4) was conducted in (b) (4) and found satisfactory.

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

The overall Tofidence (tocilizumab-bavi) control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Tofidence (tocilizumab-bavi) are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The BLA is recommended for approval from a product quality, facility, microbiology and sterility assurance perspectives.

b. Subdiscipline Recommendation:

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

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

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for Tofidence (i.e., there is no specific test method described in regulation for Tofidence that establishes an official standard of potency). We next considered whether potency is a factor for Tofidence 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 Tofidence for purposes of § 610.61(r) because lot variability is not a concern for Tofidence as Tofidence’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:

- Concurrent validation (b) (4)
- Concurrent validation (b) (4)
- Preparation and qualification of future working cell banks
- Stability monitoring for master cell bank and working cell bank
- Preparation and qualification of future working reference standards
- Stability monitoring for primary and working reference standards
- Post-approval annual stability protocol for drug substance
- Stability protocol for extension of shelf-life of drug substance

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:
- Post-approval annual stability protocol for drug product
- Stability protocol for extension of shelf-life of drug product
- Protocol for bulk drug product and finished drug product real-time supply chain study

ii. Residual risk: None

iii. Future inspection points to consider: None

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

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

U.S.-licensed Actemra (hereafter referred to as US-Actemra) is available at these strengths: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL) and 400 mg/20 mL (20 mg/mL) in vials for further dilution prior to intravenous (IV) infusion, and 162 mg/0.9 mL (180 mg/mL) in a prefilled syringe or prefilled autoinjector for subcutaneous (SC) injection. Biogen is seeking approval of 20 mg/mL BIIB800 in 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL vials for IV administration only. The Comparative Analytical Assessment (CAA) between BIIB800, US-Actemra, and E.U.-approved RoActemra (hereafter referred to as EU-RoActemra) compared a total of 18 BIIB800 lots (including 10 drug substance (DS) lots at 20 – 35 mg/mL and 8 drug product (DP) lots at 80 mg/4 mL), 14 US-Actemra lots (80 mg/4 mL, with expiry dates March 2018 - January 2023), and 17 EU-RoActemra lots (80 mg/4 mL, with expiry dates June 2018 - September 2022). The lots were adequate to capture potential lot-to-lot variability in the US-Actemra and EU-RoActemra products over time.

The 10 BIIB800 DS lots used in the CAA were manufactured between March 2018 and March 2021 using the proposed (b) (4) L scale commercial process, and included 4 process validation lots. The 8 BIIB800 DP lots used in the CAA were manufactured between April 2018 and January 2021 from 6 out of the 10 DS lots, and included 3 process validation lots as well as 2 clinical lots used in the PK similarity study and the comparative clinical study. It is acceptable to include BIIB800 DS lots in the CAA as the DS and DP formulations are identical with the only difference being protein concentration. It is also acceptable to leverage the CAA data from the BIIB800 80 mg/4 mL strength to support the comparative analytical similarity assessment of the 200 mg/10 mL and 400 mg/20 mL strengths as the BIIB800 three strengths are analytically comparable between each other with the only differences being fill volume and vial size. Although not all BIIB800 DP lots were derived from independent DS lots, for example the 2 clinical DP lots were derived from the same DS lot, independent DS and/or DP lots (not derived from the DS lots used in the same study) were used for each quality attribute, except for DP-specific attributes (e.g., protein concentration).

The CAA was comprised of extensive comparative physiochemical and functional assessment of the quality attributes of BIIB800, US-Actemra, and EU-RoActemra. The Applicant used an acceptable risk-based approach for statistical evaluation of analytical results. Statistical equivalence testing was used for assessing binding to soluble IL-6R (sIL-6R) and inhibition of IL-6 mediated proliferation in TF-1 cells because they are two critical quality attributes (CQAs) associated with biological activity and the mechanism of action (MOA). Other 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. The data evaluation methods used were consistent with FDA recommendations during product development. Results from method validation or qualification studies support the suitability of the methods used in the CAA. Comparative stability under accelerated, freeze-thaw, and forced degradation conditions of thermal stress, oxidative stress, low and high pH, mechanical stress, and light stress (photostability) also support the CAA.

Based on the OBP assessment, the BIIB800 and US-Actemra data support a demonstration that BIIB800 is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components. BIIB800 has the same strengths and dosage forms for the IV route of administration as US-Actemra. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate CQAs of BIIB800 and US-Actemra to support the demonstration that the products are highly similar. Numbers of lots 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 BIIB800 is highly similar to US-Actemra.

In addition, three-way pairwise comparisons of BIIB800, US-Actemra, and EU-RoActemra were used to establish the analytical component of the three-way scientific bridge between BIIB800, US-Actemra, and EU-RoActemra to support the relevance of the data generated from studies using EU-RoActemra 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 BIIB800, US-Actemra, and EU-RoActemra, using the same methods and statistical approaches as those to evaluate the similarity between BIIB800 and US-Actemra. The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies 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 BIIB800 is highly similar to US-Actemra and the establishment of the analytical component of the scientific bridge between BIIB800, 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 /	Quality Attribute Assessed (Analytical Methods)	Supports a Demonstration	Supports the Analytical

Functional Characteristics		of Highly Similar	Component of the Scientific Bridge
Primary structure	Amino acid sequence (LC-MS/MS)	Yes	Yes
	Molecular weight (intact mass, intact deglycosylated mass, reduced high chain, reduced light chain, deglycosylated heavy chain) (LC-MS)	Yes	Yes
Post-translational modifications	Oxidation (LC-MS/MS)	Yes	Yes
	Deamidation (LC-MS/MS)	Yes	Yes
	Glycation (LC-MS) *	Yes	Yes
Higher order structure	Disulfide bonds (LC-MS/MS)	Yes	Yes
	Free thiol content (DTNB-Ellman)	Yes	Yes
	Secondary structure (FTIR)	Yes	Yes
	Far UV and near UV (CD)	Yes	Yes
	Tertiary structure (endogenous fluorescence)	Yes	Yes
	Thermal stability (DSC)	Yes	Yes
Product-related substances / impurities	Purity (monomer) (SEC-MALS, SV-AUC, SE-HPLC *)	Yes	Yes
	Aggregates / HMW Species (SEC-MALS, SV-AUC, SE-HPLC *)	Yes	Yes
	Purity (HC + LC) (rCE-SDS)	Yes	Yes
	Purity (Intact IgG) (nrCE-SDS)		
	Fragments / LMW species (rCE-SDS, nrCE-SDS)	Yes	Yes
	Non-glycosylated HC (rCE-SDS)	Yes	Yes
	Main peak, pre-peaks, post peaks (HIC-HPLC) *	Yes	Yes
	Main peak, pre-peaks, post peaks (RP-UPLC) *	Yes	Yes
Charge profile	Isoelectric profile (cIEF)	Yes	Yes
	pI of main peak (cIEF)	Yes	Yes
	Main peak, acidic peaks, basic peaks (IEC-HPLC with & without CpB) *	Yes	Yes
Glycosylation	Glycosylation site and occupancy (LC-MS/MS)	Yes	Yes
	High mannose (HILIC-HPLC) *	Yes	Yes
	Afucosylation (HILIC-HPLC) *	Yes	Yes

	Galactosylation (HILIC-HPLC)	Yes	Yes
	Sialylation (HILIC-HPLC) *	Yes	Yes
	Sialic acid content (NANA, NGNA *) (DMB-RP-UPLC)	Yes	Yes
Biological activity (Fab mediated)	Binding to sIL-6R (ELISA)	Yes	Yes
	Competitive inhibition of sIL-6R binding to IL-6 (ELISA)	Yes	Yes
	Binding kinetics to sIL-6R (SPR)	Yes	Yes
	Binding to membrane bound IL-6R (mIL-6R) (flow cytometry) *	Yes	Yes
	Inhibition of IL-6 mediated proliferation in TF-1 cells (TF-1 proliferation inhibition bioassay)	Yes	Yes
	Inhibition of IL-6 signaling (SEAP reporter gene assay)	Yes	Yes
	Inhibition of IL-6/sIL-6R induced VEGF release in HFLS-RA (cell-based ELISA)	Yes	Yes
	Inhibition of STAT3 phosphorylation (HTRF assay)	Yes	Yes
Biological activity (Fc mediated)	FcRn binding affinity (BLI)	Yes	Yes
	C1q binding affinity (BLI)	Yes	Yes
	FcγRI binding affinity (SPR)	Yes	Yes
	FcγRIIa (131H, 131R) binding affinity (BLI)	Yes	Yes
	FcγRIIb binding affinity (BLI)	Yes	Yes
	FcγRIIIa (158V, 158F) binding affinity (BLI)	Yes	Yes
	FcγRIIIb binding affinity (SPR)	Yes	Yes
	Lack of ADCC activity in TF-1 cells or HEK-Blue IL-6 cells (reporter gene assay, PBMC-based LDH cytotoxicity assay)	Yes	Yes
	Lack of CDC activity in TF-1 cells or HEK-Blue IL-6 cells (cytotoxicity assay)	Yes	Yes
General properties	Extinction coefficient (Edelhoch method)	Yes	Yes
	Subvisible particles (HIAC, FlowCam)	Yes	Yes
	Submicron particles radius (DLS)	Yes	Yes

	Protein concentration (UV absorbance)	Yes	Yes
Stability profiles	Accelerated (25°C)	Yes	Yes
	Freeze-thaw (up to 5 cycles)	Yes	Yes
	Thermal stress (40°C, 50°C)	Yes	Yes
	Light stress (4500 ± 500 Lux)	Yes	Yes
	Oxidative stress (H_2O_2 0.01%)	Yes	Yes
	Low and high pH (pH 3.0, pH 9.0)	Yes	Yes
	Mechanical stress (200 rpm agitation at 25°C)	Yes	Yes

*: See Section D.

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

The clinical development of BIIB800 included two clinical studies that compared BIIB800 to US-Actemra and EU-RoActemra:

- "Study BAT-1806-001-CR: A randomized, double-blinded, single-dose, 3-arm parallel, comparative study to evaluate the PK and safety of BAT1806 Injection versus Actemra in healthy Chinese male subjects"

  (BIIB800, US-Actemra, and EU-RoActemra were included in the study.)

- "Study BAT-1806-002-CR: A randomized, double-blind, parallel group, active-control study to compare the efficacy and safety of BAT1806 to RoActemra in RA patients with inadequate response to methotrexate"

  (Only BIIB800 and EU-RoActemra were included in the study.)

To support the relevance of the comparative clinical data (Study BAT-1806-002-CR) 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 (Study BAT-1806-001-CR). To support the establishment of the analytical component of the scientific bridge, the Applicant included comparison of BIIB800 to US-Actemra, BIIB800 to EU-RoActemra, and US-Actemra to EU-RoActemra. The same analytical methods used for supporting a demonstration that BIIB800 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 BIIB800, US-Actemra and EU-RoActemra were met for all attributes evaluated with the following exceptions:

Glycation (LC-MS)

Levels of glycation of BIIB800 lots (8.07 – 12.21%) were found to be higher than US-Actemra and EU-RoActemra (respectively 0.72 – 1.71% and 0.69 – 1.77%). 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, and the higher level would not have an adverse effect on safety and efficacy. The Applicant performed a forced glycation study and found the rates and trends of glycation similar for forced-glycated samples from all three of the products, and the forced-glycated samples showed that glycation profile does not impact Fab-mediated biological activity. Therefore, the difference observed in the glycation of BIIB800 does not preclude a demonstration that BIIB800 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

Glycosylation (HILIC-HPLC and DMB-RP-UPLC)

BIIB800 had slightly lower level of high mannose (0.6 – 0.81%) than US-Actemra (1.96 – 2.74%) and EU-RoActemra (1.92 – 2.69%), slightly lower level of afucosylation (1.58 – 2.18%) than US-Actemra (4.94 – 5.53%) and EU-RoActemra (4.72 – 5.47%), slightly higher galactosylation content (47.31 – 53.43%) but within the quality ranges of US-Actemra (40.27 – 48.64%) and EU-RoActemra (40.93 – 49.95%), slightly higher sialylation content (2.91 – 3.62%) than US-Actemra (2.04 – 2.69%) and EU-RoActemra (1.95 – 2.93%), and slightly higher NGNA content (0.0012 – 0.0029 mol/mol) than US-Actemra (0.0003 – 0.0005 mol/mol) and EU-RoActemra (0.0003 – 0.0005 mol/mol). Individual glycosylated species are classified as low criticality attributes except for high mannose. Considering primary mechanism of action of tocilizumab and its lack of ADCC or CDC activity, the small differences observed for the individual isoforms identified above are not expected to be clinically meaningful, and do not preclude a demonstration that BIIB800 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

Purity (monomer) and HMW species (SE-HPLC)

BIIB800 had slightly lower level of HMWS (0.38 – 0.52%) compared to US-Actemra (0.71 – 0.84%) and EU-RoActemra (0.45 – 0.87%), and slightly higher level of monomer (99.44 – 99.59%) compared to US-Actemra (99.07 – 99.23%) and EU-RoActemra (98.98 – 99.40%). This small difference would not be expected to have a biological impact on the tocilizumab products and do not preclude a demonstration that BIIB800 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

Charge profile (IEC-HPLC with or without CpB)

BIIB800 had slightly higher main peak (64.40 – 71.88%) compared to US-Actemra (65.44 – 69.66%) and EU-RoActemra (63.91 - 70.22%), and slightly lower level of basic peaks (3.44 – 9.47%) compared to US-Actemra (6.48 – 11.19%) and EU-RoActemra (5.77 - 10.42%). After treated with CpB, BIIB800 had slightly lower level of basic peaks (2.64 - 8.20%) compared to US-Actemra (4.47 - 6.77%) and EU-RoActemra (3.77 - 6.37%). The minor differences observed in charge profiles are due to different levels of C-terminal lysine and C-terminal proline amidation, both are considered low criticality attributes. Therefore, the small differences would not be expected to have a biological impact on the tocilizumab products and do not preclude a demonstration that BIIB800 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

Hydrophobic interaction profile (HIC-HPLC and RP-UPLC)

Minor differences in the hydrophobic interaction profile by orthogonal methods HIC-HPLC and RP-UPLC were found between BIIB800 and US-Actemra and EU-RoActemra. Specifically, BIIB800 had a lower level of post-peaks (2.16 – 2.94%) compared to US-Actemra (2.81 – 3.02%) and EU-RoActemra (2.83 – 2.94%) by HIC-HPLC. The Applicant attributed the lower levels of post-peaks in BIIB800 to lower levels of HMWS based on the structure-activity analysis studies. Therefore, the small differences would not be expected to have a biological impact on the tocilizumab products and do not preclude a demonstration that BIIB800 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

Binding to mIL-6R (flow cytometry)

BIIB800 showed a lower relative mIL-6R binding affinity (94 – 114%) compared to US-Actemra (118 – 124%) and EU-RoActemra (97 – 137%), possibly due to method variability and limited number of lots used in the study (n = 3 for each product). Binding to mIL-6R is considered a low criticality attribute, as the sIL-6R (same binding epitope) binding assay and cell-based TF-1 proliferation inhibition bioassay (mediated by mIL-6R) can be used as surrogate assays for mIL-6R binding affinity. Therefore, the observed difference would not be expected to have a biological impact on the

tocilizumab products and do not preclude a demonstration that BIIB800 is highly similar to US-Actemra or the establishment of the analytical component of the scientific bridge.

E. Same Strength

BIIB800 has the same strengths and dosage forms (80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL in vials) for the IV route of administration as US-Actemra. Comparative protein 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 protein concentration data and manufacturing data, the 20 mg/mL BIIB800 in 80 mg/4 mL, 200 mg/10 mL and 400 mg/20 mL vials 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 BIIB800 vials is the same as that of US-Actemra.

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/s/

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09/12/2023 11:29:27 AM

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