CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761371Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date:

1. Application/Product Information

BLA number	761371
Submission Type	Original Submission
Regulatory Pathway	NME 351(a)
Associated IND/BLA	IND 100593, BLA 761053, BLA 761064, BLA 761106
Review Designation	Standard Review
Applicant	Genentech, Inc.
Indication	Multiple Sclerosis
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Ocrevus Zunovo
	Non-proprietary Name/Code Name ocrelizumab and hyaluronidase-ocsq
	OBP Naming COMBINATION: MAB HUMANIZED (IGG1) ANTI P11836 (CD20_HUMAN) [OCREVUS] AND RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]
Drug Product Description	Sterile, preservative-free, clear to slightly opalescent, colorless to pale brown solution supplied in a 50 mL single-dose vial. Each single dose vial contains 920 mg (40 mg/mL) ocrelizumab, 23,000 U (1,000 U/mL) rHuPH20, (b) (4) mg (b) (4) trehalose dihydrate, 5.5 mg glacial acetic acid, 34.3 mg (b) (4) methionine, 13.8 mg polysorbate 20, (b) (4) mg sodium acetate (b) (4), and water for injection (WFI) at pH 5.3.

	Ocrelizumab is a therapeutic recombinant humanized IgG1 monoclonal antibody. Vorhyaluronidase alfa, or rHuPH-20, is a recombinant, single chain, human enzyme protein.		
Dosage Form	Liquid		
Strength	920 mg/23 mL ocrelizumab and 23,000 U/23 mL rHuPH20		
Route of Administration	Subcutaneous		
Primary Container Closure System	Single dose vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance Drug product Immunogenicity Assay	Milos Dokmanovic	Andrea George
	ETT	Daniel Willett Scott Krull	Riley Myers
	Facility	Esther (Chani) Broner	Zhong Li
	Microbiology DS	Esther (Chani) Broner	Maxwell Van Tassell
	Microbiology DP	Jeanne Fringer	Maxwell Van Tassell

	RBPM	Musse Olani
	ATL	Andrea George/ Riley Myers
OPQ Issued Consults	N/A	

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761371 for Ocrevus Zunovo manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Ocrevus Zunovo is well-controlled and leads to a product that is pure and potent. 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:**
  Ocrelizumab- Genentech, Inc., 1000 New Horizons Way, Vacaville, CA 95688 (FEI: 3002902534); Roche Singapore Technical Operations (RSTO), Pte. Ltd., 10 Tuas Bay Link Road, Building 10, Singapore 637934 (FEI: 3007164129)
  rHuPH20- (b) (4) (b) (4)
- **Drug Product:** Roche Diagnostics GmbH, Sandhofer Strasse 116, Mannheim, Germany 68305 (FEI: 3002806559)

b. Fill size and dosage form:
Single dose vial supplied as a 920 mg/23 mL solution.

c. Dating Period:

- **Drug Product:** 24 months at 5 ± 3°C, protected from light
- **Drug Substance:**
  Ocrelizumab- (b) (4) months at (b) (4)
  rHuPH20- (b) (4) months at (b) (4)
- **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 product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: Ocrevus Zunovo is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps:

- Perform real-time ocrelizumab SC drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at regular intervals through the end of shelf life. The final results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

4. Basis for Recommendation

a. Summary:

Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) is a combination product composed of ocrelizumab, a recombinant humanized IgG1 antibody, and rHuPH20, recombinant human vorhyaluronidase alfa, developed for subcutaneous administration for treatment of multiple sclerosis (MS). Ocrelizumab and hyaluronidase-ocsq is manufactured using the same drug substance as ocrelizumab I.V. (Ocrevus).

Ocrelizumab is a humanized IgG1 monoclonal antibody directed against CD20 found on the surface of B cells. CD20 expressing B cells are thought to contribute to multiple sclerosis (MS) pathogenesis by presenting auto-antigens and co-stimulatory signals to activate T cells, secrete pro-inflammatory cytokines, potentially produce autoantibodies that activate macrophage and NK cells, and create meningeal lymphoid structures leading to inflammation and neuronal loss in the cortex.

Recombinant human hyaluronidase (rHuPH20, vorhyaluronidase alfa) is a glycosylated single chain protein enzyme that depolymerizes hyaluronan in interstitial tissue at the injection site, allowing for an increase in the volume of liquid drug product that be injected subcutaneously and facilitating drug entry into circulation.

Ocrelizumab DS is manufactured at Genentech, Inc. in Vacaville, CA, or at RSTO Singapore. (b) (4)

(b) (4)

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The overall ocrelizumab SC 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 ocrelizumab SC are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

Three ocrelizumab SC quality attributes are controlled by two emerging technologies. Raman Spectroscopy is utilized to determine the identity of drug product (b) (4) Multi-Attribute Raman Spectroscopy is utilized (b) (4)

The BLA is recommended for approval from product quality, facility, microbiology, and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with PMCs/PMRs**
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 ocrelizumab SC (i.e., there is no specific test method described in regulation for ocrelizumab SC that establishes an official standard of potency). We next considered whether potency is a factor for ocrelizumab SC 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 Ocrevus Zunovo for purposes of § 610.61(r)

because lot variability is not a concern for Ocrevus Zunovo as Ocrevus Zunovo'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: Refer to BLA 761053 for approved ocrelizumab DS and BLA 761064 for approved rHuPH20 DS

   c. Drug Product:
      i. Protocols approved: Annual stability protocol and stability protocol for the extension on DP shelf-life
      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.

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/

ANDREA L GEORGE
08/19/2024 10:47:50 AM

RILEY C MYERS
08/19/2024 10:54:13 AM

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	September 4, 2024
Assessor:	Liming Lu, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Milos Dokmanovic, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIII
Application:	BLA 761371
Applicant:	Genentech, Inc.
Submission Date:	November 13, 2023
Product:	Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq)
Dosage form(s):	Injection
Strength and Container-Closure:	920 mg ocrelizumab and 23000 units hyaluronidase per 23 mL (40 mg and 1000 units per mL) solution in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for a new product containing ocrelizumab and recombinant human hyaluronidase (rHuPH20) for subcutaneous injection for the same indication that Ocrevus (intravenous ocrelizumab) has been approved for.
Recommendations:	The prescribing information, medication guide, 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 (submitted on September 3, 2024), medication guide (submitted on September 3, 2024), container labels (submitted on August 19, 2024), and carton labeling (submitted on September 3, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on November 13, 2023)
  \\CDSESUB1\EVSPROD\bla761371\0001\m1\us\draft-labeling-text.docx
- Container Labels (submitted on November 13, 2023)
  \\CDSESUB1\EVSPROD\bla761371\0001\m1\us\11006725-920mg-vial-label.pdf

(b) (4)

- Carton Labeling (submitted on November 13, 2023)
  Carton US
  \\CDSESUB1\EVSPROD\bla761371\0001\m1\us\11006726-920mg-carton-coo-us.pdf

(b) (4)

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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), 21 CFR 600.3(k)	✓ 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 (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 label is small and could be considered a partial label. Thus, the manufacturer name without address is acceptable per 21 CFR 201.10(h)(2)(i)(1).

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

[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."

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

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

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

Comment/Recommendation: The container is enclosed in a package.

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

Comment/Recommendation: The product contains a container label.

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 has confirmed that there is no text on the ferrule and cap overseal of the vials.

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

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.

The applicant has confirmed that there is sufficient area of the container to allow for visual inspection. The viewing window between the two ends of the vial labels is approximately 3.5 mm (0.14 in). See the photo of a representative vial label affixed to a representative vial in the figure below:

(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: *The applicant has revised the ROA statement to read: "For subcutaneous injection over 10 minutes." as recommended by DMEPA.*

***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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

No misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label does not display text in Spanish.

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

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

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

Comment/Recommendation: Recommend adding the net quantity "23 mL" to the container label per 21 CFR 201.51. Ensure the net quantity appears on the PDP less prominent and away from the strength.

The applicant prefers to omit the net quantity as a standalone statement from the vial label because of space constraints. Adding it would require the font size of the surrounding text to be decreased, which in turn would impact legibility. Additionally, the net quantity of 23 mL is captured in the horizontal strength color bar, which makes it recognizable and easily distinguishable. OPQA III Labeling considers this is acceptable in consideration of the vial label space.

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

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

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

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

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

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), 21 CFR 600.3(k)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The applicant may include the Country of Origin per U.S. Customs Border and Protection regulation 19 CFR 134.11. The labeling should appear as Product of Country of Origin. Recommend revising the Country of Origin statement on the carton Singapore to read as: Product of Singapore.

The applicant has revised as requested.

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

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

[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.

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Consider adding the alternative storage conditions as follows:

Storage:

Store Ocrevus Zunovo vials **refrigerated at** 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake. Unopened Ocrevus Zunovo vials may be stored for up to 12 hours without refrigeration at a temperature up to 25°C (77°F).

To be consistent with the Prescribing Information, the applicant has revised the storage temperature/requirements on the carton to read: "Unopened Ocrevus Zunovo vials may be stored in the original carton for a cumulative time of up to 12 hours without refrigeration at a temperature up to 25°C (77°F).", which is acceptable from OPQA III labeling perspective.

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: DMEPA has recommended the following to the applicant for ROA:
The administration statement on the carton does not include the specific injection site and can be reworded for clarity. Failure to provide clarity on administration may cause administration errors. We recommend revising the statements, "(b) (4) " to read "For subcutaneous injection in the abdomen over approximately 10 minutes".

The applicant has 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

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

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

Comment/Recommendation: 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 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, trehalose, methionine, and sodium acetate.

Revise the ingredient information to the compendial names and definitions. Inactive ingredient amounts were calculated per the USP monograph definition for trehalose and sodium acetate. For example, the trehalose USP/NF monograph recognizes both trehalose dihydrate and trehalose anhydrous. However, the amount of trehalose is to be "calculated on the anhydrous basis" per the monograph DEFINITION. In other words, the approved labeling should use the inactive ingredient established name, trehalose, and the amount is expressed in terms of equivalent amount of trehalose anhydrous. Please confirm the calculated amount of trehalose from (b) (4) trehalose dihydrate per the monograph definition. Re-submit an updated Description and Composition Table in section 3.2.P.1 adding a footnote to the table that includes the calculation between mg of trehalose and mg of (b) (4) trehalose dihydrate. The footnote should serve as a link between the names and quantities presented in section 3.2.P>1 to the names and quantities presented in the Prescribing Information and carton labeling. Ensure that all inactive ingredients with a USP monograph are provided as such.

We revised the inactive ingredients in alphabetical order (see *USP General Chapters <1091> Labeling of Inactive Ingredients*).
The inactive ingredients list on the carton should read as follows:
"Each 23 mL single-dose vial contains 920 mg of ocrelizumab, 23,000 units of hyaluronidase (human recombinant), glacial acetic acid (5.5 mg), methionine (34.3 mg), polysorbate 20 (13.8 mg), sodium acetate (30.2 mg), trehalose (1889.15 mg), and water for injection at pH 5.3."

The applicant has revised the inactive ingredients list as recommended. To note, the applicant has confirmed the amount of trehalose is "1889.5 mg", we have confirmed with Product Quality Assessor and considered it is acceptable.

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: Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable.

The applicant has revised as requested.
Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with Product Quality Assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for **ocrelizumab and hyaluronidase** products (i.e., there is no specific test method described in regulation for **ocrelizumab and hyaluronidase** products that establishes an official standard of potency) and 2) Product Quality Assessors have determined that potency is not a factor within the meaning of § 610.61(r) for **Ocrevus Zunovo** because lot variability is not a concern as the manufacturing

process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

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

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

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

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

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

No misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label does not display text in Spanish.

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

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

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

Comment/Recommendation: The drug product does not contain phenylalanine.

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

Comment/Recommendation: The drug product does not contain sulfites.

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

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

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

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv) *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: *We previously revised to the required parenteral verbatim statement per 21 CFR 201.57(c)(3)(iv) in section 2. However, OND labeling disagreed and have discussed this with DMEPA. They adapt a modified version of the regulatory parenteral*

dosing statement proposed by the applicant to reflect active voice. We defer to the division for the final decision of using modified language.

(b) (4)

We revised to include the higher end of room temperature range (at or below 25°C) for clarity based on the submitted data. Please confirm.

(b) (4)

The applicant has revised as requested.

Revise the needle gauge information (e.g., "24G-25G") in the label as "26G needle" is not included in the current submitted data for evaluation.

(b) (4)

The applicant provided rationale to retain "26G needle" in the label of USPI that 26G needle with a smaller inner diameter should provide additional comfort for the patient without impacting the administration of the drug product and patient safety. When using the 26G needle, the flow rate would b (b) (4) mL/min over the 10-minute injection with a backpressure of (b) (4) si (empirically determined with the 26G injection needle) and compatible with common syringe pumps in the market. In addition, no product quality impact was observed at a flow rate of 1 mL/min to 16 mL/min (refer to P.2.6 Compatibility - Physicochemical Stability). Subcutaneous infusion sets with 26G injection needle are suitable for the administration of Ocrevus Zunovo, and the Applicant has implemented the use of subcutaneous infusion sets with 26G needle in the OCARINA II clinical trial. CMC team has concurred with the applicant's justification to include the "26G needle" in the label.

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

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to the USAN adopted name for "hyaluronidase (human recombinant)" in section 11 when discussing drug substance hyaluronidase and in the ingredients statement.

Revised to have the sterile statement before preservative-free.

We recommend removing (b) (4) (b) (4) (b) (4).

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 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, trehalose, methionine, and sodium acetate.
Revise the ingredient information to the compendial names and definitions. Inactive ingredient amounts were calculated per the USP monograph definition for trehalose and sodium acetate.

We also revised the inactive ingredients in alphabetical order (see *USP General Chapters <1091> Labeling of Inactive Ingredients*).

The applicant has 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: Revised the last paragraph describing the alternative room temperature storage for readability.

(b) (4)

The applicant has revised it with modification to clarify the time can be spread out over multiple instances of removal from the refrigerator.

(b) (4)

OPQA III labeling has no objections for the proposed modification. However, we recommended the applicant revise accordingly to the carton labeling for consistency as well. The applicant has resubmitted cartons with recommended revisions.

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: Revised the active ingredient to the proper name with 4-letter suffix.

(b) (4)

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients), the established names for inactive ingredients in your products are revised according to the USP/NF monographs titles.
Also, inactive ingredients names have been revised to appear in alphabetical order per *USP General Chapters <1091> Labeling of Inactive Ingredients*.

The applicant has 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

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on September 3, 2024)
  \\CDSESUB1\EVSPROD\bla761371\0028\m1\us\ocr-zun-uspi.docx
- Medication Guide (submitted on September 3, 2024)
  \\CDSESUB1\EVSPROD\bla761371\0028\m1\us\ocr-zun-mg.docx
- Container Labels (submitted on August 19, 2024)

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

Liming Lu

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Milos Dokmanovic

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