CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761152Orig1s000

PRODUCT QUALITY REVIEWS

LABELS AND LABELING ASSESSMENT

Date of Assessment:	December 22, 2025
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Tamanna Azam, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIV
Application:	BLA 761152
Applicant:	Omeros Corporation
Submission Date:	March 26, 2025
Product:	Yartemlea (narsoplimab-wuug)
Dosage form(s):	Injection
Strength and Container-Closure:	370 mg/2 mL (185 mg/mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the treatment of hematopoietic stem cell transplant associated thrombotic microangiopathy. This is a resubmission after complete response letter dated October 15, 2021.
Recommendations:	The prescribing information (submitted on December 22, 2025), container labels (submitted on September 2, 2025), and carton labeling (submitted on October 31, 2025) were assessed and found to be acceptable (see Appendix C) 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 December 22, 2025), container labels (submitted on September 2, 2025), and carton labeling (submitted on October 31, 2025) 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 26, 2025
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Container Labels (submitted on August 16, 2021)

(b) (4)

[redacted]

1 Page(s) of Draft Labeling has 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(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(i), 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: Historical practice has been to include the U.S license number with the manufacturer's information, even for container capable of only bearing a partial label. Add a placeholder for the "US License No. XXXX". For space considerations, you may replace the City, State, and zip code with the US license number placeholder.
The Applicant revised as requested

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(i)	✓ 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, 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

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. *Applicant's response: Omeros confirms there is no text on the ferrule or cap overseal of the vial.*

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. *Applicant's response: There is sufficient uncovered area along the full length of the vial to allow for visual inspection when the label is affixed. The inspection area is indicated in Figure 1. The label measures 47 mm in length, and the vial diameter is 50.3 mm, leaving 3.3 mm (0.33 cm) uncovered. Text on the vial label is for illustration only.*

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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

***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

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) 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

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

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100, 21 CFR299.4, 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

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

[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.

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

Comment/Recommendation: Ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name with prominence commensurate with the prominence with the proprietary name, considering all pertinent factors, including typography, layout, contrast, and other printing features.
Applicant revised as requested

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: Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

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

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

Comment/Recommendation: Consider relocating "No preservatives" to appear on the side panel after the ingredient information. *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: 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

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

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, 21 CFR 299.4, 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: FDA approved labeling is required to use the established names for drugs (i.e., drug products and ingredients) per 21 CFR 299.4. Revise the ingredient information to the compendial names and definitions. Ensure that the established names for inactive ingredients in your product are the USP/NF monographs titles: arginine hydrochloride, citric acid monohydrate, polysorbate 80, and sodium citrate.

(b) (4)

(b) (4) Submit an updated composition statement and the corresponding statement of ingredients.

Revise the contents (ingredient information) to revise the compendial names and amounts to read as follows: Each 2 mL vial contains 370 mg of narsoplimab-wuug, and arginine

hydrochloride (84.3 mg), citric acid monohydrate (1.42 mg), polysorbate 80 (0.2 mg), sodium citrate (8.6 mg), and Water for Injection, USP. Sodium hydroxide and hydrochloric acid added to adjust the pH. The pH is 5.8. *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: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for narsoplimab products (i.e., there is no specific test method described in regulation for narsoplimab 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 Yartemlea 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.

(b) (4) (b) (4)

(b) (4) 21 CFR 610.61(r) is not applicable. (b) (4)

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)	✓ Yes ☐ No ☐ N/A

USP chapter <659> Packaging and Storage Requirements	

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

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

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).*	☐ 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

Comment/Recommendation: Revised to the customary language for the route of administration in the product title, 'for intravenous use', because 21 CFR 201.57(a)(2) does not specify methods of administration as an element of the product title. *Applicant revised as requested*

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

Comment/Recommendation: Revised for consistent presentation of the dosage form for FDA approved labeling. *Applicant revised as requested*

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: Add the room temperature storage condition.
Applicant added 18 °C to 25 °C (64 °F to 77 °F)

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: Revised for consistent presentation of the dosage form for FDA approved labeling. *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), 21, CFR 299.4, 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: Added the pharmacological class. *The Applicant revised to "mannan-binding lectin-associated serine protease 2 (MASP-2)".*
Added the description of the monoclonal antibody. Added the cell line. Confirm. *Applicant revised as requested.*
Added the molecular weight. Confirm. *Applicant revised as requested.*
Added the dosage form. *Applicant revised as requested.*
Revised to the appropriate package type term. *Applicant revised as requested.*

FDA approved labeling is required to use the established names for drugs (i.e., drug products and ingredients) per 21 CFR 299.4. Revise the ingredient information to the compendial names and definitions. Ensure that the established names for inactive ingredients in your product are the USP/NF monographs titles: arginine hydrochloride, citric acid monohydrate, polysorbate 80, and sodium citrate.

(b) (4)

(b) (4)

(b) (4) Submit an updated composition statement and the corresponding statement of ingredients.

Revise the contents (ingredient information) to revise the compendial names and amounts to read as follows: Each 2 mL vial contains 370 mg of narsoplimab-wuug, and arginine hydrochloride (84.3 mg), citric acid monohydrate (1.42 mg), polysorbate 80 (0.2 mg), sodium citrate (8.6 mg), and Water for Injection, USP. Sodium hydroxide and hydrochloric acid added to adjust the pH. The pH is 5.8. *Applicant revised similarly 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: Added the dosage form. Added the identifying characteristics of the dosage form. Revised to the appropriate package type term. *Applicant revised as requested.*

(b) (4)

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

Comment/Recommendation: Include the licensed applicant name address and placeholder for US license number. *Applicant revised as requested.*

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 December 22, 2025
\\CDSESUB1\EVSPROD\bla761152\0126\m1\us\114-labeling\draft\labeling\draft-labeling-text-word.docx)

Container Labels (submitted on September 2, 2025)

(b) (4)

[redacted]

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

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 12/23/2025 09:12:46AM
GUID: 50814c7000007a3d59329f660d8ddf02

Tamanna Azam

Digitally signed by Tamanna Azam
Date: 12/29/2025 07:29:05AM
GUID: 63e54376007c186cc3cdb451cfbdc92a

BLA Executive Summary
Assessment Date: 11/26/2025

1. Application/Product Information

BLA number	761152
Submission Type	Resubmission
Regulatory Pathway	NME 351(a)
Associated IND/BLA	IND 120524
Review Designation	Class 2 resubmission
Applicant	Omeros Corporation
Indication	Hematopoietic stem cell transplant-associated thrombotic microangiopathy
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Yartemlea
	Non-proprietary Name/Code Name Narsoplimab-wuug/OMS721
	OBP Naming MAB HUMAN (IGG4) ANTI O00187 (MASP2_HUMAN) [OMS721]
Drug Product Description	Yartemlea drug product (DP) is provided as a sterile, preservative-free, clear to slightly opalescent, colorless to yellow/brown solution in single-dose vials for intravenous use. Yartemlea DP is supplied in a (b) (4) (b) (4) glass (b) (4) vial containing a volume of 2 mL solution. YARTEMLEA DP is formulated in citric acid monohydrate (1.42 mg), sodium citrate (b) (4) (b) (4), L-arginine HCl (84.3 mg), and Water for injection, at approximate pH of 5.8.

	Narsoplimab-wuug is a recombinant human monoclonal antibody of the IgG4 subclass.		
Dosage Form	Solution		
Strength	370 mg/2 mL		
Route of Administration	Intravenous administration		
Primary Container Closure System	Single dose (b) (4) glass vials		
Device Information	NA		
Co-packaged Product Information	NA		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Tamanna Azam	Phillip Angart and Yan Wang
	Drug product		
	Immunogenicity Assay		
	Facility	Jiangsong Jiang	Virginia Carroll
	Microbiology		
	RBPM	Kelly Ballard	
	ATL	Phillip Angart and Yan Wang	
OPQ Issued Consults	NA		

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

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761152 for Yartemlea manufactured by Omeros Corporation. The data submitted

in this application are adequate to support the conclusion that the manufacture of Yartemlea is well-controlled and leads to a product that is pure, safe 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: Lonza Biologics Tuas Pte. Ltd., Singapore, Singapore (FEI: 3009725845)
      - Drug Product: Vetter Pharma-Fertigung GmbH & Co. KG, Langenargen, Germany (FEI: 3002808846) for manufacture and filling; (b) (4) (b) (4) for packaging and labeling
   b. Fill size and dosage form: 370 mg/2 mL solution
   c. Dating Period:
      - Drug Product: 48 months at 2 °C to 8 °C
      - Drug Substance: (b) (4) months at (b) (4)
      - Intermediate Substance, if applicable: NA
      - For packaged products: NA
      - 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 protocol 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: Yartemlea 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. Conduct a worst-case in-use stability study to evaluate the suitability of preparation and administration conditions for narsoplimab under clinically relevant conditions. The study should assess product stability under stressed conditions including but not limited to extended light exposure as mechanical stress from mixing as well as worst-case dilutions and

volumes. All incompatibilities should be investigated to inform the labeling. Propose revisions to the labeling as appropriate.

Final Report Submission Date: October 2026

2. Perform a reproducibility evaluation for size exclusion chromatography (SEC), cation exchange chromatography (CEX), and capillary electrophoresis (CE-SDS) reduced and nonreduced with appropriate stressed stability samples to support Vetter as a quality control testing site for narsoplimab stability samples.

   Final Report Submission Date: October 2026

3. Establish an appropriately justified drug product stability specification for (b) (4) based on levels observed in clinical and commercial batches.

   Final Report Submission Date: March 2026

4. Complete the pending real-word shipping study for drug product transportation from the drug product manufacturing site to the drug product packaging and labeling facility. Perform an additional real-world shipping study for drug product transportation from the drug product packaging and labeling facility to distribution centers and/or storage warehouses. This study will be performed using representative commercial drug product lots under commercial shipping conditions and will include a total of three shipments, and the evaluation will include assessments for shipping temperature, integrity of the vials and/or packaging/labeling as well as product quality attributes from samples collected prior to and after shipment.

   Final Report Submission Date: December 2026

5. Conduct narsoplimab container closure integrity test (CCIT) validation with the (b) (4) container closure system used for the narsoplimab drug product, including assessments of sensitivity, intermediate precision, and robustness.

   Final Report Submission Date: January 2026

4. Basis for Recommendation
   a. Summary:

Yartemlea received orphan drug designation, breakthrough therapy designation, and priority review status for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA) in the initial BLA submission. HSCT-TMA is a well-recognized, multisystem, often fatal complication of HSCT. Mortality in severe cases can exceed 90%. Hematopoietic stem cell transplantation induces substantial endothelial injury. TMA appears to be one manifestation of endothelial cell injury associated with HSCT. Endothelial injury also activates the lectin pathway of complement on the endothelial cell surface. Subsequent complement-mediated activities are thought to amplify endothelial injury and dysfunction, causing or worsening clinical conditions. There are no approved therapeutics for the treatment of HSCT-TMA and this indication presents a serious unmet medical need. Narsoplimab-wuug, a human immunoglobulin gamma 4 (IgG4) monoclonal antibody, is directly against mannan-binding lectin-associated serine protease-2 (MASP-2). MASP-2 is the key effector enzyme in the lectin pathway of complement. Inhibition of MASP-2 and the lectin pathway is expected to mitigate TMA, the potentially fatal complication of HSCT.

Narsoplimab-wuug drug substance (DS) is manufactured using CHO (b) (4) cell line (b) (4)

Narsoplimab-wuug DP process includes (b) (4) (b) (4) aseptic filling, (b) (4) and storage at 2-8°C.

The overall control strategy includes control of raw materials, facilities, and equipment, manufacturing process, and adventitious agents. The conditions used in manufacturing have been sufficiently validated, and the data submitted in this application support the conclusion that the manufacture of narsoplimab-wuug is well controlled and yields a consistently high-quality product.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for

approval from a sterility assurance and microbiology product quality perspective. The facility assessors are also recommending approval of the commercial manufacture of narsoplimab-wuug DS at Lonza Biologics Tuas Pte. Ltd., Singapore, Singapore (FEI: 3009725845) and the DP at Vetter Pharma Fertigung GmbH & Co. KG, Langenargen, Germany (FEI: 3002808846).

The OPQAIII assessments (i.e., DS quality, DP quality, and validation of immunogenicity assays) and OPMA assessments (i.e., DS and DP microbiological as well as facility technical assessments) for both initial BLA submission and resubmission are located as separate documents in Panorama.

b. Subdiscipline Recommendation:

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

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

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

   b. Drug Substance:
      i. Protocols approved:

(b) (4)

(b) (4)

[redacted]

ii. Residual risk: NA
iii. Future inspection points to consider: NA

c. Drug Product:
   i. Protocols approved:
      - Stability protocol for the extension of drug product shelf life
      - Annual post-approval stability protocol
   ii. Residual risk: NA
   iii. Future inspection points to consider: NA

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/

YAN WANG
11/26/2025 08:22:57 AM

First Approval for Indication/Expedited or Breakthrough Assessment: Yes

Recommendation:
BLA: Complete Response

BLA Number: 761152
Assessment Number: 01
Assessment Date: 08/23/2021

Drug Name/Dosage Form	YARTEMLEA- narsoplimab-wuug, OMS721/Injection
Strength/Potency	370 mg/2 mL (185 mg/mL) solution in a (b) (4) glass (b) (4) vial
Route of Administration	Intravenous (IV) administration
Rx/OTC dispensed	Rx
Indication	Hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA)
Applicant/Sponsor	Omeros Corporation
US agent, if applicable	n/a

Product Overview:

YARTEMLEA (narsoplimab-wuug) is a recombinant human monoclonal antibody of the IgG4 subclass. Narsoplimab-wuug specifically binds to human mannan-binding lectin-associated serine protease-2 (MASP-2), the key effector enzyme in the lectin pathway of complement. Thrombotic microangiopathy (TMA) appears to be one manifestation of endothelial cell injury associated with hematopoietic stem cell transplant (HSCT). Lectin pathway activation plays a critical role in the innate immune response to endothelial cell injury that can result from HSCT. Narsoplimab-wuug is expected to inhibit MASP-2 and the lectin pathway to mitigate this potentially fatal complication of HSCT-TMA. Narsoplimab-wuug drug substance (DS) is manufactured using Chinese hamster ovary (CHO) cell culture (b) (4) (b) (4) YARTEMLEA (narsoplimab-wuug) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to yellow/brown solution for intravenous (IV) administration. YARTEMLEA drug product (DP) is supplied in a (b) (4) glass (b) (4) vial containing a volume of 2 mL solution. YARTEMLEA DP is formulated in citric acid monohydrate (1.42 mg), sodium citrate (b) (4), L-arginine HCl (84.3 mg), and Water for injection, at approximate pH of 5.8.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Chen Sun	OPQ/OBP/DBRR II
Drug Product		
Immunogenicity	Bruce Huang	OPQ/OBP/DBRR II
Labeling	Koung Lee	OPQ/OBP
DS Microbiology and Facility	Zhao (Joe) Wang	OPQ/OPMA/DBM
DP Microbiology and Facility	Maria MartinManso	OPQ/OPMA/DBM
Facility Team Lead	Zhong Li	OPQ/OPMA/DBM
Microbiology Team Lead	Candace Gomez-Broughton	OPQ/OPMA/DBM
Regulatory Business Project Manager	Kelly Ballard	OPQ/OPRP/DRBPMI/RBPMB I
Application Team Lead	Yanming An	OPQ/OBP/DBRR II
OBP Review Chief	Xianghong Jing	OPQ/OBP/DBRR II

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Courtney Hamilton	ORO/DROCHEN
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Carrie Diamond	OND/OCHEN/DNH
Pharmacology/Toxicology	Pedro DelValle, Bo Lee, Geeta Negi/Todd Bourcier (TL)	OND/OCHEN/DPTCHEN
Clinical Pharmacology	LaiMing Lee/Sudharshan Hariharan (TL)	OTS/OCP/DCEP
Statistics	Sarabdeep Singh/Yeh Fong Chen (TL)	OTS/OB/DBIX

1. Names:

a. Proprietary Name: YARTEMLEA
b. Trade Name: YARTEMLEA
c. Non-Proprietary Name/USAN: narsoplimab-wuug
d. CAS Name: 2108782-45-0
e. Common Name: OMS721
f. INN Name: narsoplimab
g. OBP systematic name: MAB HUMAN (IGG4) ANTI O00187 (MASP2_HUMAN) [OMS721]

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 761152/0002	04/29/2020
STN 761152/0003	08/05/2020
STN 761152/0004	09/29/2020
STN 761152/0005 (response to IR#1 OPMA)	10/16/2020
STN 761152/0006 (response to IR#2 OPMA)	10/26/2020
STN 761152/0008 (response to IR#3 OBP)	12/04/2020
STN 761152/0009 (response to IR#4 OPMA)	12/23/2020
STN 761152/0010 (response to IR#5 OPMA)	12/31/2020
STN 761152/0013 (response to IR#6 OPMA)	01/13/2021
STN 761152/0015 (response to IR#7 OBP)	02/05/2021
STN 761152/0022 (response to IR#8 OBP)	03/31/2021
STN 761152/0027 (response to IR#9 OBP)	04/19/2021
STN 761152/0029 (response to IR#10 OBP)	04/27/2021
STN 761152/0030 (responses to IR#11 & 12 OBP)	04/28/2021
STN 761152/0031 (response to IR#10 OBP)	04/30/2021
STN 761152/0034 (response to IR#13 OPMA)	05/06/2021
STN 761152/0035 (response to IR#14 &15 OBP)	05/07/2021
STN 761152/0037 (response to IR#16 OBP)	05/17/2021
STN 761152/0040 (response to IR#17 & 18 OPMA)	05/27/2021
STN 761152/0041 (response to IR#16 OBP)	06/07/2021
STN 761152/0042 (response to IR#10 OBP)	06/28/2021
STN 761152/0046 (response to IR#19 OPMA)	07/21/2021
STN 761152/0049 (response to IR#20 OBP& #21 OPMA)	07/29/2021
STN 761152/0055 (response to IR#21 OPMA)	08/20/2021

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed
(b) (4)	V	(b) (4)		2	Adequate	N/A
	III					
	III			2	Adequate	N/A

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	120524	Omeros Corp.-sponsored IND under which OMS721 was developed and meetings were held

3. Consults: None.

4. Environmental Assessment of Claim of Categorical Exclusion:

   Omeros claims a categorical exclusion from the requirements of environmental assessment for narsoplimab under the provisions of 21 CFR 25.31(b and c). Narsoplimab is manufactured outside of the US, and when exposed to the environment, is not expected to significantly alter the concentration or distribution of the substance or degradation products in the US environment. Categorical Exclusion is appropriate for this product and the claim is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

This application will not be approved during this assessment cycle due to clinical only deficiencies. From a product quality perspective, the Office of Product Quality (OPQ), CDER, does not note any product quality deficiencies that would preclude approval of STN BLA 761152 for YARTEMLEA manufactured by Omeros Corp. Because the application will not be approved in this cycle, the non-complete response issues related to product quality listed below will be communicated to the sponsor in the FDA Complete Response (CR) letter. If manufacturing changes are made before the sponsor submits their responses to the CR deficiencies, additional assessment may be needed during the next assessment cycle.

B. Summary of Non-Complete Response Issues:

1. Provide low endotoxin recovery (LER) hold time study summary report and data from two additional lots of narsoplimab drug product.
2. Submit the container closure integrity test (CCIT) method validation study summary report and data. The CCIT method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (*i.e.,* less than or equal to 20 µm) and note that a more sensitive and consistent method for dye detection (*e.g.,* spectrophotometry) is recommended. Perform annual sterility test in lieu of CCIT in the stability program until the CCIT method validation is complete.

C. Benefit/Risk Considerations:

YARTEMLEA received orphan drug designation, breakthrough therapy designation, and priority review status for the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA). HSCT-TMA is a well-recognized, multisystem, often fatal complication of HSCT. Mortality in severe cases can exceed 90%. Hematopoietic stem cell transplantation induces substantial endothelial injury. TMA appears to be one manifestation of endothelial cell injury associated with HSCT. Endothelial injury also activates the lectin pathway of complement on the endothelial cell surface. Subsequent complement-mediated activities are thought to amplify endothelial injury and dysfunction, causing or worsening clinical conditions. There are no approved therapeutics for the treatment of HSCT-TMA and this indication presents a serious unmet medical need. Narsoplimab, a human immunoglobulin gamma 4 (IgG4) monoclonal antibody, is directly against mannan-binding lectin-associated serine protease-2 (MASP-2). MASP-2 is the key effector enzyme in the lectin pathway of complement. Inhibition of MASP-2 and the lectin pathway is expected to mitigate TMA, the potentially fatal complication of HSCT.

The overall control strategy includes control of raw materials, facilities, and equipment, manufacturing process, and adventitious agents. The conditions used in manufacturing have been sufficiently validated, and the data submitted in this application support the conclusion that the manufacture of narsoplimab is well controlled and yields a consistently high-quality product.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. And the OPMA assessors are also recommending approval of the commercial manufacture of narsoplimab DS at Lonza Biologics Tuas Pte Ltd., Singapore FEI: 3009725845 and YARTEMLEA DP at Vetter Pharma Fertigung GmbH & Co. KG, Langenargen, Germany FEI: 3002808846.

The OBP assessments including DS quality, DP quality, and validation of immunogenicity assays. OPMA DS and DP microbiological and facility technical assessments are located as separate documents in Panorama.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRRII and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPMA/DBM.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Binding to MASP-2 and inhibit lectin pathway of complement. (Potency)	Efficacy	Intrinsic to molecule	(b) (4)	
Primary Sequence and Disulfide Bond	Efficacy and immunogenicity	Intrinsic to molecule		

CQA (type)	Risk	Origin	Control Strategy	Other
High molecular weight species (HMWS) (product-related impurity)	Efficacy, pharmacokinetics and immunogenicity	Manufacturing process and storage conditions. Can form due to agitation, temperature, or light exposure.	(b) (4)	
Low molecular weight species (LMWS) (product-related impurities)	Efficacy, pharmacokinetics and immunogenicity	Manufacturing process and storage conditions. LMWS may be caused by agitation, temperature, or light		
(b) (4) (product related impurity)	Efficacy	DS manufacturing process and storage conditions		
Acidic variants (product related impurity)	Efficacy, pharmacokinetics and immunogenicity	DS manufacturing process and storage conditions		
Basic variants (product-related substance)	Efficacy, pharmacokinetics and immunogenicity	DS manufacturing process and storage conditions		
Higher order structure	Efficacy, immunogenicity	Intrinsic to molecule		
Heavy and light chains (purity)	Efficacy, immunogenicity	DS manufacturing process		

B. Drug Substance [Narsoplimab-wuug] Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy
Appearance, color and clarity (general)	Safety	Manufacturing process	(b) (4)
Protein Concentration (general)	Efficacy, pharmacokinetics, safety	Manufacturing process	
pH (general)	Efficacy, safety	Formulation and stability	
Host Cell Proteins (process-related impurity)	Safety and immunogenicity	Derived from host cell line	
Host Cell DNA (process-related impurity)	Safety	Derived from host cell line	
(b) (4) (process-related impurity)	Safety and immunogenicity	Process-related impurity (b) (4) (b) (4)	
Osmolality (general)	Safety	Manufacturing process	
(b) (4) (process-related impurity)	Safety	(b) (4)	
(b) (4) (process-related impurity)	Safety		
Virus (enveloped and non-enveloped) (contaminant)	Safety	Contamination during manufacture	
Endotoxin (contaminant)	Safety, Purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.	
Bioburden (contaminant)	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Bioburden can be introduced by raw materials and throughout the manufacturing process	

CQA (type)	Risk	Origin	Control Strategy
Mycoplasma (contaminant)	Safety	Contamination during manufacture	(b) (4)
(b) (4) (general)	Safety, stability	Manufacturing process	

- Description: Narsoplimab is a human immunoglobulin gamma 4 (IgG4) monoclonal antibody consisting of 2 heavy chains of 445 amino acids and 2 lambda light chains of 212 amino acids with the IgG4 disulfide bond pattern. It is comprised of variable regions of human origin, fused to IgG4 heavy chain and lambda light chain constant region. Each heavy chain contains a single serine to proline mutation in the hinge region and a single N-linked glycosylation site at the ^{295}asparagine residue. Post-translational modifications of narsoplimab include oxidation, deamidation, N-terminal pyroglutamic acid formation, and processing of the C-terminal lysine of the heavy chain. The theoretical molecular weight of narsoplimab calculated from the mass of the polypeptide chains combined is 143,087 Da. The theoretical isoelectric point is 8.36.

- Mechanism of Action (MoA): Narsoplimab binds to mannan-binding lectin associated serine protease 2 (MASP-2) and inhibits lectin pathway of complement.

- Potency Assay:

    - Binding Enzyme-Linked Immunosorbent Assay (ELISA): A colorimetric ELISA is used to assess the binding potency of narsoplimab to the recombinant human MASP2 (rhuMASP-2). The rhuMASP-2 is used as the capture reagent to coat a 96-well plate; narsoplimab is added to bind to MASP-2. Detection is achieved through the binding of a horseradish peroxidase (HRP) conjugated goat anti-human IgG [Fc] polyclonal antibody to narsoplimab with final colorimetric detection through addition of HRP substrate 3,3′,5,5′-TMB. Narsoplimab binding directly correlates with narsoplimab concentration.

    - Functional Enzyme-Linked Immunosorbent Assay (ELISA): the assay utilizes the Wieslab® MBL kit to measure MASP-2 response due to an activation of the mannose-binding lectin (MBL) complement pathway. Human pooled serum, containing MASP-2, is incubated in Diluent MP, which blocks both the classical and alternative complement pathways, and only allows activation of the MBL complement pathway. Narsoplimab DS is serially diluted and added to the blocked human serum to bind to MASP-2 in a dose-dependent manner. The MASP-2/narsoplimab mixture in serum is added to the mannan-coated plates; unbound MASP-2 is activated and C5b-C9 deposition occurs. The formation of C5b-C9 is detected with anti-C5b-C9 monoclonal antibody conjugated to alkaline phosphatase (C5b-C9-AP). The p-nitrophenyl phosphate 9pNpp) substrate is added to develop a color and absorbance is measured at 405 nm. C5b-C9 deposition correlates inversely with narsoplimab DS concentration. A relative potency value is computed based on the ratio of the IC50 of the reference standard curve and a test sample curve.

- Reference Materials: A two-tiered reference material system is in place as per ICH Q6B recommendations. The current primary reference standard (PRS) was derived from a process performance qualification (PPQ) Lot 844227 manufactured at Lonza with the commercial process in

November 2019. A portion of the vials were designated as PRS Lot PRS844227 and the remaining was designated as working reference standard (WRS) Lot 844227ARS. The PRS will be used to quality future WRS batches. The WRS will be used for release, stability and characterization testing of narsoplimab DS and DP. The current reference standards are suitable for their intended use in narsoplimab testing. The reference standards are stored at (b) (4) and tested annually for up to 120 months. The testing methods, acceptance criteria and testing time points of the stability protocol are adequate, and the stability data will be updated while available. The sponsor will submit a protocol for the qualification of future primary and working reference standards as a Prior Approval Supplement (PAS).

- Critical starting materials or intermediates: (b) (4)

(b) (4)

- Manufacturing process summary: (b) (4)

(b) (4)

(b) (4)

- Container closure: The drug substance container closure system (b) (4) (b) (4)

  The container closure for stability program consists of (b) (4) (b) (4) representing the container closure used in manufacturing.

- Dating period and storage conditions: The applicant conducted real-time stability studies at (b) (4) for 3 clinical batches and 5 process validation batches. These data are also supported by accelerated and stressed stability studies. These data support a dating period of (b) (4) (b) (4) The applicant committed to place one batch of narsoplimab DS on stability (b) (4) that the product is manufactured. The stability testing program is adequate and consistent with ICH Q5C recommendations.

C. Drug Product [YARTEMLEA] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy
Appearance, color and clarity (general)	Safety	Manufacturing process	(b) (4)
Particulates	Safety	Manufacturing process, product degradation	
Extractable volume (general)	Safety, efficacy	Manufacturing process, storage conditions	

CQA (type)	Risk	Origin	Control Strategy
Protein concentration (general)	Efficacy	Manufacturing process	(b) (4)
Polysorbate-80	Safety, stability	Manufacturing process	
Sub-visible particles (general)	Safety	Manufacturing process, product degradation	
pH (general)	Safety, efficacy	Formulation	
Osmolality (general)	Safety, stability	Formulation	
Endotoxin (contaminant)	Safety, purity and immunogenicity	Raw materials; microbial contamination during the manufacturing process	
Sterility (contaminant)	Safety, purity, efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced during DP manufacture or through a container closure integrity failure	
Container closure integrity	Safety (maintenance of sterility during shelf-life)	Container closure breaches during storage. May be impacted by storage conditions.	

- Potency and Strength: Yartemlea drug product contains narsoplimab drug substance of 370 mg in a nominal volume of 2 mL solution (nominal concentration of 185 mg/mL). The potency assays are the same ELISA assays as those described in the Drug Substance section of this review.

- Summary of Product Design: Yartemlea is supplied as a sterile, preservative-free solution in a (b) (4) glass (b) (4) vial, containing narsoplimab DS of 370 mg in a nominal volume of 2 mL solution. Yartemlea is further diluted in (b) (4) 5% dextrose for intravenous infusion.

- List of Excipients: Excipients include polysorbate 80 (0.2 mg), citric acid monohydrate (1.42 mg), sodium citrate (b) (4), L-arginine hydrochloric acid (84.3 mg), water for injection (~1.6 mg).

- Reference Materials: The same reference standard is used for Drug Product as for Drug Substance. Refer to the Drug Substance reference standard section above.

- Manufacturing process summary: The manufacturing process for Drug Product includes the following steps: (b) (4)

(b) (4) (b) (4). The commercial batch size is (b) (4).

Four consecutive batches at the commercial scale were manufactured and analyzed to validate the manufacturing process. Manufacturing process parameters were within pre-specified parameters, and product quality attributes were within specification limits. These data support a well-controlled process that will consistently produce a high-quality product and that is adequate from a product quality review perspective.

All drug product-contact equipment and components are sterilized and depyrogenated using validated processes. The DP is sterilized (b) (4) (b) (4) (b) (4). Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at DP lot release. Container closure integrity test using a validated dye ingress method is included in the stability program. OPMA recommends approval of the DP manufacturing process from a product quality microbiology and sterility assurance perspective.

- Container closure: The primary packaging material for Yartemlea Drug Product consists of a (b) (4) glass, (b) (4) 2 mL (b) (4) vial (b) (4), stoppered with a 13 mm (b) (4) (b) (4) rubber stopper (b) (4).

- Dating period and storage conditions: The sponsor conducted real-time, accelerated, and thermal-stressed stability studies on 4 PPQ lots and 1 clinical Drug Product lot. These data support a dating period of (b) (4) months when stored at 2 to 8°C.

- List of co-package components, if applicable: None.

D. Biopharmaceutics Considerations: None.

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations: None

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacture. In process and release testing: Bioburden, endotoxin, protein concentration, residual protein A,	Lonza Biologics Tuas Pte Ltd. 35 Tuas South Ave. 6, Singapore, Singapore 637377, Singapore	936939342/ 3009725845	-----	Section 704(a)(4) records review	Approve

residual HCP, residual host cell DNA. Storage of MCB and WCB.					
Manufacture and storage of MCB and WCB	Lonza Biologics Plc 228 Bath Road, Slough, Berkshire SL14DX, UK	230794810/ 1000583959	------	Waived	Approve
Release testing: adventitious agents/viral safety testing of unprocessed bulk harvest and MCB and WCB	(b) (4)		-----	Waived	Approve
Release testing: adventitious agents/viral safety testing of unprocessed bulk harvest and MCB and WCB			-----	Waived	Approve
Adventitious agents/viral safety testing of MCB and WCB			-----	Waived	No evaluation necessary
DS and DP Release and stability testing Physicochemical. Stability sample storage			-----	Waived	Approve
DS and DP Release and stability testing biological (binding potency assay)			-----	Waived	Approve
DS and DP Release and stability testing Biological (functional potency assay)			-----	Waived	Approve

DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug product manufacturing Visual inspection In process, release and stability compendial testing: Storage of stability samples	Vetter Pharma-Fertigung GmbH & Co. KG Eisenbahnstrasse 2-4, 88085 Langenargen, Germany	344217323/ 3002808846	-----	Waived	Approve
Visual inspection Drug product in process, release and stability compendial testing	Vetter Pharma-Fertigung GmbH & Co. KG Schutzenstrasse 87 and 99-101, 88212 Ravensburg, Germany	316126754/ 3002270322	-----	Waived	Approve
Visual inspection Drug product in process, release and stability compendial testing	Vetter Pharma-Fertigung GmbH & Co. KG Mooswiesen 2, 88214 Ravensburg, Germany	312670654/ 3005987757	----	Waived	Approve
Visual inspection warehousing	Vetter Pharma-Fertigung GmbH & Co. KG Helmut-Vetter-Strasse 10, 88213 Ravensburg, Germany	341629292/ 3009560142	----	Waived	Approve
Labeling, packaging and serialization	(b) (4)		-----	Waived	Approve

H. **Facilities:** In lieu of a pre-license on-site inspection (PLI) for the drug substance manufacturing facility, Lonza Biologics Tuas Pte Ltd (FEI 3009725845), a review of manufacturing site records under Section 704(a)(4) was conducted by Zhao Wang (OPQ/OPMA) and Chen Sun (OPQ/OBP) based on the facility inspection history and the similarity between the manufacturing processes.

The manufacturing records requested covered the manufacture of drug substance with respect to Product Quality, Production, Laboratory Control, Materials, Facilities and Equipment Systems. Based on the records review, it was recommended that the proposed drug substance manufacturing facility be acceptable to support the approval of the BLA761152.

The pre-license inspection of the drug product site Vetter Pharma-Fertigung GmbH & Co. KG (Langenargen Eisenbahnstrasse) was waived because of the site's compliance status and its recent MRA inspection (b) (4) and FDA surveillance inspection (September 2018).

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
(b) (4)

ii. Outstanding assessment issues/residual risk: None.
iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:
- stability protocol for the extension of drug product shelf life
- annual stability protocol

ii. Outstanding assessment issues/residual risk: None.
iii. Future inspection points to consider: None.

Yanming An

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Xianghong Jing

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/s/

YANMING AN
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