CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761391Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 12/4/2024

1. Application/Product Information

BLA number	761391
Submission Type	Original
Regulatory Pathway	NME 351(a)
Associated IND/BLA	117122
Review Designation	Standard Review
Applicant	Galderma Laboratories, L.P.
Indication	Treatment of adults and pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies
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 (DCC-AI (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 761391 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) (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 (PMCs were discussed and communicated during the review of BLA 761390):

4721-3 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

4721-4 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] Data regarding PMC 4682-2, which was issued for BLA 761390, were submitted for BLA 761391 and were found acceptable.

4. Basis for Recommendation

a. Summary:

Note: BLA 761390 (priority review) and BLA 761391 (standard review) for Nemluvio were submitted on December 13, 2023 for different indications. An assessment of Module 3 was primarily performed for BLA 761390. The CMC content of eCTD documents for BLA 761390 and 761391 is identical (the sequence numbers and supporting documents numbers for BLA 761390 and 761391 are not identical due to different clinical teams and communications with the applicant for both BLAs).

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]

(b) (4)

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 will be conducted (b) (4) (b) (4) (PMC 4721-3). Regarding PMC 4682-2 (issued for BLA 761390), data were submitted during the review cycle of BLA 761391 and were found acceptable. Additional test to evaluate sub-visible particles (b) (4) µm in size will be developed and implemented in drug product release and annual stability programs (PMC 4721-4). These product quality issues will be communicated to the sponsor (b) (4) (b) (4) 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) (b) (4) (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) (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
12/10/2024 01:06:19 PM

LABELS AND LABELING ASSESSMENT

Date of Assessment:	December 5, 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 761391
Applicant:	Galderma Laboratories, L.P., Dallas, TX 75201
Submission Date:	December 13, 2023
Product:	Nemluvio (nemolizumab-ilto)
Dosage form(s):	For injection
Strength and Container-Closure:	30 mg single-dose prefilled dual-chamber pen (autoinjector)
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment for the treatment of moderate-to-severe atopic dermatitis
Recommendations:	The prescribing information, patient information labeling, instructions for use (December 2, 2024), and container label (submitted on August 1, 2024) and carton labeling (submitted on August 9, 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 (N/A)
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. We previously assessed container labels, carton labeling, prescribing information, patient labeling, and instructions for use.[1]

Container[2] Label Evaluation

30 mg single-dose prefilled dual-chamber pen (autoinjector) container labels submitted on August 1, 2024, are identical to labels determined to be acceptable in our previous assessment. OPQA III Labeling has no additional recommended revisions.

Package[3] Labeling Evaluation

30 mg single-dose prefilled dual-chamber pen (autoinjector) carton labeling submitted on August 1, 2024, needs to include a revision to remove the "(b) (4)" statement for consistency with the Prescribing Information and Instructions for Use, which instructs to shake the pen to dissolve the medication. *The Applicant revised as requested*.

CONCLUSION

The prescribing information, patient information labeling, instructions for use (December 2, 2024), and container label (submitted on August 1, 2024) and carton labeling (submitted on August 9, 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 February 20, 2024
\\CDSESUB1\EVSPROD\bla761391\0008\m1\us\draft-labeling-text-tc.doc)

Patient Information (submitted on December 13, 2023
\\CDSESUB1\EVSPROD\bla761391\0001\m1\us\draft-labeling-text-ppi.pdf)

[1] Borders-Hemphill V. Labels and Labeling Assessment. STN 761390 nemolizumab-ilto Labeling Assessment. Silver Spring (MD): FDA, CDER, OPQ, OPQAIII (US); 2024 July 18. P36.
[2] 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.
[3] 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.

Instructions for Use Pen (submitted August 1, 2024
\\CDSESUB1\EVSPROD\bla761391\0035\m1\us\dcc-ai-ifu-text.doc)

(b) (4)

Container Labels
Autoinjector (submitted August 1, 2024)

(b) (4)

3 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[4,5] and Labeling[6] Standards

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓Yes ☐No ☐N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓Yes ☐No ☐N/A

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

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

Comment/Recommendation: Added "prefilled". *Applicant revised as requested*

[4] 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.
[5] 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.
[6] 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.

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.

Deleted (b) (4) to match instructions.
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 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: 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) (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 (b) (4)
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*	☐Yes ☐No ☒N/A

Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	

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 (b) (4) *The Applicant added* (b) (4) "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 (b) (4). *The Applicant revised similarly as requested.* (b) (4) (b) (4) (b) (4) *Per product quality assessor, based on applicant's data in the application,* (b) (4) *has no effect on product quality [for the supplied product].*

(b) (4)

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: (b) (4) (b) (4) (b) (4) *Per product quality assessor, based on applicant's data in the application,* (b) (4) *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 December 2, 2024 \\CDSESUB1\EVSPROD\bla761391\0046\m1\us\draft-labeling-text.doc)

Instructions for Use (submitted on December 2, 2024 \\CDSESUB1\EVSPROD\bla761391\0046\m1\us\dcc-ai-ifu-text.doc)

Patient Information (submitted on December 2, 2024 \\CDSESUB1\EVSPROD\bla761391\0046\m1\us\draft-labeling-text-ppi.doc)

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

Container Labels

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 12/05/2024 12:01:59PM
GUID: 50814c7000007a3d59329f660d8ddf02

Mamta Kapoor-Bhushan

Digitally signed by Mamta Kapoor-Bhushan
Date: 12/05/2024 12:04:09PM
GUID: 54a2e25f000678567e4c58aaef83a8f5

PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
Memorandum of Review to the File

Application ID	BLA 761391
Submission Type	Original BLA
Drug Product Name	nemolizumab (CD14152) humanized IgG2 monoclonal antibody recognizing the interleukin-31 receptor alpha chain (IL-31Rα)
Strengths	30mg per unit
Dosage Form	lyophilized powder for solution for injection
Administration Route	subcutaneous
Indication	Treatment of moderate-to-severe atopic dermatitis (AD) in patients12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4)
Applicant Name	Galderma Laboratories, L.P.
US License Number	2289
Application Type	351 (a)
Primary Reviewer	Liqun Zhao, Pharmaceutical Scientist, OPQ/OPMA/DPMAV
Secondary Reviewer	Maxwell Van Tassell, PhD, SPQA, OPQ/OPMA/DPMAV Zhong Li, PhD, SPQA, OPQ/OPMA/DBMAVI
Goal Date	Dec 13, 2024

Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and is recommended for Approval.
- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation (DS):

Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4) (b) (4). Bioburden and endotoxin samples are monitored at each critical step of the manufacturing process and at DS release. Microbial control of the (b) (4) was demonstrated by microbial monitoring in their lifetime studies. Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Endotoxin	Safety, Purity	Raw materials, manufacturing process	(b) (4)	

			(b) (4)
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials, manufacturing process	

List of Submissions Assessed (Table):

Document Description (Sequence #)	Date Received
SN0001/SD1	12/12/2023
SN0019/SD19	4/17/2024

Application Submission Background

Galderma Laboratories L.P. has submitted this BLA for NEMLUVIO (nemolizumab-ilto) 30 mg/0.49 mL for the treatment of moderate-to-severe atopic dermatitis (AD) in patients ≥12 years old, who are inadequately controlled by topical therapies (b) (4).

Nemolizumab is a humanized IgG2 recombinant monoclonal antibody. The drug is provided as a sterile, preservative-free, white lyophilized powder in single-dose together with prefilled pen (b) (4) Water for injection is provided also. Nemolizumab is intended to be used as subcutaneous injection.

The CMC section of BLA 761391 is identical to that of BLA 761390. BLA 761390 was approved on August 12, 2024.

This review contains an assessment to the Nemolizumab drug substance quality microbiology and facilities evaluations.

Reviewer's Comment: For Information

MODULE 3.2.S

S.1 General Information

Nemolizumab is a recombinant humanized monoclonal antibody based on a human immunoglobulin G2 (IgG2) framework. It consists of two heavy chains and two light chains. The antibody is produced in Chinese hamster ovary (CHO) cells.

Reviewer's Comment: For Information

S.2 Manufacture

(b) (4)

40 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
Memorandum of Review to the File

Application ID	BLA 761391
Submission Type	Original BLA
Drug Product Name	Nemolizumab (Nemluvio)
Strengths	30mg per unit
Dosage Form	lyophilized powder for solution for injection
Administration Route	subcutaneous
Indication	Treatment of moderate-to-severe atopic dermatitis (AD) in patients 12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4) (b) (4)
Applicant Name	Galderma Laboratories, L.P.
US License Number	2289
Application Type	351 (a)
Primary Reviewer	Bo Chi, Ph.D., CDER/OPQ/OPMA/DPMAVI
Secondary Reviewer	Maxwell Van Tassell, Ph.D., SPQA, CDER/OPQ/OPMA/DPMAV Zhong Li, Ph.D., SPQA, CDER/OPQ/OPMA/DPMAVI
Goal Date	12/13/2024

Recommendation for Approvability:

- This BLA was reviewed from a sterility assurance perspective and is recommended for Approval with the following post-marketing commitment(s):

  The following shipping validation studies will be conducted from a temperature control perspective and the validation data will be provided in a PMC report:

  - *Conduct three shipping validation runs* (b) (4) (b) (4) *to cover dual chamber cartridge (DCC) shipping* (b) (4) (b) (4) *to the USA.*
  - (b) (4)
  -

- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OPQA.

Summary Basis of Recommendation (DP):

All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. The drug product is sterilized (b) (4)

(b) (4)

All proposed DP manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

Drug Product CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety, Purity, and Efficacy	Manufacturing process, failure of the container closure integrity	(b) (4)	
Endotoxin (Contaminant)	Safety, Purity	Raw materials, manufacturing process		
Container closure integrity (Sterility assurance)	Safety (Sterility assurance)	Breach during manufacture or storage		

List of Submissions Assessed (Table):

Document Description (Sequence #)	Date Received
Original BLA submission (0001)	12/12/2023
Sequence numbers according to 761390	
Response to IR (0005)	2/5/2024
Response to IR (0014)	3/25/2024
Response to IR (0022)	4/30/2024
Response to IR (0030)	6/5/2024
Response to IR (0032)	6/13/2024
Response to IR (0034)	6/21/2024
Response to IR (0036)	7/8/2024
Response to IR (0041)	7/26/2024
Response to IR (0042)	7/31/2024
Sequence number according to 761391	
Shipping validation data (0041)	10/16/2024

List of DMFs Assessed (Table):

DMF #	Item Referenced	Date Reviewed	Finding	Document Reference
[redacted]	[redacted]	4/6/2023	Adequate	[redacted] 61R01
		8/7/2023	Adequate	64R01
		4/21/2023	Adequate	20R01
		2/12/2024	Adequate	M21R01

Application Submission Background

Galderma Laboratories has submitted this Biologics License Application (BLA) for nemolizumab for the treatment of moderate-to-severe atopic dermatitis (AD). The drug product (DP) [redacted]: Dual-chamber Cartridge-Auto Injector (DCC-AI) [redacted]. The drug substance (DS) is manufactured at Chugai Pharma Manufacturing Co., Ltd., Tokyo, Japan. The DP is [redacted] filled at [redacted].

The DCC-AI is assembled at [redacted]. This application contains CMC information in an eCTD format.

This review contains an assessment of the nemolizumab drug product section of the BLA from a sterility assurance and product quality microbiology perspective.

MODULE 1
1.14 LABELING
Dosage and administration

Nemolizumab DP should be administered by subcutaneous injection.

- The product is supplied as a single-dose pre-filled dual-chamber pen [redacted].
- The recommended dosage for patients [redacted] is an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks [redacted].
- [redacted]

Reviewer's comment: The [redacted] DCC-AI are single-dose administered by subcutaneous injection. The label does not require a microbiology review.

Dual chamber cartridge (DCC)

MODULE 3.2.P
P.1 Description and Composition of the Drug Product

- The DP is provided as a sterile, white lyophilized powder for solution for injection in single-use, single-dose dual chamber cartridge (DCC) with no preservatives.

- Each DCC contains 30 mg of nemolizumab in chamber 1 [redacted] and water for injection (WFI) for reconstitution in chamber 2. The [redacted].
    - DP formulation before lyophilization: [redacted] nemolizumab, [redacted] sucrose, [redacted] trometamol / tris hydrochloride, [redacted] Arginine Hydrochloride, [redacted] Poloxamer 188
    - DP formulation after reconstitution: 61.5 mg/mL nemolizumab, [redacted] sucrose, [redacted] trometamol / tris hydrochloride, [redacted] Arginine Hydrochloride, [redacted] Poloxamer 188, pH 7.0
- The target fill volume allows a nominal injection volume of 0.49 mL to deliver a 30 mg dose.
- [redacted]
- The DCC is assembled into an autoinjector and further labeled.

P.2 Pharmaceutical Development

[redacted]

87 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

BLA STN 761391

Nemluvio (nemolizumab-ilto) 30 mg/0.49 mL

Drug Product
(b) (4)
Dual Chamber Cartridge-Autoinjector (DCC-AI)

Galderma Laboratories, L.P.

Mamta Kapoor-Bhushan, Ph.D., Primary Assessor
Jacek Cieslak, Ph.D., Application Technical Lead

Office of Product Quality Assessment III (OPQA III)
Division of Product Quality Assessment XVI (DPQA XVI)

OPQA III CMC Review Data Sheet

1. BLA#: 761391

2. Assessment Date: 07/30/2024

3. Primary Assessment Team:

Discipline	Assessor	Branch/Division
Drug substance (DS)	Xiaoxiao Pan	OPQ/OPQA III/DPQA XVI
Drug product (DP), DS and DP release and stability specifications, and immunogenicity assays	Mamta Kapoor-Bhushan	OPQ/OPQA III/DPQA XVI
Inspection of DS site	Jacek Cieslak	OPQ/OPQA III/DPQA XVI
Labeling	Vicky Borders-Hemphill	OPQ/OPQA III
DS Facilities/ Microbiology	Liqun Zhao	OPQ/OPMA/DPMA V
DP Facilities/ Microbiology	Bo Chi	OPQ/OPMA/DPMA V
Team Leads	Jacek Cieslak Maxwell Van Tassell Zhong Li	OPQ/OPQA III/DPQA XVI OPQ/OPMA/DPMA V OPQ/OPMA/DPMA V
OPQ RBPM	Anita Brown	OPQ/OPRO/DRBPM II
Application Technical Lead	Jacek Cieslak	OPQ/OPQA III/DPQA XVI

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	H. F. Van Horn, III	
Regulatory Chief	Susan Rhee	Division of Dermatology and Dentistry (DDD)
Division Director	Jill Lindstrom	
Cross-disciplinary Team Lead	Snezana Trajkovic	
Medical (clinical) Officer	Sena Lee Amy Woitach (CDTL)	
Pharm/Tox	Jianyong (Jerry) Wang Barbara Hill (TL)	
Clinical Pharmacology	Nisha Kwatra Chinmay Shukla (TL)	
Biometrics	Daeyoung Lim Matthew Guerra (TL)	
DMEPA	Lisa Huang, Madhuri Patel	CDER/OSE/OMEPRM/DMEPA I
OSI team	Stephanie Coquia Michele Fedowitz	CDER/OC/OSI/DCCE/GCPAB

4. Major GRMP Deadlines:
Filing Meeting: January 24, 2024
Mid-cycle internal meeting: May 14, 2024
Mid-cycle Applicant meeting: June 03, 2024
Late-cycle internal meeting: August 5, 2024
Late-cycle Applicant meeting: August 29, 2024
Secondary Review Due: September 24, 2024

Wrap-up Meeting: October 15, 2024
PDUFA Action Date: December 13, 2024

5. Communications with Sponsor and OND:
Refer to the drug substance assessment.

6. Submission Assessed:

Submission (**BLA 761390)**	Date Received	Review Completed (Yes/No)
SD#1/eCTD 0001	12/12/2023	Yes
SD#29/eCTD 0028 (IR#1 response to DP)	05/28/2024	Yes
SD#30/eCTD 0028 (OPMA IR#1 response)	06/05/2024	Yes
SD#32/eCTD 0032 (OPMA IR response)	06/13/2024	Yes
SD#33/eCTD 0033 (IR#2 response to DS and DP)	06/20/2024	Yes
SD#39/eCTD 0039 (IR#3 response to DS and DP)	07/22/2024	Yes
BLA 761391		
SD#42/eCTD 0041 (PMC- US shipping validation)	10/16/2024	Yes

7. Drug Product Name/Code/Type:

a. Proprietary Name: Nemluvio
b. Trade Name: Nemluvio
c. Non-Proprietary Name/USAN: Nemolizumab-ilto
d. CAS Name: 1476039-58-3
e. Common Name: CIM331
f. INN Name: Nemolizumab
g. Compendial Name: N/A
h. Chemical/Biological product name: Recombinant humanized anti-human interleukin-31 receptor A (IL-31RA) monoclonal antibody targeting IL-31RA
i. OBP systematic name: MAB HUMANIZED (IGG2) ANTI Q8NI17 (IL31R_HUMAN) [CIM331]
j. Other names: CD14152

8. Pharmacological Category: interleukin-31 receptor antagonist

9. Dosage Form: Injection, lyophilized, for solution, supplied as
- A single-dose dual chamber cartridge administered by auto-injection device, (b) (4)

10. Strength/Potency:
(i): The concentration/strength of the Drug Product: 30 mg/0.49 mL (61.5 mg/mL after reconstitution)
(ii): Type of potency assay(s): A cell-based assay to determine the potency of nemolizumab drug substance and drug product by blocking the binding of human interleukin-31 (hIL-31) to hIL-31 receptor (hIL-31R), which in turn inhibits the downstream signal transduction pathway of hIL-31R.

11. Route of Administration: Subcutaneous injection

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced and link to LOA	Comments (status)
(b) (4)			No review required as all the relevant information related to compatibility with the product was provided in the BLA.

13. Inspectional Activities:

A pre-license inspection of nemolizumab drug substance manufacturing facility at Chugai Pharma Manufacturing Co. Ltd. at Ukima, Tokyo, Japan (FEI: 3004109596) was conducted on March 18-29, 2024, by OPQ/OPMA and OPQ/OPQAIII in support of BLA 761390 and 761391. A five-item FDA Form 483 was issued to the facility. Facility Status Assessment: Approve - Based on Inspection.

A pre-license inspection of nemolizumab drug product (DCC-AI) manufacturing facility at (b) (4) (b) (4) was conducted on (b) (4) by OPQ/OPMA and OPQ/OPQAIII in support of BLA 761390 and 761391. A four-item FDA Form 483 was issued to the facility. Facility Status Assessment: Approve - Based on Inspection.

(b) (4)

14. Consults Requested by OPQA III:
CDRH evaluated the (b) (4) dual chamber cartridge, and autoinjector for BLA 761390 and BLA 761391. The device constituent parts of the combination product are approvable.

15. Quality by Design Elements:
The following was submitted in the identification of QbD elements (check any that apply):

	Design Space

x	Design of Experiments
x	Formal Risk Assessment/Risk Management
x	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: none

17. Administrative: signatures (end of this document)

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation
The Office of Product Quality Assessment III recommends approval of BLA 761391 for Nemluvio (nemolizumab-ilto) manufactured by Galderma Laboratories, L.P. from a product quality perspective based on the review of the information and data provided in the application.

II. List of Deficiencies to be Communicated
None

III. List of Post-Marketing Commitments/Requirements
PMC 1: To implement a test for additional sub-visible particles testing (b) (4) µm in size in the drug product release and annual stability programs for (b) (4) dual chamber cartridge (b) (4)
Final Report Submission: 10/2025

IV List of Protocols
Refer to the Drug substance assessment for the complete list of protocols.

V. Assessment of Common Technical Document- Quality Module 1
A. Environmental Assessment of Claim of Categorical Exclusion
The applicant claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). The applicant indicates that no extraordinary circumstances exist with respect to this product. There is no indication that additional environmental information is warranted. The claim of categorical exclusion is deemed acceptable.

VI. Primary Container Labeling Assessment
Refer to review by Vicky Borders-Hemphill.

VII. Assessment of Common Technical Document- Quality Module 3.2
This document.

VIII. Assessment of Immunogenicity Assays- Module 5.3.1.4
The immunogenicity assays for nemolizumab are based on bridging electrochemiluminescence (ECL) assay to screen, confirm, determine titer, and cell-based bioassay to characterize the neutralization activity (a cell-based IL-31 receptor A blockade assay) of the anti-drug antibodies present in the nemolizumab-treated patients during the pivotal phase 3 clinical studies. The method validation data support that the assays are suitable for the intended purposes. Refer to Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies of this document.

Contents

116 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

P DRUG PRODUCT (Dual Chamber Cartridge-Autoinjector (DCC-AI)

3.2.P.1 Description and Composition of the Drug Product

The drug product (DP) is a sterile, white lyophilized powder for solution for injection in single-use, single-dose dual chamber cartridge-autoinjector (referred to as DCC-AI or AI by the applicant) with no preservatives.

DCC diagram

The DCC consists of a (b) (4) glass barrel with a (b) (4) middle and rear plunger, and closure part (b) (4) snap-on cap and (b) (4) closure disk). The DCC is placed in auto-injector subassemblies ((b) (4) (AI). The AI is labeled and packaged with other supporting documents in a folded carton box (see Section 3.2.P.7 for details).

Nemolizumab DCC-AI composition

Table 3.2.P.1-1 Composition of Nemolizumab Drug Product

Ingredients	Amount per cartridge[a]	Nominal amount per cartridge[b]	Concentration		Function	Specification
			Before lyophilization	After reconstitution		
Chamber 1						
Nemolizumab	(b) (4)	30 mg	(b) (4)	61.5 mg/mL	Active ingredient	In-house
Sucrose		25.8 mg		(b) (4)	(b) (4)	USP-NF/Ph. Eur.
Trometamol[c]		0.10 mg				USP-NF/Ph. Eur.
Tris hydrochloride		(b) (4)			pH adjusting agent	In-house
(b) (4) Arginine hydrochloride	(b) (4)	9.5 mg			(b) (4)	USP-NF/Ph. Eur.
Poloxamer 188		0.15 mg				USP-NF/Ph. Eur.
Chamber 2						
Water for Injection		NA	NA	NA	Diluent for reconstitution	USP-NF/Ph. Eur.
Ph. Eur. =European Pharmacopoeia, USP-NF =United States Pharmacopeia and National Formulary, q.s. =quantity sufficient, NA =not applicable						
(b) (4)						

Nemolizumab sterile, white lyophilized powder is stored in the front chamber of the DCC (chamber 1) and water for injection (WFI) in the rear chamber of the DCC (chamber 2). The reconstitution solution consists of 61.5 mg/mL (30 mg/0.49 mL) nemolizumab in DCC for single use. DCC is assembled with autoinjector (AI) subassemblies (DCC-AI).

All excipients used in the DP formulation except Tris hydrochloride (Tris-HCL) are compendial (USP, NF, Ph. Eur.) (b) (4)).

Maximum dose: Based on Section 5.3.5.2. clinical protocol#RD.06.SIR.202699 for Phase 3 study, maximum dose for ≥90 kg patient is 2 x 30 mg =60 mg i.e., two AIs. *One AI is required for usual dose.* For target filling volume and proposed volume ranges in chamber 1 and chamber 2, refer to Section 3.2.P.2.4 in this memo.

***Assessor's comments**: Nemolizumab DP is a dual chamber cartridge in an autoinjector (AI) wherein the cartridge consists of lyophilized drug powder (in chamber 1) and water for injection (in chamber 2). DP composition (b) (4) (b) (4) mg/mL). Sufficient information on DP description and composition is provided. Note that for usual dose, only one AI is required. Also note that DP composition in DCC-AI (per cartridge (b) (4). The applicant has been asked to justify the filling volumes in chamber 1 and chamber 2.*

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance (DS) and ***3.2.P.2.1.2 Excipients:*** (b) (4)

3.2.P.2.2 Drug Product

(b) (4)

87 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page