CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761390Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 8/4/2024

1. Application/Product Information

BLA number	761390
Submission Type	Original
Regulatory Pathway	NME 351(a), Breakthrough
Associated IND/BLA	117122
Review Designation	Priority Review
Applicant	Galderma Laboratories, L.P.
Indication	Treatment of adults with prurigo nodularis
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Nemluvio
	Non-proprietary Name: nemolizumab-ilto
	OBP Naming: MAB HUMANIZED (IGG2) ANTI Q8NI17 (IL31R_HUMAN) [CIM331]
Drug Product Description	Drug product is supplied (b) (4): - a single-dose dual chamber cartridge administered by auto-injection device (DCC-AI), pen (b) (4)
	The product is supplied as single-dose DCC-AI (b) (4) containing 30 mg of nemolizumab-ilto lyophilized powder and 0.49 mL of diluent, water for injection. The resulting concentration after reconstitution is 61.5 mg/mL of nemolizumab-ilto.
	Nemolizumab-ilto is recombinant humanized anti-human interleukin-31 receptor A (IL-31RA) monoclonal antibody targeting IL-31RA.
Dosage Form	Lyophilized powder for solution for injection

Strength	30 mg/0.49 mL (b) (4)		
Route of Administration	Subcutaneous		
Primary Container Closure System	DCC-AI - glass barrel, middle plunger, rear plunger and a closure part including snap-on cap and closure disk. (b) (4)		
Device Information	The DCC-AI (pen) injection system (b) (4) used to deliver the drug product. Device information is assessed by CDRH and the review will be documented separately.		
Co-packaged Product Information	Not applicable		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	Xiaoxiao Pan	Jacek Cieslak
	Drug product	Mamta Kapoor-Bhushan	
	Immunogenicity Assay	Mamta Kapoor-Bhushan	
	Facility	Liqun Zhao (DS) Bo Chi (DP)	Zhong Li
	Microbiology	Liqun Zhao (DS) Bo Chi (DP)	Maxwell Van Tassell
	RBPM	Anita Brown	
	ATL	Jacek Cieslak	
OPQ Issued Consults	CDRH	Colleen Lawrimore	Shruti Mistry

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761390 for Nemluvio manufactured by Galderma Laboratories, L.P. The data submitted in this application are adequate to support the conclusion that the manufacture of Nemluvio 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.

(b) (4)

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** Chugai Pharma Manufacturing Co., Ltd. (CPMC)
- 5-1, Ukima 5-Chome, Kita-ku, Tokyo, 115-8543 Japan
- **Drug Product DCC-AI:** (b) (4)

(b) (4)

b. Fill size and dosage form:

30 mg lyophilized powder in DCC-AI (b) (4) for injection.

c. Dating Period:

- **Drug Product DCC-AI:** 24 months at 2°C to 8°C

(b) (4)

- **Drug Substance:** (b) (4)
- **Stability Option:**
  - For stability protocols:
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:

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

e. Draft Phase 4 (Post-Marketing) Commitments:

4682-1 Conduct three shipping validation runs [redacted] to cover dual chamber cartridge (DCC) shipping [redacted] to the USA from a temperature control perspective. Provide the report and summary validation data.

Final Report Submission: 10/25

4682-2 Conduct one shipping validation run in summer 2024 for final packaged autoinjector (AI) to validate the shipping from [redacted] to the US distribution sites from a temperature control perspective. Provide the report and summary validation data.

Final Report Submission: 10/24

4682-3 Implement a test for sub-visible particles [redacted] µm in size in the drug product release and annual stability program for dual chamber cartridge presentation.

Final Report Submission: 10/25

[redacted]

4. Basis for Recommendation

a. Summary:

Nemolizumab-ilto is recombinant humanized anti-human interleukin-31 receptor A (IL-31RA) monoclonal antibody targeting IL-31RA for the treatment of adults with prurigo nodularis.

The drug substance manufacturing process consists of [redacted]

The overall Nemluvio 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 assessment of manufacturing information provided in the application concluded that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. Additional shipping validation studies (b) (4) (PMC 4682-1) and one shipping validation run in summer for final packaged autoinjector (AI) (4682-2) will be performed. Additional test to evaluate sub-visible particles (b) (4) in size will be developed and implemented in drug product release and annual stability programs (PMC 4682-3). The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The manufacturing processes and overall control strategies for Nemluvio are appropriately established to ensure consistency and quality of the final safe product; therefore, lot variability is not a concern. OPQ recommends approval of the commercial manufacture of nemolizumab-ilto drug substance at Chugai Pharma Manufacturing Co. (Tokyo, Japan), drug product DCC-AI at (b) (4) All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from a product quality, facility, microbiology, and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate 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 Nemluvio (i.e., there is no specific test method described

in regulation for Nemluvio that establishes an official standard of potency). We next considered whether potency is a factor for Nemluvio 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 Nemluvio for purposes of § 610.61(r) because lot variability is not a concern for Nemluvio as Nemluvio's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:
- Protocol for the production of a new working cell bank
- Concurrent lifetime validation protocol for (b) (4)
- Concurrent lifetime validation protocol for (b) (4)
- Protocol for Reprocessing (b) (4) and final filtration
- Drug substance stability protocol

ii. Residual risk: none

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:
- Qualification and requalification protocols for primary and working reference standards
- Drug product stability protocol
- Real-world shipping study protocol

ii. Residual risk: Refer to Sections 3e and 4 of this document regarding discussion of shipping studies and assays used for release and stability testing of drug substance and drug product and associated PMCs.

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/

JACEK CIESLAK
08/09/2024 08:45:53 AM

LABELS AND LABELING ASSESSMENT

Date of Assessment:	July 18, 2024
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Mamta Kapoor-Bhushan, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761390
Applicant:	Galderma Laboratories, L.P., Dallas, TX 75201
Submission Date:	December 12, 2023
Product:	Nemluvio (nemolizumab-ilto)
Dosage form(s):	For injection
Strength and Container-Closure:	30 mg single-dose prefilled dual-chamber pen (autoinjector) (b) (4)
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment for the treatment of prurigo nodularis
Recommendations:	The prescribing information, patient labeling, instructions for use (submitted on July 17, 2024), and container label and carton labeling (submitted on June 26, 2024) 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).

(b) (4)

CONCLUSION

The prescribing information, patient labeling, instructions for use (submitted on July 17, 2024), and container label and carton labeling (submitted on June 26, 2024) 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 December 12, 2023
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Patient Information (submitted on December 12, 2023
\\CDSESUB1\EVSPROD\bla761390\0001\m1\us\draft-labeling-text-ppi.doc)

Instructions for Use (submitted March 20, 2024

(b) (4)

\\CDSESUB1\EVSPROD\bla761390\0011\m1\us\dcc-ai-ifu-text.doc)

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

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i), 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

Comment/Recommendation: Revise to the appropriate dosage form, "for injection"
The Applicant revised as requested

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓Yes ☐No ☐N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	☐Yes ☐No ☒N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	☐Yes ☐No ☒N/A

Comment/Recommendation: (b) (4)

[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."

(b) (4)

For the autoinjector label: Revise to the name of the manufacturer appearing on FDA form 356h, "Galderma Laboratories, L.P.". *The Applicant revised as requested*

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓Yes ☐No ☐N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓Yes ☐No ☐N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, 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

Comment/Recommendation: The supplied product is a lyophilized powder, revise the strength presentation from "30 mg/0.49 mL" to read as "30 mg". *The Applicant revised as requested*

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

Comment/Recommendation: (b) (4)

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

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: The Applicant confirms that sufficient area of the container (b) (4) *will remain uncovered so that the visual inspection can be conducted post labeling.*

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: (b) (4)

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

Comment/Recommendation: Provide the location and format of the NDC number on (b) (4) autoinjector label *The Applicant revised as requested*

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

Comment/Recommendation: Revise from "(b) (4)" to "Must be reconstituted before injection" *The Applicant revised as requested*
Revise to the appropriate dosage form, "for injection". *The Applicant revised as requested*

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

Comment/Recommendation: Ensure that a linear barcode appears on [redacted] the autoinjector label and show the location on the label mockup.
Applicant's response: The linear barcode has been added to all packaging components [redacted] except when space did not allow for this [redacted] We acknowledge the appearance of the barcode on the pen container label, [redacted]

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, 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

Comment/Recommendation: Include storage information post reconstitution. *The Applicant revised as requested and responded that "The Applicant has added the statement "After reconstitution, use NEMLUVIO (b) (4) pen within 4 hours or discard." to the DCC-AI pen label and all packaging components (b) (4) except when space did not allow for thi (b) (4)*

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

Comment/Recommendation: For all carton labeling, revise to the appropriate dosage form, "for injection". *The 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

[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.

Comment/Recommendation: Ensure that all carton labeling, (b) (4), is revised to have the name and address of the manufacturer appearing on FDA form 356h and include the placeholder for the US License Number as follows:
"Galderma Laboratories, L.P.
Dallas, TX 75201
US License Number XXXX"

Applicant's response: All carton and container labeling (b) (4) *has been updated* (b) (4) *to include the name and address of Galderma Laboratories, L. P. and a placeholder for the US license number except when space did not allow for this* (b) (4) *Interim Applicant comment, "The Agency has requested that the NDC number, manufacturing name and address as well as license number placeholder be added to the nemolizumab carton* (b) (4) *and container labels. Please consider that the DCC-AI is packaged in a carton that includes a glued partition that is an integral part of the carton* (b) (4) *Therefore, we propose to exclude the NDC number, name and address of manufacturer, and US license number from the DCC-AI partition (i.e. not add as requested).* Acceptable

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: (b) (4)

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

Comment/Recommendation: Revise the strength presentation from 30 mg/0.49 mL" to read as "30 mg". *The Applicant revised as requested*

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

Comment/Recommendation: Revise from [redacted] (b) (4) [redacted]" to read as follows: "Alternatively, NEMLUVIO carton containing unused prefilled pen [redacted] (b) (4) may be stored at room temperature [up to 77°F (25°C)] for up to a single period of 90 days. Date removed from refrigerator __/__/__." Ensure that the line to write the date removed from the refrigerator is located near the room temperature storage instructions. *The Applicant revised as requested*

Relocate on a new line and revise from "[redacted] (b) (4) [redacted]." to read as follows: "After reconstitution, use NEMLUVIO pens [redacted] (b) (4) within 4 hours or discard." To match prescribing information. *The Applicant revised as requested*

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓Yes ☐No ☐N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐Yes ☐No ☒N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓Yes ☐No ☐N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓Yes ☐No ☐N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐Yes ☐No ☒N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100, 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: Revise from (b) (4) ." to read as follows:

"Each prefilled (b) (4) pen] has a dual chamber and one chamber contains 30 mg of nemolizumab-ilto with inactive ingredients arginine hydrochloride (9.5 mg), poloxamer 188 (0.15 mg), sucrose (25.8 mg), trometamol (0.10 mg), and tris hydrochloride for pH

adjustment. The other chamber contains Water for Injection. Following reconstitution, each prefilled [redacted] pen] delivers 30 mg/0.49 mL." *The Applicant revised as requested but did not revise to the concentration of the solution after reconstitution as* "Following reconstitution, each pen delivers 30 mg/0.49 mL." *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 nemolizumab products (i.e., there is no specific test method described in regulation for nemolizumab 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 Nemluvio 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. 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 revised as requested*

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓Yes ☐No ☐N/A
Recommended labeling practices references: 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

Comment/Recommendation: (b) (4)

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

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) 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

Comment/Recommendation: Revise from "See package insert for dosage and administration information" to read as follows: "Dosage: See Prescribing Information". *The Applicant revised as requested*

Revise the contents list from "Package insert" to "Prescribing Information" *The Applicant revised as requested*

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: Revise to the appropriate dosage form, "for injection". *The 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: Deleted "(b) (4)" to provide a concise presentation of the information and deleted (b) (4) *The Applicant revised as requested*
Revise to the appropriate dosage form, for injection *The Applicant revised as requested*
Revise to the appropriate strength presentation for a lyophilized powder
The Applicant revised the strength presentation to include the deliverable amount after reconstitution and stated "The Applicant proposes the following revision to appropriately

reflect the strength of the solution after reconstitution. (b) (4) "

Revise to the primary expression of strength for this lyophilized powder (30 mg) which is the expression for the supplied product and to match the label claim provided on the proposed container and carton labeling. Highlights DFS is a concise presentation of FPI DFS and thus the strength after reconstitution is not to be provided here. *The 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: Storage information for the supplied product. This storage information is in section 16 How Supplied/Storage and Handling). *The Applicant revised as requested*
Added the verbatim statement per 21 CFR 201.57(c)(3)(iv) for visual inspection
The Applicant revised as requested

Relocated the reconstituted concentration from section 16
The Applicant revised as requested

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓Yes ☐No ☐N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling*	✓Yes ☐No

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*	☐N/A

Comment/Recommendation: Revise to the appropriate dosage form, for injection *The Applicant revised as requested*

Revise to the appropriate strength presentation for a lyophilized powder, 30 mg.
The Applicant revised the strength presentation to include the deliverable amount after reconstitution and stated "The Applicant proposes the following revision to appropriately reflect the strength of the solution after reconstitution. (b) (4) ”

Revise to the primary expression of strength for this lyophilized powder (30 mg) which is the expression for the supplied product and to match the label claim provided on the proposed container and carton labeling. The strength (concentration) after reconstitution has been included in the preparation section (2.5). *The Applicant revised as requested*

Added the identifying characteristics of the dosage form, white *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), 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: Deleted redundant information *The Applicant revised as requested*
We included the inactive ingredient nominal amounts per your 3.2.P.1 submission and revised the paragraph for readability.
The applicant revised back to "L-arginine hydrochloride”
The USP monograph title is to be used in labeling and thus this has been revised to "arginine hydrochloride" *The Applicant revised as requested*
The pH was revised to 6.7 to 7.3 per DP specifications. *The Applicant revised as requested*

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐Yes ☐No ☒N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓Yes ☐No ☐N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓Yes ☐No ☐N/A

Comment/Recommendation: the deliverable amount after reconstitution was relocated to Dosage and Administration section 2.4. *The Applicant added "to deliver 30 mg nemolizumab-xxxx after reconstitution."*

We revised for consistent language found in sections 2.5 and 11 as: "Following reconstitution, each prefilled pen (b) (4) delivers 30 mg/0.49 mL of nemolizumab-xxxx" *The Applicant revised as requested*

Detailed storage conditions for reconstituted and/or diluted products should be described in the DOSAGE AND ADMINISTRATION section rather than the HOW SUPPLIED/STORAGE AND HANDLING section. This information was relocated to section 2 (Dosage and Administration 2.4). *The Applicant revised similarly as requested. The Applicant proposes removing "Do not shake" from the first paragraph as shaking has no effect on the lyophilized NEMLUVIO during the storage step. Per product quality assessor, based on applicant's data in the application, shaking has no effect on product quality [for the supplied product].*

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

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓Yes ☐No ☐N/A

Comment/Recommendation: Ensure that the dosage form, for injection, is provided consistently throughout all labeling. *The Applicant revised as requested*

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓Yes ☐No ☐N/A

Comment/Recommendation: Revise refrigerator storage conditions to match prescribing information to include "until the expiration date" *The Applicant revised as requested*

PATIENT INFORMATION LABELING	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓Yes ☐No ☐N/A

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓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

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022*). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).*	✓Yes ☐No ☐N/A

Comment/Recommendation: Ensure that the dosage form, for injection, is provided consistently throughout all labeling *The Applicant revised as requested*
Revise to the appropriate strength presentation for a lyophilized powder, 30 mg *The Applicant revised as requested*

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022*). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)*	✓Yes ☐No ☐N/A

Comment/Recommendation: *The Applicant proposes removing "Do not shake" from the first paragraph as shaking has no effect on the lyophilized NEMLUVIO during the storage step. Per product quality assessor, based on applicant's data in the application, shaking has no effect on product quality [for the supplied product].*

INSTRUCTIONS FOR USE

INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	☐Yes ☐No ☒N/A

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓Yes ☐No ☐N/A
Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022*).* *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 July 17, 2024 \\CDSESUB1\EVSPROD\bla761390\0038\m1\us\uspi-draft-labeling-clean.doc)
Instructions for Use (submitted on July 17, 2024 \\CDSESUB1\EVSPROD\bla761390\0038\m1\us\dcc-ai-ifu-text.doc)
Patient Information (submitted on July 17, 2024 \\CDSESUB1\EVSPROD\bla761390\0038\m1\us\draft-labeling-text-ppi.doc)

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

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 7/18/2024 09:58:37AM
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Mamta Kapoor-Bhushan

Digitally signed by Mamta Kapoor-Bhushan
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