CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761391Orig1s000

OTHER REVIEW(S)

MEMORANDUM

HUMAN FACTORS STUDY RESULTS MEMO

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 15, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761391
Product Name, Dosage Form, and Strength:	Nemluvio[a] (nemolizumab-ilto)[b] injection, 30 mg
Applicant/Sponsor Name:	Galderma Laboratories, L.P. (Galderma)
TTT ID #:	2024-7726-1
DMEPA 1 Safety Evaluator:	Lisa Huang, PharmD, MPH, BCGP
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised dual chamber autoinjector (DCC-AI) instructions for use (IFU) via email on November 7, 2024 for Nemluvio for the 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. The Division of Dermatology and Dentistry (DDD) requested that we review the IFU for Nemluvio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors study results review.[c]

2 DISCUSSION AND CONCLUSION

The Applicant implemented our recommendations to:

- Revise the image in Step 8 and 9 so that users can better identify the dissolved particles.

[a] The proposed proprietary name Nemluvio was found conditionally acceptable on March 13, 2024.
[b] The proposed nonproprietary name suffix -ilto was found conditionally acceptable on June 11, 2024.
[c] Huang, L. Human Factors Study Reports Review for Nemluvio (BLA 761391). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUL 30. TTT ID No.: 2024-7726; 2024-7724.

- Change the image for Step 17 to better portray the full image of the sharps container and revise the title to read "*Throw away (dispose of) Nemluvio in a sharps disposal container*".
- Include the statement *"In adolescents (ages 12 to 17 years old), it is recommended that NEMLUVIO be given by or under supervision of a trained adult or caregiver"* since we do not have data to support this task in this user group.

The Applicant did not implement our recommendation to increase the prominence of the activation knob. The Applicant provided the following rationale to retain the current design and implement any potential design or IFU updates in a post-approval supplement:

> "*The DCC-AI has been designed to prevent incorrect sequencing of steps and ensures that users cannot remove the gray cap before turning the activation knob. Based on data available to date, the Applicant does not believe that a design change is necessary. Given that priority review status has been granted for this BLA to allow expedited availability of Nemluvio to PN patients, the Applicant proposes to monitor usage in the post-marketing phase and, if necessary, submit any potential design improvements via the appropriate post-approval supplement. As any modifications to the current user interface can impact the HFE validation, potential changes will be assessed to ensure no unintended use errors are introduced.*" In this specific instance, we find the Applicant's rationale reasonable.

Based on the provided information, we have no additional recommendations for the revised Nemluvio DCC-AI IFU at this time.

APPENDIX A. LABEL AND LABELING RECEIVED ON NOVEMBER 7, 2024

BLA 761391 SCPI.pdf

Applicant's response to our July 9, 2024, recommendations available via EDR:
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/s/

LISA HUANG
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 14, 2024
To:	H.F. Van Horn III, PharmD Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** David Foss, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	NEMLUVIO (nemolizumab-ilto)
Dosage Form and Route:	for injection, for subcutaneous use
Application Type/Number:	BLA 761391
Applicant:	Galderma Laboratories, L.P.

1 INTRODUCTION

On December 13, 2023, Galderma Laboratories, L.P., submitted for the Agency's review original Biologics License Application (BLA) 761391 NEMLUVIO (nemolizumab-ilto) lyophilized powder solution for injection. The proposed indication is treatment of moderate-to-severe atopic dermatitis (AD) in patients > 12 years old, who are inadequately controlled by topical therapies (b) (4) (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on January 29, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for NEMLUVIO (nemolizumab-ilto) lyophilized powder solution for injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft NEMLUVIO (nemolizumab-ilto) PPI and IFU received on December 13, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2024.
- Draft NEMLUVIO (nemolizumab-ilto) Prescribing Information (PI) received on [Month Day, Year], revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2024.
- Approved DUPIXENT (dupilumab) comparator labeling dated September 27, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022).
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
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DMPP-OPDP review of nemolizumab-ilto (NEMLUVIO) BLA 761391 PPI and IFU

DAVID F FOSS
11/14/2024 01:25:24 PM

LASHAWN M GRIFFITHS
11/14/2024 01:44:41 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 8, 2024

To: Howard F. Van Horn, Regulatory Project Manager,
Division of Dermatology and Dentistry (DDD)

Hamid Tabatabai, Clinical Reviewer, DDD

Matthew White, Associate Director for Labeling, DDD

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for NEMLUVIO® (nemolizumab-ilto) for injection, for subcutaneous use

BLA: 761391

Background:
In response to DDD's consult request dated January 29, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Nemluvio.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on November 7, 2024, and our comments are provided below.

OPDP comments on the proposed PPI/IFU will be sent under separate cover, either as a combined OPDP and Division of Medical Policy Programs (DMPP) review or a separate OPDP review.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on November 7, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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DAVID F FOSS
11/08/2024 04:51:00 PM

Consultation Memorandum

Division of Neurology 2

Date:	October 11, 2024
To:	Howard F. Van Horn III, Pharm D, MBA Regulatory Health Project Manager Division of Regulatory Operations for Division of Dermatology and Dentistry Center for Drug Evaluation and Research
From:	Kevan VanLandingham, MD, PhD Clinical Reviewer Division of Neurology 2 Office of Neuroscience Center for Drug Evaluation and Research Philip Sheridan, MD, Clinical Team Leader Division of Neurology 2 Office of Neuroscience Center for Drug Evaluation and Research
Through:	Paul R. Lee, MD, PhD, MA Director (Acting) Division of Neurology 2 Office of Neuroscience Center for Drug Evaluation and Research
Subject:	Consultation Memorandum
Application:	BLA 761391
Applicant/Sponsor:	Galderma Laboratories, L.P.
Drug Product:	Nemluvio (Nemolizumab)
Date of Request:	July 23, 2024

Patient Narratives provided in response to information request: September 5, 2024

Consult Request

The Division of Dermatology and Dentistry (DDD) Clinical Team has consulted DN2 concerning the results of the multinational clinical trials RD.06.SPR.118161 and RD.06.SPR.118169, entitled Randomized, Double-blind, Placebo-controlled Studies to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis. DDD has identified an increased incidence in the active drug arms versus the placebo arms for the Preferred Terms seizure/epilepsy, syncope, and presyncope and some other PTs that might be related to seizure (psychogenic tremor, psychomotor hyperreactivity, and vestibular nystagmus with "brownout" and global hyperreflexia).

Seizure/epilepsy/tremor	**Syncope/presyncope**
SPR118161- (b) (6)	**SPR118161** (b) (6)
SPR118169-	**SPR118161**
SPR118169-	**SPR118161**
SPR118169-	**SPR118161**
	SPR118169
	SPR118169
	SPR118169
	SPR118169

DDD posed two questions:

1. Does Neurology think there is a causal relationship between nemolizumab and these treatment emergent adverse events (TEAEs)?
2. And if so, does Neurology recommend inclusion in labeling?

Regulatory History

In order to address the questions in this consult request, an information request was sent to the Applicant, requesting a clinical update for all subjects who experienced events of potential seizure and syncope while receiving nemolizumab during all clinical trials in the nemolizumab atopic dermatitis (AD) development program. The Applicant was also asked to provide case level data.

On September 5, 2024, detailed narratives were provided by the Applicant, with the exception of subject SPR 118169 (b) (6) for the syncope/presyncope Preferred Terms group.

A literature review regarding seizures/epilepsy in patients with atopic dermatitis/allergic disorders was also conducted by the DN2 reviewer.

Clinical Background

- **Review of Patient Narratives**

In clinical studies of nemolizumab in healthy volunteer subjects (SPR.201590 and CIM001JP), there were no reports of seizure or syncope.

As noted in the table in the consult request reproduced above, there were 4 cases of preferred terms specified as **seizure/epilepsy/tremor/hyperactivity**.

Subject (b) (6) was a 17-year-old woman with history of AD and depression, treated with duloxetine and mirtazapine, who had a "single episode of epilepsy" while being treated with nemolizumab (without detailed description of the event, diagnosed as epilepsy). No testing (EEG or neuroimaging) was reported. The subject was treated with low dose VPA (150 mg daily). Quetiapine was added 1 week after the event. There was no past history of seizure, and no further events consistent with seizures were reported.
DN2 IMPRESSION: A single seizure is not epilepsy. The dose of VPA was substantially subtherapeutic. While the event could have been an isolated seizure, the episode was more likely due to either an adverse event related to the concomitant medications or a nonepileptic event, which would be a diagnosis of exclusion after complete evaluation.

Subject (b) (6) was a 25-year-old woman with a history of AD and episodic syncope for several years, who had a "single event of epilepsy" while being treated with nemolizumab. The details of the event were not provided. The subject received no additional therapy.
DN2 IMPRESSION: This event was most likely syncope in this subject with a history of syncope, possibly convulsive syncope which is a nonepileptic phenomenon. In any patient with a history of syncope, the most likely diagnosis for clonic movements is convulsive syncope rather than seizure. If there had been no clonic activity associated with the event, it most likely would have been another syncopal event, of unclear etiology (i.e., vasovagal, orthostatic hypotension, cardiac arrythmia, hypoglycemia, etc.).

Subject (b) (6) was a 24-year-old woman with a history of AD, anxiety, and depression, who experienced muscle spasms while being treated with nemolizumab. She was hospitalized and work up included (DEFINE) CT and MRI (imaging locations not specified) and ECG and laboratory tests (not specified) were all normal. She was treated with duloxetine with a diagnosis of psychogenic tremor, and she had no further events. She continued nemolizumab treatment.
DN2 IMPRESSION: Given the history of anxiety, the most likely cause of the tremor would have been a manifestation of the pre-existing anxiety disorder, possibly a panic attack. A diagnosis of psychogenic tremor would be one of exclusion. Seizures are unlikely to be the cause of the tremor.

Subject (b) (6) was a 14-year-old o girl a history of AD, who had an event of hyperactivity while being treated with nemolizumab. She was treated with quetiapine, and the event was reported as ongoing at the end of the study. While in the long-term extension study (LTE), she was diagnosed with bipolar disorder.
DN2 IMPRESSION: Hyperactivity was likely due to the diagnosis of bipolar disorder, and not related to seizures.

As shown in the table above reproduced from the consult request, there were 8 reported cases of syncope/presyncope, with 7 cases having narratives submitted by the Applicant in response to an information request. Case **SPR11816** (b) (6) will not be discussed, because no additional data was provided.

Subject (b) (6) was a 12-year-old girl with a history of AD and "epilepsy" not otherwise specified (NOS), treated with levetiracetam, who had a near syncopal event on Study Day 1 of treatment. ECG was normal. Blood pressure during the event was not noted. No seizure activity was reported. There was no prior history of near syncope. The event resolved without further evaluation or treatment. She was diagnosed with vasovagal reaction, without further recurrence. She continued on nemolizumab in the LTE.
DN2 IMPRESSION: Near syncope due to vasovagal reaction.

Subject (b) (6) was a 47-year-old woman with a history of AD, positional vertigo, anxiety, depression, and fibromyalgia, who had a near syncopal event on Study Day 52 of treatment. ECG was normal. Blood pressure during the event was not noted. No further work up was conducted. There was no prior history of near syncope. She was diagnosed with vasovagal reaction, without further recurrence. She continued on nemolizumab in the LTE.
DN2 IMPRESSION: Near syncope due to vasovagal reaction.

Subject (b) (6) was a 61-year-old man with a history of AD, who experienced syncope on Study Day 113. Prior to the day of the syncopal event, the subject had normal blood pressure. On the day of the event, blood pressure was elevated, with readings of 162/100 and 139/84, and ECG showed 1st degree AV block. There was no prior history of syncope. The subject decided to withdraw from the study.
DN2 IMPRESSION: Syncope in setting of 1st degree AV block.

Subject (b) (6) was a 20-year-old man with a history of AD who had syncope on Study Day 215. ECG and blood pressure findings during the study were reportedly within normal limits. No blood pressure or ECG was obtained during the event. He was treated with IV acetaminophen. He did not have recurrence of syncope. He continued on nemolizumab in the LTE.
DN2 IMPRESSION: Syncope.

Subject (b) (6) was a 15-year-old boy with a history of AD and asthma. On Study Day 32, he fainted. The event recovered the same day. ECG was normal. Blood pressure during the event was not noted. He had no past history of fainting, but he did not have breakfast on the morning of the event, and the day was noted as being extremely hot. There was no prior history of fainting. He was diagnosed with syncope, without further recurrence. He continued on nemolizumab in the LTE.
DN2 IMPRESSION: Syncope in the setting of potential hypoglycemia and extreme heat exposure.

Subject (b) (6) was a 31-year-old woman with a history of AD, who had syncope on Study Day 346. On the day of the event, she vomited, and was subsequently noted to be

hypokalemic and in 1st degree AV block. She was treated with potassium (route not specified) and IV acetaminophen, with resolution of the syncope and hypokalemia. The 1st degree AV block persisted. She completed the study on Study Day 351.
DN2 IMPRESSION: Syncope, in the setting of 1st degree AV block, vomiting, and hypokalemia.

Subject (b) (6) was a 17-year-old man with a history of AD, who had syncope on Study Day 289, while on placebo. He had a similar event during screening for this study. This event occurred during phlebotomy. He was given 1 Liter of IV fluids without recurrence. Prior to the study, he had never had syncope. ECG was normal. He had no further events of syncope. He continued on nemolizumab in the LTE.
DN2 IMPRESSION: Syncope due to vasovagal reaction.

- **Literature Review by DN2 Clinical Reviewer**

Chen (2014) used the Taiwan National Health Insurance Research Database, which had 35,312 patients with AD but without a history of epilepsy, and 35,312 age-/gender-matched controls that were enrolled between 1998 and 2008, and followed to the end of 2011, to identify the development of epilepsy. Subjects with AD had a higher incidence of developing epilepsy (0.94 vs. 0.27/1,000 person-years, $p < 0.001$) than the control group. The Cox regression model showed that atopic dermatitis increased the risk of developing epilepsy (hazard ratio [HR] 2.91, 95% confidence interval [CI] 2.23–3.82) after adjusting for demographic data and medical comorbidities. Sensitivity tests showed consistent findings (HR 2.32, 95% CI 1.68–2.96) after excluding the first year of observation. In addition, asthma (HR 1.34, 95% CI 1.04–1.72) and allergic rhinitis (HR 1.34, 95% CI 1.04–1.73) were related to the risk of epilepsy. Subjects with AD were associated with an increased risk of developing epilepsy in later life. Further studies would be needed to investigate the underlying mechanisms.

Silverberg (2014) used the 2007–2008 National Survey of Children's Health, a US population-based study of 91,642 children aged 0–17 years to determine the association between the prevalence of epilepsy and allergic disease, including asthma, AD/eczema, hay fever, and food allergies. Multivariate logistic regression models were constructed that controlled for confounding variables: Children with ≥1 allergic disease had more epilepsy in their lifetime than nonallergic children (logistic regression, adjusted odds ratio [95% confidence interval] = 1.79 [1.37–2.33]). Lifetime prevalence (2.30 [1.50–3.52]) and one-year prevalence of asthma (2.00 [1.41–2.84]), AD/eczema (1.73 [1.17–2.56]), hay fever (1.93 [1.41–2.65]) and food allergies (2.69 [1.38–4.01]) were associated with increased odds of ever being diagnosed with epilepsy. Severe atopic dermatitis/eczema (3.89 [1.34–11.32]) was associated with higher odds of epilepsy compared with mild/moderate disease.

The literature supports an increased incidence of epilepsy in patients with AD. However, the narratives submitted by the Applicant are not suggestive of epilepsy occurring in the nemolizumab studies.

Recommendations

Question 1. Does Neurology think there is a causal relationship between nemolizumab and these TEAEs?

No, based on the limited data available, DN2 does not consider the events described as epilepsy, tremors, hyperactivity, syncope or near syncope to be related to nemolizumab exposure. Most of the syncope events appeared to have etiologies that were clearly not attributable to nemolizumab exposure. However, none of these subjects had an appropriate work up to definitively exclude seizures and, without a clearly established etiology, a definitive conclusion regarding an association between these events and nemolizumab exposure, and whether these events represent potential seizures, cannot be rendered, but what evidence exists does not constitute strong evidence that a causal relationship exists. There was no obvious pattern or predictability to the occurrence of these events and no apparent correlation with initiation or administration of nemolizumab. The events did not recur, and none of these subjects had recurrence of the events while in the studies, and so there does not appear to be a consistent safety signal present.

Question 2. If so, does Neurology recommend inclusion in labeling of these events?

No. DN2 does not recommend updating the labeling to include these events in response to these adverse event reports because there is not a clearly defined safety signal present. The evidence for a definitive identification of these events as being seizures in this clinical trial population is lacking. Routine pharmacovigilance for Nemluvio in the postmarketing setting should remain adequate to continue surveillance for a potential signal of seizures, syncopal events, tremors, or hyperactivity.

References

Chen JMH, Wu IYH, Su TP, et al. Risk of epilepsy among patients with atopic dermatitis: a nationwide longitudinal study. Epilepsia (2114) 55:1307-1312. doi: 10.1111/epi.12667

Silverberg JI, Joks R, Durkin HG. Allergic disease is associated with epilepsy in childhood: a US population-based study. Allergy 69 (2014) 95-103. doi:10.1111/all.12319, corroigenda doi: 10.1111/all.12499

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KEVAN E VANLANDINGHAM
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BLA 761391 Consult Review by DN2 for DDD

PHILIP H SHERIDAN
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PAUL R LEE
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 17, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761391
Product Name, Dosage Form, and Strength:	Nemluvio (nemolizumab-ilto)[a] for injection, 30 mg
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Galderma Laboratories, L.P.
FDA Received Date:	December 13, 2023, February 20, 2024, August 1, 2024 and August 9, 2024
TTT ID #:	2023-7482
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder nemolizumab-ilto is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 INTRODUCTION

As part of the approval process for Nemluvio (nemolizumab-ilto) for injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Nemluvio Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Galderma Laboratories, L.P. previously submitted the proposed product Nemluvio (nemolizumab-ilto) under BLA 761390 for review on December 14, 2023 for the treatment of prurigo nodularis and under BLA 761391 on December 13, 2024 for the proposed treatment of moderate-to-severe atopic dermatitis in patients ≥ 12 years old. BLA 761390 was approved on August 12, 2024 (b) (4)

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761391.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed Nemluvio Patient Package Insert (PPI), Instructions for Use (IFU), container labels, and carton labeling and determined that they are acceptable from a medication error perspective.

However, the proposed Nemluvio Prescribing Information (PI) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Dermatology and Dentistry (DDD) in Section 4.

4 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

Table 2. Identified Issues and Recommendations for the Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights and Full Prescribing Information – Section 2 Dosage and Administration			
1.	The dosage and administration section, includes the abbreviations "(b) (4)" and "(b) (4)".	Abbreviations such as "(b) (4)" and "(b) (4)" can be misinterpreted and pose risk of medication dosing errors.	We recommend removing the "(b) (4)" and "(b) (4)" to avoid confusion.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Nemluvio received on February 20, 2024 from Galderma Laboratories, L.P..

Table 3. Relevant Product Information for Nemluvio (BLA 761391)	
Initial Approval Date	N/A
Nonproprietary Name	nemolizumab-ilto
Indication	treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4) (b) (4)
Dosage Form	for injection
Strength	30 mg
Route of Administration	subcutaneous
Dose and Frequency	The recommended dosage of NEMLUVIO in patients aged 12 years and older is: - An initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (b) (4). - After 16 weeks of treatment, for patients who achieve clear or almost clear skin, a dosage of 30 mg every (b) (4) (b) (4) 8 weeks (b) (4) may be considered at prescriber's discretion. (b) (4)

Table 3. Relevant Product Information for Nemluvio (BLA 761391)

How Supplied

for injection is a sterile, preservative-free, white lyophilized powder available in single-dose, prefilled pen (b) (4) containing nemolizumab-xxxx in one chamber and the diluent, Water for Injection, in the other chamber. (b) (4)

Each carton contains:

- 1 single-dose prefilled pen, (b) (4) (b) (4)

Presentation	Pack size	NDC #
(b) (4)		
Pre-filled Pen	Pack of 1 pen	0299-6220-15
(b) (4)		

Storage

(b) (4)

Container Closure

(b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Nemluvio labels and labeling submitted by Galderma Laboratories, L.P..

- Prescribing Information received on February 20, 2024, available from \\CDSESUB1\EVSPROD\bla761391\0008\m1\us\draft-labeling-text-tc.doc
- Patient Package Insert received on December 13, 2023, available from \\CDSESUB1\EVSPROD\bla761391\0001\m1\us\draft-labeling-text-ppi.pdf
- Instructions for Use received on August 1, 2024, available from \\CDSESUB1\EVSPROD\bla761391\0035\m1\us\dcc-ai-ifu-text.doc
- Container Label received on August 1, 2024
- Carton Labeling received on August 9, 2024
- Professional Sample Container Label received on August 1, 2024
- Professional Sample Carton Labeling received on August 9, 2024

B.2 Container Label(s) and Carton Labeling Images

Container label(s)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On August 28, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Nemluvio' search identified six previous review(s)[c,d,e,f,g,h], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Patel, M. Label and Labeling Review for Nemluvio (BLA 761390). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 10. TTT ID No.: 2023-7476.

[d] Patel, M. Label and Labeling Review Memo for Nemluvio (BLA 761390). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 11. TTT ID No.: 2023-7476-1.

[e] Patel, M. Label and Labeling Review Memo for Nemluvio (BLA 761390). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUL 03. TTT ID No.: 2023-7476-2.

[f] Huang, L. Human Factors Study Reports Review for Nemluvio (BLA 761390 and BLA 761391). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUL 30. TTT ID No.: 2024-7724 and 2024-7726.

[g] Fung, M. Human Factors Study Results Memo for Nemluvio (BLA 761390). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUL 31. TTT ID No.: 2024-7724-1.

[h] Patel, M. Labeling Review Memo for Nemluvio (BLA 761390). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 AUG 09. TTT ID No.: 2023-7476-3.

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MADHURI R PATEL
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09/18/2024 01:00:56 PM

Clinical Inspection Summary

Date	9/9/2024
From	Stephanie Coquia, MD, Reviewer Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Hamid Tabatabai, MD, Clinical Reviewer Amy Woitach, MD, Clinical Team Leader H.F. Van Horn, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
BLA #	761391
Applicant	Galderma Laboratories, L.P.
Drug	Nemolizumab
NME (Yes/No)	Yes, at time of the submission of this BLA
Therapeutic Classification	Interleukin-31 receptor alpha antagonist
Proposed Indication	For the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4) (b) (4)
Consultation Request Date	2/6/2024
Summary Goal Date	9/13/2024
Action Goal Date	12/13/2024
PDUFA Date	12/13/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Galderma Laboratories, L.P., submitted clinical data for Nemolizumab injection from Studies SPR118161 (NCT03985943) and SPR118169 (NCT03989349).

The proposed indication is for the treatment of moderate-to-severe atopic dermatitis (AD) in patients aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4)

Three clinical investigators (Drs. Trullenque, Kalowska, and Reich) were inspected. The inspections did not find significant concerns regarding the study conduct or oversight of the clinical trials or Good Clinical Practice (GCP) or regulatory compliance, and based on the results of these inspections, the data generated by the inspected clinical investigators appear acceptable in support of the proposed indication.

II. BACKGROUND

Galderma Laboratories, L.P. seeks approval of a biologics license application (BLA) for nemolizumab injection. In support of the BLA, the Applicant submitted clinical data from two phase 3 studies, SPR118161 and SPR118169. The following is a summary of the study protocols and key study information relevant to the clinical inspections.

Study Design

These were nearly identical, phase 3 randomized, double-blind, placebo-controlled, multicenter, parallel-group studies that evaluated the efficacy and safety of nemolizumab in adult and adolescent subjects with moderate-to-severe AD.

Objectives and Endpoints

The primary objective of each study was to assess the safety and efficacy of nemolizumab after a 16-week treatment period in adult and adolescent subjects with moderate-to-severe AD not adequately controlled with topical treatments.

The co-primary efficacy endpoints of both studies were:

- The proportion of subjects with an Investigator's Global Assessment (IGA) success at Week 16, defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥2-point reduction from baseline
- The proportion of subjects with Eczema Area and Severity Index (EASI)-75 at Week 16, defined as ≥75% improvement in EASI from baseline

Changes in the Peak Pruritus Numeric Rating Scale (PP NRS) scores from baseline were secondary endpoints of interest.

Key Eligibility Criteria

- ≥12 years
- Chronic AD according to the American Academy of Dermatology Consensus Criteria for ≥2 years
- At both the screening and baseline visits:
    - EASI score ≥16
    - IGA score ≥3
    - AD involvement ≥10% of the body surface area
    - PP NRS score ≥ 4
- Documented history within 6 months of the screening visit of inadequate response to topical medications, such as topical corticosteroids (TCS) or topical calcineurin inhibitors
- None of the following:
    - Body weight <30 kg
    - Required rescue therapy for AD during the run-in period prior to the baseline visit or expected to require rescue therapy within 2 weeks following the baseline visit

- Previous treatment with nemolizumab
- Experienced worsening of AD or failed to achieve minimal improvement after a full 16-week course of dupilumab
- Intolerance to TCS or for whom TCS was not advisable
- Confounding skin condition that may have interfered with study assessments

Study Conduct

For Study SPR118161, 161 sites enrolled at least one subject. A total of 620 subjects were randomized to nemolizumab, and 321 subjects were randomized to placebo. The first subject was randomized on August 9, 2019. The last subject visit was August 11, 2022.

For Study SPR118169, 120 sites enrolled at least one subject. A total of 522 subjects were randomized to nemolizumab, and 265 subjects were randomized to placebo. The first subject was randomized on August 13, 2019. The last subject visit was September 26, 2022.

RESULTS

1. **Dr. Gretel Trullenque (SPR118161, Site 8801)**
   1021 Ives Dairy Road, Suite 214
   Miami, FL 33179-2537

Inspection Dates: May 14 – 24, 2024

This investigator was inspected as a routine PDUFA inspection for Study SPR118161. This was the first FDA inspection for this investigator.

Subject-related source documents reviewed for the 13 randomized subjects included: informed consent forms (ICFs) and assent forms, subject-level informed consent logs, protocol deviation logs, electrocardiograms (ECGs), laboratory reports, progress notes, and documentation of demographics, concomitant medications, vital sign measurements, physical examinations, investigational product (IP) administration, IGA, EASI, PP NRS, and BSA involvement.

Study-related documents reviewed included: Institutional Review Board (IRB), monitor, and sponsor correspondence; signed investigator agreements; delegation of authority and screening and enrollment logs; site protocol deviation log; training records; laboratory certification; financial disclosure forms; and IP accountability records.

No unreported serious adverse events (SAEs) were identified. The following discrepancies and corresponding unreported protocol deviations (if applicable) were noted when the subject source data were compared to the data submitted in the BLA or in the Electronic Data Capture (EDC) System:

Subject ID	Treatment Arm	Discrepancy	Source Documentation	Data submitted to the BLA/EDC	Comment
(b) (6)	Placebo	Subject Race	White	Black or African American	No effect on safety analysis of drug; treated with placebo
	Nemolizumab	Triamcin* concomitant medication start date *required (not prohibited)	12/02/2020 (Randomization date)	(b) (6) (Dispensed date)	Medication was to be initiated during the screening period, i.e., prior to the randomization date. Unlikely to impact efficacy as study compared AD severity at Week 16 to baseline/randomization status.
	Placebo	Baseline EASI Lower Extremity Excoriation score	2	3	No effect; subject still met EASI eligibility criterion (EASI 20.5) and still achieved EASI-75 (total score decreased by 84% from baseline)

2. **Dr. Monika Kalowska (SPR118161, Site 6064)**
   Ul. Kosiarzy
   Warszawa, NA 02-953 Poland

   Inspection Dates: July 15 – 19, 2024

This investigator was inspected as a routine PDUFA inspection for Study SPR118161. This was the first FDA inspection for this investigator.

Subject-related paper and electronic records for 19 of the 21 enrolled subjects reviewed included: ICFs, medical records, laboratory reports, ECGs, clinic notes, and documentation of subject eligibility, randomization, AEs, study visits, concomitant medications, disease assessments (IGA, EASI component, and PP NRS scores), and IP accountability.

Study- and site-related documents and records reviewed included: the protocol and amendments; sponsor, monitor, and ethics committee correspondence; site delegation of authority, monitoring, screening and enrollment, storage temperature, IP accountability, and protocol deviation logs; financial disclosure forms; signed investigator agreements; training records; and documentation of AE reporting.

Source data at the site was compared to the data submitted in the NDA. There was no evidence of underreporting of adverse events or protocol deviations. No discrepancies were identified between the efficacy source data (IGA, EASI component, and daily PP NRS scores) at the site and the data submitted in the BLA.

3. **Dr. Adam Reich (SPR118169, Site 5495)**
   Ul. Fryderyka Szopena 2
   Rzeszoq, Podkarpackie, 35-055 Poland

   Inspection Dates: May 6 – 10, 2024

This investigator was inspected as a routine PDUFA inspection for Study SPR118169. This was the first FDA inspection for this investigator.

Subject-related paper and electronic records for the 48 screened (40 randomized) subjects were reviewed and included: IP and subject device accountability records, ICFs and assent forms, study worksheets, eligibility criteria checklists, laboratory reports, medical records, progress notes, and documentation of subject visits, randomization assignments, procedures, efficacy endpoints (IGA, EASI component, and daily PP NRS scores), AEs, discontinuations, patient-reported outcomes, and concomitant medications.

Study- and site-related documents and records reviewed included: signed investigator agreements, ICF and assent form approvals, site delegation and screening and enrollment logs, site-level protocol deviation and informed consent logs, training records, sponsor and ethics committee correspondence, pharmacy and laboratory manuals, financial disclosure forms, IP accountability records, and monitoring reports.

There was no evidence of underreporting of AEs or protocol deviations. No discrepancies were identified between the efficacy source data and the data submitted in the BLA.

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Primary reviewer
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

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OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

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/s/

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JENN W SELLERS
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Clinical Outcome Assessment Review Memorandum

COA Tracking ID:	C2024027
BLA#; Referenced IND:	BLA 761391; IND 117122
Applicant:	Galderma Laboratories, L.P.
Established Name/Trade Name:	Nemolizumab
Indication:	Treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4) (b) (4).
Review Division:	Division of Dermatology and Dentistry
Clinical Reviewer	Sena Lee, M.D., PhD
Clinical Team Leader (TL)	Amy Woitach, DO, MS
Senior Regulatory Project Manager:	H. F. Van Horn III, PharmD, MBA
COA Reviewer:	Yasmin Choudhry, M.D.
COA Deputy Director:	Selena Daniels, PharmD, PhD
COA Director:	David Reasner, PhD
Date Consult Request Received:	January 23, 2024
Date Submission Received:	December 13, 2023
Instruments reviewed:	• Sleep Disturbance Numeric Rating Scale ☒ Patient-reported outcome (PRO)
	• Subject Sleep Diary ☒ Patient-reported outcome (PRO)

This clinical outcome assessment (COA) consult review is provided as a response to a request for consultation by the Division of Dermatology and Dentistry (DDD) regarding BLA 761391 [DARRTS Reference ID: 5315445].

In this submission, the Applicant is seeking approval of nemolizumab[1] for the treatment of moderate to severe atopic dermatitis (AD)[2] in pediatric (≥ 12 years) and adult subjects whose disease is not adequately controlled with topical prescription therapies (b) (4) (b) (4) (b) (4). two multi-center randomized, double-blind, placebo-controlled phase 3 studies (Studies RD.06.SPR.118161 and RD.06.SPR.118169; hereon referred to as Studies ARCADIA 1 and ARCADIA 2, respectively).

The primary objective of this review is to evaluate from a COA perspective (b) (4)

[1] Nemolizumab is a humanized anti-human interleukin-31 receptor A (IL-31RA) monoclonal antibody. By binding to IL-31RA, nemolizumab competitively blocks the binding of IL-31 to its receptor, thereby blocking subsequent transduction of the IL-31 signal into the cell. Interleukin-31 is a cytokine involved in pruritus of different conditions such as atopic dermatitis, prurigo nodularis, and chronic kidney disease-associated pruritus.
[2] Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by pruritus (itching), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification.

(b) (4)

The data from Studies ARCADIA 1 and ARCADIA 2 demonstrated that nemolizumab had a statistically significant greater proportion of participants with an improvement of >4 from baseline in weekly average SD NRS compared to placebo at Week 16. Despite achievement of statistical significance, the data are difficult to interpret due to the construction of the instrument (refer to Issues Identified section for more details).

(b) (4)

Review Conclusions

The Applicant submitted an evidence dossier for the SD NRS. The SD NRS was reviewed for content validity. Because of issues related to content validity (See Issues Identified section), the other measurement properties and score interpretability of the SD NRS was not reviewed.

Review Summary

- The SD NRS assesses one aspect of sleep disturbance (i.e., sleep loss).
- The Applicant has provided insufficient evidence to support content validity of the SD NRS.
- The Applicant tested the other measurement properties (reliability, construct validity, and ability to detect change) of the SD NRS, however, while important, it does not replace or rectify problems with content validity.
- It is unknown whether a 4-point improvement in the SD NRS is clinically meaningful due to the surrounding content validity issues.

Key Issues Identified

Issue #1: Content validity

- Insufficient qualitative evidence to support that sleep disturbance is an important concept to the target AD population. Participants were not queried regarding what AD associated impact was most important or bothersome to them.

- Sleep disturbance may not always be directly due to AD. Based on the qualitative findings, approximately one-third of adults (n=7/19, 35%) and adolescents (n=3/7, 30%) attributed sleep disturbance solely to the itching from their AD. Further, half (50%) of the adult participants provided a reason other than symptoms of AD for their sleep disturbance.

- The SD NRS, which is a single item, does not reflect the entirety of the sleep disturbance concept. Based on the qualitative data. there are different aspects of sleep

disturbance which vary across participants (e.g., difficulty falling/staying asleep, nighttime awakenings, early morning awakening, lack of sleep, unspecified sleep disturbance). However, the SD NRS only assesses "sleep loss" as a whole. Further, it is unclear what attribute of sleep loss is being measured with the SD NRS (e.g., severity, frequency, amount of sleep) as participants in the qualitative study interpreted the item differently. For example, one participant perceived the item to measure how much AD affected their sleep while another participant interpreted it as how much sleep they lost.

- It is unknown whether participants understood the SD NRS response scale after migrating from paper to an electronic format. There is concern regarding the formatting and layout changes of the response scale which may have been the result of migration from paper to electronic mode. Specifically, the placement of the anchors ("No sleep loss" and "I did not sleep at all") spans over 2-3 points at each end of the NRS in the electronic format, while it should have been located at the 0 and 10 points similar to the original paper format. It is unclear whether a usability study was conducted in the target population.

Issue #2: Data interpretability

- Because the SD NRS is a single item, it is unclear which aspect of sleep loss is improving and/or worsening.
- For the measurement concept of sleep loss, the NRS is not directly interpretable without descriptors at the intermediate level.
- While the Applicant administered the Subject Sleep Diary (SSD) to supplement the SD NRS, it provides limited information about the participant's sleep experience due to the variability of the participants' experience. Further, qualitative findings indicated that sleep disturbance or sleep loss may not be directly due to AD. For example, over half of the participants (adults: n=12/20, 60.0%; adolescents: n=14/10, 70.0%) woke up during the night for other things outside of their condition (e.g., going to bathroom, drinking water). These factors make data interpretation difficult.

Recommendations for Future Studies

For future clinical trials in this indication, Applicants should consider the following:

- Qualitative studies should be designed to provide a complete understanding of the concept of interest (i.e., sleep disturbance, sleep loss) in the target population. Specifically, understand which dimensions of sleep disturbance or sleep loss may be most relevant in the target population to inform the trial endpoints. It is important that the concepts selected to measure are based on aspects of the condition that are expected to have a meaningful impact on how patients feel or function in daily life, as well as guided by patient input.
- For a multidimensional concept, the content of the COA should ideally reflect the entirety of the concept in order for scores on a COA to be interpreted as indicators of a patient's status with respect to the concept.
- Testing both numeric and verbal rating scales in cognitive interviews to determine which scale type is the most appropriate to measure the selected symptom(s).

Regulatory Background and Materials Reviewed

- There have been previous communications with the Applicant regarding their COA measurement strategy for AD, the most recent include the following:

    - Type C Preliminary Comments dated April 16, 2020:
        - Expressed continued concern that the assessment of itch-related sleep disturbance via SSD may not yield meaningful, interpretable data in the AD population.
        - (b) (4)

    - Type B Meeting Minutes IND 117122 dated May 8, 2019:
        - Reiterated the limitations of the SD NRS and SSD for assessment of itch-related sleep disturbance in the AD population.
        - Communicated that the adequacy of the SD NRS and SSD would be a review issue.

    - Type B (End-of Phase 2) Meeting Minutes IND 117122 dated September 17, 2018:
        - Disagreed that a single item could sufficiently measure itch-related sleep disturbance due to its multidimensionality. Communicated that this item should be supplemented with a sleep diary and possibly other objective measures to adequately evaluate this concept.
        - Identified specific limitations of the SSD.

(b) (4)

(b) (4)

A list of materials reviewed are shown in Table 1 (shown on next page).

Table 1. Materials reviewed

Document	SDN	eCTD#	Date Received

BLA submission including: • Study body report and protocols for Studies ARCADIA 1 and 2 • (b) (4) • Evidence dossier for SD NRS and SSD EVM-22873 dated 31 Jan 2020 • Evidence dossier for SD NRS and SSD EVM-25004 dated November 6, 2023, Version 1.0 • EVM-25004 Appendix D-Exit interview substudy transcripts v1 dated 06 Oct 2023 • EVM-25004 Results of subgroup analysis, Appendix E of EVM-25004 exit interview sub-study report dated 06 Oct 2023 • EVM-25004 Phase III Exit interview sub-study with subjects with moderate to severe AD. Final report dated 06 Oct 2023 Version 2	1	0001	13 Dec 2023

Communications and Reviews	**DARRTS Ref ID**	**Date**
Type C Preliminary Comments IND 117122	4593293	16 April 2020
Type B Meeting Minutes IND 117122 IND 117122	4430247	08 May 2019
Type B End-of Phase 2 Meeting Minutes IND 117122	4321775	17 Sept 2018
Previous COA Review: C2020132_IND 117122_Choudhry	4598554	27 April 2020
Previous COA Review: C2019045_IND 117122_Choudhry	4406909	10 April 2019
Previous COA Review: C2018223_IND 117122_Choudhry	4360362	16 Dec 2018

Trial Design and Study Endpoints

Studies ARCADIA 1 and ARCADIA 2

Studies ARCADIA 1 and 2 were identical multicenter, randomized, double-blind, placebo-controlled, multicenter, parallel-group, phase 3 studies that assessed efficacy and safety of nemolizumab in adults and adolescents (≥12 years) with moderate-to-severe AD with a

documented history of inadequate response to topical AD medication(s). Eligible participants must also have had:

- An EASI score ≥ 16 at both the screening and baseline visits,
- An IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits,
- AD involvement ≥ 10% of body surface area (BSA) at both the screening and baseline visits
- A Peak (maximum) Pruritus Numeric Rating Scale (PP-NRS) score[3] of at least 4.0 at the screening and baseline visit.

For a complete list of the inclusion and exclusion criteria, refer to Sections 8.3.2 and 8.3.3 of the clinical study protocols for Studies ARCADIA 1 and ARCADIA 2.

The study endpoints for Studies ARCADIA 1 and ARCADIA 2 were:

Co-primary efficacy endpoints:

- Proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) at Week 16
- Proportion of subjects with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16

Secondary COA efficacy endpoint(s) (alpha controlled):

- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 16
- Proportion of subjects with PP NRS < 2 at Week 16
- Proportion of subjects with an improvement of sleep disturbance NRS (SD NRS) ≥ 4 at Week 16
- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 4
- Proportion of subjects with PP NRS < 2 at Week 4
- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 2
- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 1
- Proportion of subjects with EASI-75 and improvement of PP NRS ≥ 4 at Week 16
- Proportion of subjects with IGA success and improvement of PP NRS ≥ 4 at Week 16

Reviewer's comment(s): *There were several other secondary endpoints that were not adjusted for multiplicity. For a complete list of the study endpoints, refer to Section 6 of the clinical study protocols for Studies Olympia 1 and Olympia 2.*

[3] Screening PP NRS score will be determined by a single PP NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit. Baseline PP NRS score will be determined based on the average of daily PP NRS scores (score ranging from 0 to 10) during the 7 days immediately preceding baseline (rounding is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding baseline is required for this calculation.

COA Description(s)

Sleep Disturbance Numerical Rating Scale (SD NRS)

The SD NRS is a single-item patient-reported outcome (PRO) instrument designed to assess sleep loss related to symptoms of PN using an 11-point scale NRS ranging from 0 ("No sleep loss") to 10 ("I did not sleep at all"). The recall period is the previous 24 hours. The SD NRS was administered electronically daily from Screening (Visit 1) to Week 16. A copy of the SD NRS is in Appendix A.

For Studies ARCADIA 1 and ARCADIA 2, the SD NRS generated a weekly score that ranged from 0 to 10, with higher scores indicating greater sleep loss. The baseline weekly SD NRS score was determined based on the average of the SD NRS (score ranging from 0 to 10) during the seven days immediately preceding baseline (rounding to nearest whole number is not permitted). This calculation required a minimum of four daily scores (out of seven days immediately preceding the visit) across all study visits.

Subject Sleep Diary (SSD):

The SSD is an 11-item PRO instrument designed to record the subject's sleep pattern daily and how PN-related symptoms (e.g., itch, burning) can affect sleep. The diary collects information on self-reported sleep characteristics, such as time of getting into bed, time of attempting to fall asleep, time it takes to fall asleep, number and duration of awakenings related to PN and other causes, time of the final awakening, time getting out of bed, perceived quality of sleep, and restfulness after night sleep. Items are rated using various response scales (e.g., drop-down menu, free text, 5-point verbal rating scale). There is no specified recall period. The SSD was to be completed once daily in the morning and if possible, within one hour of getting out of bed. The content of the SSD is in Appendix B of this review. The screenshots of the SSD are available in Appendix B of the evidence dossier.

The SSD generates domain scores. Mean weekly SSD domain scores can be obtained based on the average of the SSD score or metric collected during seven consecutive days. The weekly scores were calculated at each visit of the treatment period; this calculation of the mean weekly SSD parameter/ domain scores required a minimum of four entries (out of seven days immediately preceding the visit) across all study visits.

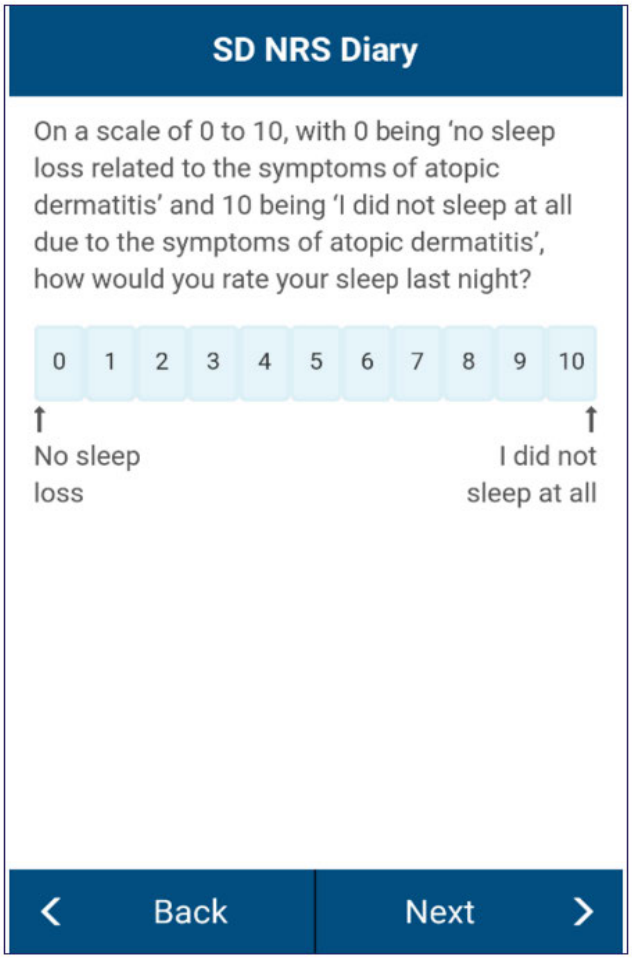
Reviewer's comment(s): *While there is no specified recall period, the diary is intended to be used to record the participant's sleep pattern the night before.*

Appendices

Appendix A: Sleep Disturbance Numeric Rating Scale (SD NRS)
Appendix B: Content of Subject Sleep Diary (SSD)
Appendix D: Summary of qualitative research

Appendix A: Sleep Disturbance Numeric Rating Scale (NRS)

Handheld device electronic SD NRS version:



Appendix B: Content of Subject Sleep Diary (SSD)

General Instructions	
Morning Sleep Diary	
The next two screens will provide you with some general questions that are meant to help you understand your Sleep Diary. Tap Next to continue. **What is a Sleep Diary?** A sleep diary is designed to gather information about your daily sleep pattern. **How often and when do I fill out the sleep diary**? Twice daily on designated days, once in the morning and if possible, within one hour of getting out of bed, and once daily in the evening. Tap Next to continue. **What do the words "bed" and "day" mean on the diary?** This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep. **Will answering these questions about my sleep keep me awake?** This is not usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate. Tap Next to continue. You will now complete your Morning Sleep Diary. Tap Next to continue.	
Item Question/Instruction/Response Option(s)	**Item Question/Instruction/Response Option(s)**
1. What time did you get into bed? ***Instructions:*** *Enter the time that you got into bed. This may not be the time you began "trying" to fall asleep.* [Time:]	7. In total, how long did these **awakenings related to other things (for example to drink water, to go to the bathroom)** last? ***Instructions:*** *For example, if you woke 4 times during the night: 5 minutes (to go to the bathroom), 35 minutes (to scratch), 5 minutes (to drink water) and 20 minutes (to scratch), only two times were related to other things, for a total of 10 minutes (5 + 5 =10 minutes).* [Hours:] [Minutes:]
2. What time did you try to go to sleep? ***Instructions:*** *Record the time that you began "trying" to fall asleep.* [Time:]	8. What time did you wake up for the day? **Instructions:** *Record the last time you woke up in the morning.* [Time:]
3. How long did it take you to fall asleep? ***Instructions:*** ***Beginning at the time you entered** in question 2, how long did it take you to fall asleep.* [Hours:] [Minutes:]	9. What time did you get out of bed for the day? ***Instructions:*** *What time did you get out of bed with no further attempt at sleeping? This may be different from the time you wake in the morning (e.g., you may have woken up at 6:35 a.m. but did not get out of bed to start your day until 7:20 a.m.)* [Time:]

General Instructions

4. How many times did you wake up **due to the symptoms of atopic dermatitis (for example itching, burning)**, not counting the final time you woke up for the day?

Instructions:

For example, if you fell asleep at 11pm, and woke up at 2am (to go to the bathroom), 4am (to scratch), 5am (to drink water), 6 am (to scratch) and finally woke up at 7:30am, you woke up twice due symptoms of atopic dermatitis.

[Free-text box for a number]

10. How would you rate the quality of your sleep?

Instructions:

"Sleep Quality" is your sense of whether your sleep was good or poor.

- ☐ *Very poor*
- ☐ *Poor*
- ☐ *Fair*
- ☐ *Good*
- ☐ *Very Good*

5. In total, how long did the **awakenings related to the symptoms of atopic dermatitis (for example itching, burning)** last?

Instructions:

For example, if you woke up 4 times during the night: 5 minutes (to go to the bathroom), 35 minutes (to scratch), 5 minutes (to drink water) and 20 minutes (to scratch), only two times were related to the symptoms of atopic dermatitis, for a total of 55 minutes awake (35+20=55 minutes).

[Hours:]

[Minutes:]

11. How rested or refreshed did you feel when you woke-up for the day?

Instructions:

*This refers to how you felt after you were done sleeping for the night, **during the first few minutes** that you were awake.*

- ☐ Not at all rested
- ☐ Slightly rested
- ☐ Somewhat rested
- ☐ Well-rested
- ☐ Very-well rested

6. How many times did you wake up, **for other things (for example to drink water, to go to the bathroom)**, not counting the final time you woke up for the day?

Instructions:

For example, if you fell asleep at 11pm, and woke up at 2am (to go to the bathroom), 4am (to scratch), 5am (to drink water), 6 am (to scratch) and finally woke up at 7:30am, you woke up twice due to other things not related to atopic dermatitis.

[Free-text box for a number]

Closing Message

Thank you. You have provided all required responses. You can check your responses by selecting Back.

Select OK and then Next when ready to save your responses.

- ☐ Ok

Evening Sleep Diary

The next two screens will provide you with some general questions that are meant to help you understand your Sleep Diary.

Tap Next to continue.

What is a Sleep Diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? Twice daily on designated days, once in the morning and if possible, within one hour of getting out of bed, and once daily in the evening.

Tap Next to continue.

What do the words "bed" and "day" mean on the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep.

Will answering these questions about my sleep keep me awake? This is not usually a problem.

You should not worry about giving exact times, and you should not watch the clock. Just give your best estimate.

Tap Next to continue.

General Instructions	
You will now complete your Evening Sleep Diary. Tap Next to continue.	
Item Question/Instruction/Response Option(s)	**Item Question/Instruction/Response Option(s)**
Q1. How many times did you nap? ***Instructions:*** *A "nap" is a time you decided to sleep during the day, whether in bed or not in bed. Count all the times you napped at any time from when you first got out of bed in the morning until you got into bed again at night.* [Free-text box for a number]	Q3. How many times did you doze off? ***Instructions:*** *"Dozing" is a time you may have nodded off for a few minutes, without meaning to, such as while watching TV. Count all the times you dozed at any time from when you first got out of bed in the morning until you got into bed again at night.* [Free-text box for a number]
Q2. In total, how long did you nap? ***Instructions:*** *Estimate the total amount of time you spent napping. For example,* *if you napped twice, once for 30 minutes and once for 60 minutes, please add them up (30+60=90 minutes or 1 hour 30 minutes).* [Hours:] [Minutes:]	Q4. In total, how long did you doze off? ***Instructions:*** *Estimate the total amount of time you spent dozing. For example, if you dozed twice for 5 minutes, please add them up (5+5=10 minutes).* [Hours:] [Minutes:]
Closing Message	
Thank you. You have provided all required responses. You can check your responses by selecting Back. Select OK and then Next when ready to save your responses. ☐ Ok	

Appendix C: Summary of Qualitative Research

The Applicant completed the following instrument development activities to evaluate the content validity of the SD NRS and SSD:

- Literature review
- Expert Input
- Patient input (hybrid concept elicitation and cognitive interviews in adults; cognitive interviews in adolescents; exit interviews)

A summary of the results for each activity and instrument is described below. Refer to the Applicant's PRO evidence dossier (SDN 1, received date December 13, 2023) for full details regarding the methodology and results of each activity.

Literature review

A literature review was conducted to identify PRO measures used in AD to collect patient experience data. A total of 34 PRO measures were identified, two of which were AD-specific PRO measures. The six instruments most frequently used to assess AD-related SD included:

- Single-item (i.e., SCORAD Sleep Loss VAS)
- Multi-item PROs (i.e., Patient-Oriented Eczema Measure [POEM], Pittsburgh Sleep Quality Index [PSQI], Medical Outcomes Study [MOS] Sleep, Patient-Reported Outcomes Measurement Information System [PROMIS]-SD, and PROMIS-sleep-related impairment).

The Applicant concluded that none of the identified PROs were specifically designed and validated to assess sleep disturbance in patients with AD. Per the Applicant, the MOS-Sleep, PROMIS-SD, or PSQI are relevant in terms of coverage of the sleep disturbance concept, however, they noted that these instruments fail to accurately capture the daily variations of sleep disturbance. They further indicated that patients may have difficulties averaging their response to these measures due to 1 week recall period.

Expert input

- SD NRS
  The evidence dossier indicates that the original SD NRS was developed by the Sponsor clinical team. However, there is no other additional information provided to summarize the expert input.

- SSD
  The evidence dosser indicates that feedback from clinical experts were used to develop the Consensus Sleep Diary (CSD)[4], in which the SSD was initially adapted from. However, there is no other additional information provided to summarize the expert input.

[4] The CSD is a tool for tracking nightly subjective sleep in patients with insomnia. The CSD has a morning and an evening version. The content validity of the CSD was evaluated in six focus groups that included 46 self-diagnosed individuals: 14 good sleepers, 18 with insomnia, and 14 with sleep apnea.

Patient input

The Applicant conducted hybrid concept elicitation and cognitive interviews in US adults and adolescents with moderate-to-severe AD and moderate-to-severe pruritus for the following objectives:

- Evaluate the content relevance of the SD NRS.
- Assess patient understanding of the instructions, items, response options, recall period of the SD NRS, as well as ease of completion.
- Explore the patients' perspectives on meaningful change on the SD NRS.
- Provide recommendations on any revisions to the SD NRS and/or justification for the

This section will summarize the results specific to the SD NRS and SSD.

- 30 participants (n= 20 adults; n= 10 adolescents) with AD were interviewed via telephone (90 minutes each).
    - Adult sample
        - The majority of the participants were White (n=8/20, 40.0%) and Asian (n=7/20, 35.0%), female (n=12/20, 60.0%) with a mean age of 33.5 ± 12.8 years (range 18-63).
    - Adolescent sample
        - The majority of the participants were Asian (n=5, 50%) and White (n=4, 40%), female (n=5/10, 50.0%) with mean age of 14 years ± 1.9 years (range 12-17 years).

Reviewer's comments: *The level of education for the qualitative sample was not included in the qualitative study report.*

Concept elicitation

- Adult sample
    - The most commonly reported symptom was itching (reported by 100%; n=30) of the participants. Of note, 50% (n=10/20) of the adult participants did not report itching spontaneously.
    - Participants described their AD experience as having dry skin (n=11/20, 55%), bleeding (n=8/20, 40%), inflamed skin (n=7/20, 35%) and open wounds (n=6/20, 30%).
    - Participants described that their itching was variable based on their certain conditions. Most adults (n=9/20, 45%) mentioned that the weather and day to day (non-specific) caused an increase in itching.
    - Most participants (n=19/20, 95%) noted that itch occurrence was daily.
    - One-quarter of participants described their itch by rating it on a scale of 0 to 10, moving from ''not severe'' to ''very severe''. The scores provided were 3 (n=1/20, 5%), 6 (n=1/20, 5%), 7 (n=2/20, 10%), and 8 (n=1/20, 5%).
    - Adults indicated the itch affecting their legs (n=10/20, 50%), arms (n=8/20, 40%), back (n=7/20, 35%), face (n=5/20, 25%), everywhere (n=5/20, 25%), chest (n=4/20, 20%), neck (n=4/20, 20%), stomach (n=3/20, 15%), hands (n=2/20, 10%),

knees (n=2/20, 10%), elbows (n=2/20, 10%), breasts (n=2/20, 10%), wrists (n=1/20, 5%), feet (n=1/20, 5%), torso (n=1/20, 5%), ankles (n=1/20, 5%), chin (n=1/20, 5%), shoulders (n=1/20, 5%) and abdominal area (n=1/20, 5%).

- More than half of the participants (n=11/20, 55%) endorsed experiencing emotional impacts because of the itch. Several adult participants also described the emotional and psychological impacts of their skin condition sharing the ‘‘annoyance’’ (n=1/20, 5%), ‘‘stress’’ (n=1/20, 5%), ‘‘self-consciousness’’ (n=1/20, 5%), ‘‘bad feeling’’ (n=3/20, 10%), ‘‘inability to function’’ (n=2/20, 10%) and ‘‘subconscious scratching they undergo’’ (n=1/20, 5%).
- Some participants (n=7/20, 35%) indicated having negative impacts on their social life due to the itch.
- Half of the participants (n=10/20, 50%) reported experiencing impacts on their daily activities. A third of the participants (n=7/20, 35%) reported having an impact on their physical activities (e.g., inability to go to pools, participate in sporting events).
- Most participants (n=16/20, 80%) reported experiencing issues falling asleep related to itch, as well as having issues staying asleep due to itch (n=18/20, 90%).
- Most participants (n=14/20, 70%) reported having the quality of their sleep being impacted by the itch.
- Most participated reported experiencing night-time awakenings (n=18/20, 90%), trouble falling asleep (n=16/20, 80%), and feeling unrested (n=12/20, 60%). Some participants also experienced day time fatigue or sleepiness (n=11/20, 55%), a feeling as if they did not get enough sleep (n=6/20, 30%) and early morning awakening (n=1/20, 5%).
- Most participants (n=14/20, 70%) reported daily sleep disturbance. For those who did not experience the disturbance daily, noted that it occurred once a week, once or twice a week, a “couple times” a week, or 2 or 3 times a week (n=1/20, 5% for each). Some participants (n=2/20, 10%) did not specify the number of days a week the disturbance occurred.
- Responses regarding the number of nighttime awakenings due to AD symptoms and duration of awakenings varied.
- Of those asked, a third of participants (n=7/19, 35%) attributed the sleep disturbance solely to the itching from their AD. The remaining participants attributed the sleep disturbance to both itching and other non-AD causes (e.g., consuming caffeinated drinks (e.g., Monster, coffee), bright streetlights shining in, and wearing bothersome clothing, or having asthma (n=1/20, 5% for each)).
- Most participants (n=12/19, 63%) mentioned feeling more tired, fatigued, or drowsy during the day. Some participants (n=6/19, 32%) discussed an impact on work, while others (n=2/19, 11%) said it impacted their mood, reporting feeling impatient, snappy, irritable, or not “cheery.”

- Adolescent sample
  - Participants described their AD experience as having dry skin (n=6/10, 30%), flaking (n=5/10, 50%), bleeding (n=3/10, 30%), burning (n=3/10, 30%) redness (n=3/10, 30%), and pain (n=3/10, 30%).
  - Most participants (n=9/10, 90%) endorsed a daily occurrence of itch.

- Participants described their itch as not too bad (n=3/10, 30%), not as bad (moderate) (n=2/10, 20%) and pretty bad (n=3/10, 30%).
- Participants reported the itching affecting their neck (n=6/10, 100%), arms (n=4/10, 40%), knees (n=3/10, 30%), elbows (n=4/10, 40%), legs (n=5/10, 50%), ears (n=1/10, 10%), ankles (n=1/10, 10%) and everywhere (n=1/10, 10%).
- Some participant (n=4/10, 40%) endorsed experiencing emotional impacts because of itch. These participants experienced ‘‘depression’’ (n=1/10, 10%), ‘‘self-consciousness’’ (n=1/10, 10%), ‘‘embarrassment’’ (n=1/10, 10%) and ‘‘frustration’’ (n=1/10, 10%) as the most commonly mentioned emotional impacts by participants.
- Two adolescents (n=2/10, 20%) reported having negative impacts on their social life due to the itch.
- One participant (n=1/10, 10%) reported experiencing impacts on their daily activities. While others (n=4/10, 40%) reported having an impact on their physical activities (e.g., inability to go to pools, participate in sporting events).
- Most participants (n=6/10, 60%) reported experiencing issues falling asleep related to itch, as well as having issues staying asleep due to itch (n==8/10, 80%).
- A third of participants (n=3/10, 30%) reported having the quality of their sleep being impacted by the itch.
- Most participants reported experiencing night-time awakenings (n=8/10, 80%), followed by experiencing trouble falling asleep (n=6/10. 60%) and daytime fatigue or sleepiness (n=5/10, 50%). Less than half of them experienced early morning awakening, a feeling as if they did not get enough sleep, and feeling unrested (n=4/10, 40% for each).
- The majority of participants (n=7/10, 70% each) experienced sleep disturbance 3 days a week, a “few times” a week, “weekly,” or not every day. A smaller percentage of adolescents (n=3/10, 30%) than adults experienced sleep disturbance daily.
- Responses regarding the number of nighttime awakenings due to AD symptoms and duration of awakenings varied.
- Of those asked, a third of participants (n=3/7, 30%) attributed the sleep disturbance solely to the itching from their AD. They noted AD-related symptoms impacted their sleep with itching being mentioned most commonly (n=5/7, 71%), followed by inflammation (n=1/7, 14%).
- Of those asked, half of the participants (n=5/9, 56%) also described feeling more tired, fatigued, or drowsy during the day. Most participants (n=6/9, 67%) also experienced an impact on school.

Reviewer’s comment(s):

- *While the qualitative sample included an important demographic subgroup (i.e., Asians) for AD, the sample was missing other important demographic subgroups (i.e.,*

Blacks). AD has been found to occur more frequently in Asian and Black individuals than Whites[5].

- *The qualitative sample included 10 adolescents, which may not have been sufficient numbers based on the saturation tables.*
- *It is unclear what the extent of importance of sleep disturbance is to the target population as it appears participants were not asked about how important or bothersome this impact was in relation to other impacts. Further, only a third of participants in both the adult and adolescent sample reported itch as the cause of their sleep disturbance.*
- *There are many different aspects of sleep disturbance. Based on the qualitative data, most adult and adolescent participants reported experiencing nighttime awakenings and issues falling asleep related to itch. This reviewer notes that fewer adolescents reported that sleep quality was impacted by itch compared to adults. It is unclear how sleep quality was defined.*

Cognitive interviews

- SD NRS
  - Adult sample
    - All participants (n=20/20, 100%) completed the SD NRS and provided descriptions of their understanding that aligned with its intended meaning.
    - All participants reported that it was 'easy' or 'very easy' to select a response on the 0-10 scale SD NRS.
    - Most participants (n=19/20, 95%) described the "No sleep loss" anchor as intended.
    - Among participants who completed the SD NRS scale (n=20/20, 100%), a few (n=5/20, 25%) provided suggestions for improving the item. Of these adults,
      - Some (n=3/20, 15%) suggested replacing the abbreviation "AD" with "atopic dermatitis."
      - A couple of them (n=2/20, 10%) also suggested adding "eczema" in parenthesis next to "atopic dermatitis."
      - Two participants (n=2/20, 10%) recommended changes to the response options, one of whom (n=1/20, 5%) recommended reducing the response option scale to 1 to 5, while the other (n=1/20, 5%) recommended adding "getting better" next to the anchor description of "no sleep loss."

  - Adolescent sample
    - All participants (n=10/10, 100%) completed the SD NRS and provided descriptions of their understanding that aligned with its intended meaning.
    - Most participants (n=9/10, 90%) stated that it was easy to select a response to the question.

[5] Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups-Variations in epidemiology, genetics, clinical presentation and treatment. Exp Dermatol. 2018 Apr;27(4):340-357. doi: 10.1111/exd.13514. PMID: 29457272.

- All adolescent participants (n=10/10, 100%) explained the meaning of the "No sleep loss" and "I cannot sleep at all" anchors properly.
- A couple of participants (n=2/10, 20%) suggested including the term "eczema" instead of "atopic dermatitis." One participant (n=1/10, 10%) recommended adding a description under the response option for 5 on the scale.

Reviewer's comment(s):
While the Applicant's conclusion was that most of the participants had no issues with the overall understanding/clarity of the SD NRS, this reviewer notes the following:

- *It remains unclear what attribute of sleep loss is being measured with the NRS (e.g., severity, frequency, amount of sleep).*
- *The recall period of the SD NRS was not cognitively tested.*

Overall, the Applicant has provided insufficient evidence to support the content validity of the SD NRS. Due to the content validity issues, the other measurement properties and score interpretability of the SD NRS was not reviewed.

- SSD
  - Adult sample
    - All participants (n=20/20, 100%) completed the SSD.
    - Most participants (n=18/20, 90%) expressed favorable opinions of the SSD.
    - A third of participants (n=7/20, 35%) recommended at least 1 additional item. The following questions were suggested:
      - ''how many times a week or month do you get so frustrated with your inability to sleep that you either end up staying awake?''
      - ''do you always choose to take [sleep] medication to help you fall asleep?''
      - ''how much do you shower a day as a result of itching from dry skin?''
      - ''what kind of soap do you use?''
      - ''how severe is the itching?''
      - ''how long did the itching last?''
    - Less than half of participants (n=9/19, 47%) confirmed that they read the instructions prior to completing the SSD.
    - Most participants (n=16/20, 80%) reported that they could differentiate between the questions in the SSD that had to be completed in the morning and in the evening.
    - Three-quarters of the participants stated that the examples in the SSD were helpful.
    - When asked if any of the instructions or examples for the individual Sleep Diary items needed to be reworded, less than one-quarter of participants (n=4/20, 20%) commented that one or more instructions should be needed improvement.

  - Adolescent sample
    - All participants (n=10/10, 100%) completed the SSD.
    - All participants (n=10/10, 100%) expressed favorable opinions of the SSD.

- Most participants (n=8/10, 80%) shared that they read the instructions.
- Most participants (n=7/10, 70%) reported that they could differentiate between the questions in the SSD that had to be completed in the morning and in the evening.
- All participants (n=10/10, 100%) stated that the examples in the SSD were helpful.

Reviewer's comment(s):
While the Applicant concludes that the majority of the participants had a good understanding of the SSD, the Applicant also noted that half of the participants (n=15/30, 50%) did not read the instructions prior to completing the paper version of the diary because there were included at the end of the diary. It appears the position of the instructions for the SSD were changed for the phase 3 studies. For the pivotal studies, the SSD was administered electronically, and participants were instructed to complete the nighttime-related items once daily in the morning (i.e., within 1 hour of getting out of bed), with the daily SD NRS. Day time-related items were to be completed once daily in the evening, with the PP NRS and AP NRS. Morning and evening alarms were implemented in the device to remind the patients to complete the diary and minimize missing assessments.

This reviewer acknowledges that the SSD provides information about the participant's sleep experience. However, it is still unclear which aspects of sleep disturbance or loss is of most importance to patients with AD. This reviewer observed that the responses to the SSD items were variable based on the ranges provided around participants responses to the SSD. As such, each participant tends to have a unique sleep experience. Further, the qualitative findings indicated that sleep disturbance or sleep loss may not be directly due to AD. For example, other non-AD factors reported included consumption of caffeinated drinks (e.g., Monster, coffee), bright streetlights shining in, wearing bothersome clothing, having asthma, school-related stress, using the phone before bed, etc. All of these factors make data interpretation difficult.

Exit Interviews[6]
The Applicant also conducted one-on-one telephone interviews (90 minutes) in a subset of participants from Study ARCADIA 1 for the following objectives:

- Understand the meaning and importance of changes in patients' experience of AD that are potentially associated with the study treatment, including the AD-associated symptoms (e.g., itching, dry skin, skin redness, skin pain) and impacts on health-related quality of life (HRQoL) domains (e.g., impact in sleep, emotions, and daily activities)—specifically, which aspects trial participants perceive as most relevant and meaningful.
- Provide additional supportive evidence on the relevance and importance of the SD concept to the target population.
- Document the relationship between itching and SD related concepts.
- Describe the patients' experiences with the disease during the trial (i.e., perceived change and magnitude of change) by relevant subgroups (when sample size permits)

[6] EVM-25004 dated 6 October 2023 Version 2: Phase III (CD141152) Exit Interview Sub-study with Subjects with Moderate to Severe Atopic Dermatitis, Final Report (SDN 1)

including by age group (adolescents vs adults), treatment arm (nemolizumab vs placebo) and severity group strata at baseline (patients from the PP NRS ≥7 group strata vs patients from the PP NRS <7 group strata).
- Collect information about treatment expectations and satisfaction.

Trial participants were interviewed at the end of the initial treatment period i.e., within two weeks following week 16 visit.

The results of the exit interviews are summarized as follows (Note the results presented are specific to itch and sleep disturbance):

- A total of 73 patients were interviewed across four participating countries: United States (US) (n=40/73, 55%), Canada (n=18/73, 25%), Australia (n=8/73, 11%), and Great Britain (n=7/73, 10%. Of these, 66 were adults (n=66/73, 90%) and 7 were adolescents (n=7/73, 10%).
- Over half of participants were female (n=38/73, 52%) with a mean age of 37.4 years (SD = 16.3; median [range] = 33 [13-70]).
- At baseline, 51 participants (n=51/73, 70%) had moderate-to severe itch (PP NRS ≥7).
- Over three-quarters of the patients (n=61/73, 84%) were classified as non-responders (as defined as a subject whose Eczema Area and Severity Index (EASI) score experienced ≥75% improvement from baseline and have an Investigator's Global Assessment (IGA) score of 0 or 1 and a ≤ 2-point reduction from baseline at Week 16).
    - Ten adults (n=10/66, 15%) and two adolescents (n=2/7, 29%) were responders.
- The most commonly reported symptoms were: itch (n=73/73, 100%), dry skin (n=70/73, 96%), skin redness (n=66/73, 90%), peeling/scaly/flaky skin (n=63/73, 86%), bleeding skin (n=60/73, 82%), open wounds (n=58/73, 80%), painful skin (n=51/73, 70%), sensitive skin (n=50/73, 69%), skin discoloration (n=45/73, 62%), and burning sensation (n=43/73, 59%).
- Of the patients who reported their worst or most burdensome symptom at the study entry, all patients mentioned itch (n=43/43; 100%). Other most frequently reported symptoms considered worst were peeling/flaky/scaly skin (n=9/43; 21%), skin redness (n=8/73; 19%), painful and dry skin (each reported by n=6/73; 14%) and burning sensation (n=5/73; 12%).
- Patients were asked to assess the severity of their itch at study entry and at the time of the interview on a 0 to 10 scale (0=not severe and 10=extremely severe). The mean severity [range] of itch was 8.1 [2.0–10.0] at study entry and 3.2 [0.0–10.0] at the time of the interview, showing a 4.9-point improvement among the total population interviewed.
- Regarding change in symptom severity,
    - By age group (adults vs adolescents): Adolescent patients reported the largest improvements in severity for most of the symptoms except for skin bleeding, open wounds, lumps/ bumps/ blisters. Results should be interpreted with caution given the small sample size in the adolescent group.
    - By severity strata (≥ 7 or < 7 on the PP NRS): Patients with less severe itching at study entry (PP NRS < 7 severity group strata) reported the largest improvements for most of the symptoms, except for painful pain, sensitive skin, and skin scabs/crusts.

    - Treatment arm (nemolizumab vs placebo): Patients on nemolizumab demonstrated the largest improvements in symptom severity for most of the symptoms, except for skin discoloration and skin inflammation/flare.
- Patients were asked whether the AD symptoms that they had been experiencing prior to the study changed ("worsening" or "improvement") or stayed the same ("no change") during the clinical trial. Results on change and magnitude of change are as follows:
    - Seventy-two patients (n=72/73, 99%) reported on change in itch during the clinical trial, with most patients experiencing an improvement (n=62/72, 86%). The remaining patients either experienced no change or worsening of itch (n=5/72, 7% each). Among those who reported a change (n=72/73, 99%),
    - Over two-thirds of participants reported that the itch change was meaningful (n=61/72, 85%).
    - Among the patients who reported on the magnitude of change (n=62/72, 85%), almost all patients reported either "a little better" (n=12/62, 19%) or "much better" (n=47/62, 76%). The remaining three patients either reported "much worse" (n=2/62, 3%) or "same" (n=1/62, 2%).
- All seventy-three patients (n=73/73; 100%) reported experiencing itch prior to the clinical trial, 69 (95%) mentioned it spontaneously and 4 (5%) endorsed this when probed.
    - Most patients used synonyms to describe their itch experiences, such as "itching/itchy/itchiness" (n=26/35; 74%) and "scratch/scratching" (n=9/35; 26%). Thirteen patients (n=13/73; 18%) reported that their itch caused other symptoms.
    - Thirty patients (n=30/73; 41%) provided a description of their itch severity. Several descriptors were identified, with the severity described as "really bad," "extreme," and "very itchy" (n=5/30; 17% each), "severe" (n=4/30; 13%), "the worst" (n=3/30; 10%), and "intense" (n=2/30; 7%). Other patients reported that the severity was "pretty severe," "moderate," "15 out of 10," and "would leave skin red" (n=1/30; 3% each).
    - Fifty patients (n=50/73; 69%) provided a description of their itch frequency. Of these patients, 42 experience itch continuously (n=42/50; 84%), described as "everyday" (n=25/42, 60%), "seven days a week" (n=7/42; 17%), "daily" (n=4/42; 10%), "all the time," "never goes away," and "constantly" (n=2/42; 5% each).
    - Most patients (n=8/12; 67%) described varied experiences, noting that itching would fluctuate (n=4/8; 50%): "come and go" "come in bursts," appear "all of the sudden," and get better then worse again (n=1/8; 13% each). The remaining 4 patients (n=4/12; 33%) reported that their itch was consistent "throughout the day" (n=2/4; 50%), was "pretty much persistent" during the day, and that they "couldn't get rid of the itch" (n=1/4; 25% each).
- Participants reported a total of 45 AD-related impacts across six domains which included emotional impacts (n=68/73, 93%), daily activities (n=66/73, 90%), SD (n=63/73, 86%), social impacts (n=52/73, 71%), relationship impacts (n=39/73, 53%) and other AD impacts (n=28/73, 38%).
    - More than half of the study participants reported the following impacts: night-time awakenings (n=57/73, 78%), difficulty falling asleep (n=49/73, 67%),

unspecified sleep disturbance (n=48/73, 66%), impact on clothing (n=46/73, 63%) embarrassment/self-consciousness (n=46/73, 63%), frustration/anger (n=46/73, 63%), anxiety/worry (n=40/73, 55%), feeling unrested/unrefreshed (n=39/73, 53%), sleep disturbance-related daytime fatigue/tiredness (n=38/73, 52%), sports (n=38/73, 52%), and lack of sleep (n=37/73, 51%).
    - Of the subjects who reported their worst or most burdensome impacts at the study entry (n=52/73, 71%), over a third of participants reported impacts related to sleep disturbance as the worst impact. With respect to specific most bothersome or worst AD impacts across impact domains, the most frequently reported were unspecified sleep disturbance (n=13/52, 38%), embarrassment/self-consciousness (n=12/52, 23%), impact on clothing (n=6/52, 12%), and difficulty falling asleep (n=5/52, 10%).
- The majority of participants (n=63/73, 86%) reported experiencing 11 sleep disturbance impacts prior to the trial. Of these, six impacts were reported by at least 50% of the study population and included night-time awakenings (n=57/73, 78%; spontaneous: n=37; probed: n=20), difficulty falling asleep (n=49/73, 67%), unspecified sleep disturbance (n=48/73, 66%), feeling unrested/unrefreshed (n=39/73, 53%), daytime fatigue/tiredness (n=38/73, 52%), and lack of sleep (n=37/73, 51%).
    - With respect to the worst or most burdensome impact prior to the study, 38% of patients (n=20/52) reported sleep disturbance as worst impact i.e., unspecified sleep disturbance (n=13/52; 25%), difficulty falling asleep (n=5/52; 10%), night-time awakening (n=2/52; 3%), and daytime fatigue or tiredness (n=1/52; 2%). Of these, who reported night-time awakening (n=57/73, 78%) and difficulty falling asleep (n=49/73, 67%), 75% and 67% of patients attributed these impacts to itch and/or scratching due to their AD (n=43/57 and n=33/49, respectively). Twenty-two patients (n=22/48, 46%) described unspecified sleep disturbances due to itching/scratching.
- Patients were asked whether the AD impacts that they had been experiencing prior to the study changed ("worsening" or "improvement") or stayed the same ("no change") during the clinical trial. Then, they were asked about the magnitude of change on a 5-point scale (much worse, little worse, same, little better, much better). Results on change and magnitude of change included the following:
    - Overall, among the participants who reported a change in SD impacts (41% to 85% of subjects), most (≥73% to 88%) reported an improvement in all concepts. A lower proportion of subjects (10% to 27%) reported no change, while worsening was reported by up to 8% of the subjects.
    - The proportion of participants, who reported improvements in sleep disturbance concepts, was higher by 18-42% in the nemolizumab group compared to those in the placebo group, largest differences were observed for feeling unrested/ unrefreshed (42% difference), difficulty failing asleep (38% difference), and lack of sleep (39% difference).
    - Among patients who reported a change in sleep disturbance impacts (14% to 85%),
        - Over a third reported a meaningful change in nighttime awakenings (n=15/39, 38.5%)

        - Half reported a meaningful change in difficulty falling asleep (n=13/26, 50.0%)
- Approximately half of patients (n=33/68, 49%) confirmed their difficulty to fall asleep was related to AD. The remaining patients reported that the difficulties were either "sometimes" (n=19/68, 28%) or not related (n=16/68, 24%) to AD.
- Most participants (n=47/73, 64%) reported the study treatment met their expectations. Some participants believed the treatment did not meet their expectations (n=13/73, 18%) or reported no expectations (n=7, 10%).

Reviewer's comment(s):
Per the Applicant, the qualitative exit interview sub-study sample was found to be representative of the phase 3 clinical trial. The notable exceptions were within countries and clinical responder groups. Patients within the US (32.6% difference), Canada (14.7% difference), and the non-responder group (13.6% difference) were overrepresented in the sub-study sample. The responses from the study sample do not appear to be consistent to the sample being non-responders (i.e., participants are reporting changes or improvement in itch and sleep disturbance despite not achieving AD clearance).

The exit interviews do support the relevance of itch in AD. While the data does demonstrate that participants experience impacts in sleep disturbance, similar to previous qualitative research, it is still unclear what aspect of sleep disturbance is most important to this target population. Over a third of participants (n=20/52, 38%) reported impacts related to sleep disturbance as the worst impact, however the exact nature of sleep disturbance impact was not specified by participants (n=13/52, 38%). This further corroborates that there may be secondary factors other than AD that could result in sleep disturbance.

Due to time constraints, the interviewers were not able to elicit data on perceived change in all eleven sleep disturbance impacts. As such, some of the results are difficult to interpret as the denominator is not clearly specified in the study report.

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/s/

YASMIN A CHOUDHRY
08/01/2024 03:53:02 PM

SELENA R DANIELS
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HUMAN FACTORS STUDY REPORTS REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 30, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761390 and BLA 761391
Product Type:	Combination Product (Biologic-Device)
Product Name, Dosage Form, and Strength:	Nemluvio[1] (nemolizumab-ilto)[2] injection, 30 mg
Device Constituent:	(b) (4) Dual Chamber Autoinjector (AI)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Galderma Laboratories, L.P. (Galderma)
Submission Date:	December 12, 2023; January 10, 2024; February 6, 2024; March 21, 2024; April 22, 2024
TTT ID #:	2024-7726; 2024-7724
DMEPA 1 Human Factors Evaluator:	Lisa Huang, PharmD, MPH
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP
DMEPA 1 Director:	Mishale Mistry, PharmD, MPH

[1] The proposed proprietary name Nemluvio was found conditionally acceptable on March 13, 2024.

[2] The proposed nonproprietary name suffix -ilto was found conditionally acceptable on June 11, 2024.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) study results reports submitted under BLA 761390 and BLA 761391 for Nemluvio (nemolizumab-ilto) injection 30 mg, [redacted] (b) (4) [redacted] dual chamber autoinjector (AI) for the indications listed in Table 2 below.[3]

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

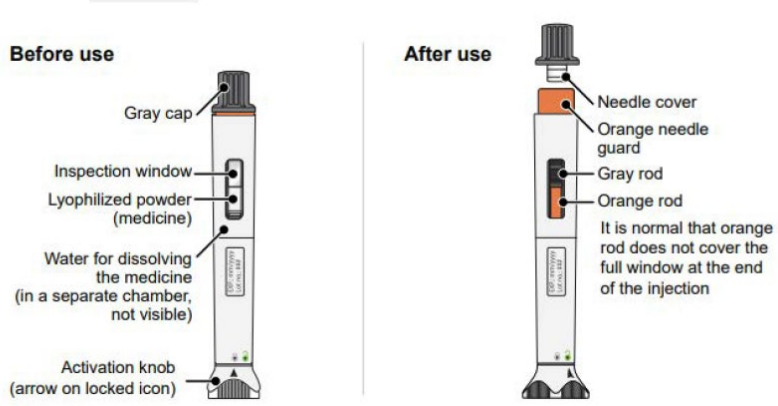
Material Reviewed	Section/Appendix
Product Information/Prescribing Information	Section 1.1
Background Information Previous HF Reviews (DMEPA)	Section 1.2
Human Factors Study Reports	Appendix A
Information Requests Issued During the Review	Appendix B
Labels and Labeling	Appendix C
Detailed List of Use Errors, Use Difficulties, And Close Calls for Section 3.1	Appendix D

[3] The Applicant uses the abbreviations [redacted] (b) (4) [redacted] dual chamber cartridge autoinjector (DCC AI) throughout their submissions for these device presentations.

1.1 PRODUCT DESCRIPTION

Table 2. Relevant Product Information for Nemluvio	
Initial Approval Date	N/A
Active Ingredient	Nemolizumab-ilto
Indication	• Atopic Dermatitis (AD): Adult and adolescent patients aged 12 years and older with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies (b) (4) (b) (4)[4] • Prurigo Nodularis: (PN): Adults aged 18 years and older
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	• (b) (4) dual chamber AI: 30 mg
Dose and Frequency	**AD** • Adolescent (≥ 12 years) and adult patients: initial dose of 60 mg (two 30 mg injections in different injection sites), followed by 30 mg every 4 weeks • The maintenance dose might be 30 mg every (b) (4) 8 weeks **PN** • Adult patients with a body weight below 90 kg: an initial dose of 60 mg (two 30 mg injections in different injection sites), followed by 30 mg every 4 weeks • Adult patients with a body weight ≥ 90 kg: 60 mg (two 30 mg injections in different injection sites) every 4 weeks
How Supplied	(b) (4) • Pre-filled, (b) (4) single-dose dual chamber AI o 30 mg lyophilized powder with 0.49 mL water for injection
Storage	Store under refrigerated conditions 2°C to 8°C (36°F to 46°F) in the original carton. Protect from direct sunlight. Can be stored at room temperature up to 25°C (77°F) for up to 90 days.

[4] Nemluvio [Prescribing Information] for Atopic Dermatitis indication. Available from: \\CDSESUB1\EVSPROD\bla761391\0001\m1\us\annotated-draft-labeling-text.pdf

Container Closure/Device Constituent	(b) (4) **Dual Chamber AI:** 
Intended Users	• AD: patients 12 years and older; caregivers; healthcare professionals (HCPs) • PN: adult patients; caregivers; HCP
Intended Use Environment	• Home; clinic

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On January 15, 2024, we searched previous DMEPA reviews relevant to this current review using the terms, *"IND 117122", "BLA 761390", "BLA 761391"* and *"nemolizumab"*. Our search identified six reviews, and we considered our previous recommendations to see if they are applicable for this current review. See details below.

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(b) (4)

- On June 21, 2021, Galderma submitted an HF validation protocol for their proposed dual chamber AI for the atopic dermatitis and prurigo nodularis indications under IND 117122. We reviewed the protocol and provided recommendations.[10]
- On May 20, 2022, Galderma submitted clarifying questions regarding the acceptability of their HF validation study methodology in response to recommendations that we made during the previous HF validation study protocol review for their proposed dual chamber AI. We provided responses to the clarifying

(b) (4)

[10] Kumar, N. HF Protocol Review for Nemolizumab (IND 117122). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 NOV 30. RCM No.: 2021-1216.

questions and confirmed our previous recommendations were implemented or considered.[11]

- On December 12, 2023, and on December 13, 2023, respectively, Galderma submitted biological applications (BLA) for (b) (4) dual chamber AI for the treatment of PN under BLA 761390 and for the treatment of AD under BLA 761391. The submissions included HF validation study results reports, which are the subject of this review.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 2 presents a summary of the HF validation studies designs. See Appendix A for more details on the study designs.

Table 2. Study Methodology for the Human Factors (HF) Validation Studies

Study Design Elements	Details provided by Galderma
User Groups	(b) (4) **Dual-chamber cartridge auto-injector study** Adult patients: 35 Lay caregivers: 31 Adolescent patients: 38 Healthcare providers: 15 Total: 119
Training	(b) (4) <u>Dual chamber AI study:</u> • Participants did not receive training

[11] Barlow M. HF Protocol Clarifying Questions Review for Nemolizumab (IND 117122). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 AUG 15. RCM No.: 2021-1216-1.

Test Environment & Materials	The study facility test room simulated a home environment or doctor's office. The following materials were available to the participants: **Dual chamber AI study** (b) (4) Hand sanitizer and/or sink, cotton balls, gloves, gauze, alcohol wipes, sharps container Did not include refrigerator or small cabinet (b) (4) (b) (6) Dual Chamber AI study: (b) (4)

Sequence of Study		(b) (4)
	Dual chamber AI study	
	Use Scenario 1	Deliver 1st dose simulated injection
	Break	20-minute decay period**
	Use Scenario 2	Deliver 2nd dose simulated injection Adult, Caregiver, & HCPs: simulated 2 injections Adolescents: simulated 1 injection
	Use Scenario 3	N/A
	Knowledge Tasks	Knowledge tasks
	Debrief interview to collect subjective feedback for root cause analysis (**RCA**)	
	** Regarding the 20-minute decay period, see Section 2.1.2 below.	

2.1 DISCUSSION OF METHODOLOGY

(b) (4)

2.1.2 DUAL CHAMBER CARTRIDGE AUTOINJECTOR

During the course of our review, we noted that the Applicant included a 20-minute decay period between Use Scenario 1 (participants delivering their first dose simulated injection) and Use Scenario 2 (participants delivering their second dose simulated injection). Furthermore, we note that in Use Scenario 1, participants delivered one injection whereas in Use Scenario 2, adults, caregivers and HCP user groups simulated two injections and adolescents simulated one injection. The Applicant indicated that the 20-minute break was to simulate the learning decay "*period that would occur between doses during actual use"* based on the *"Ebbinghaus Forgetting Curve*." We note that in actual use, the initial dose for all patients consists of two 30 mg injections, followed by a maintenance dose of either 30 mg or 60 mg every 4 weeks. Therefore, the simulated Use Scenarios 1 & 2 were not reflective of actual use with respect to the number of injections for administration of an initial dose followed by the maintenance dose. However, we do note that adults, caregivers and HCP user groups simulated a dose requiring two injections. With respect to adolescents (aged ≥ 12 years) administering an initial dose of 60 mg (2 injections) for the Atopic Dermatitis (AD) indication, we recommend that the Division consider the first dose be administered by a healthcare provider or caregiver for this user group, since we do not have data to support this task in this user group (see Table 5 below). For more details regarding the study results analyses, see Section 3 below.

[12] See FDA Guidance for Industry and Food and Drug Administration Staff *Applying Human Factors and Usability Engineering to Medical Devices*, February 2016. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices.

3 RESULTS AND ANALYSES

In this section, we have carefully reviewed each reported issue (i.e., use error, use difficulty), Galderma's URRA, the participants' subjective feedback, Galderma's root cause analysis and Galderma's comments to determine if the results indicate that the user interfaces have been appropriately designed to support the safe and effective use of the proposed products. In Table 3 and 4 below, we document our points of dissent with Galderma's findings. Additionally, Appendix D provides the observed use task and knowledge task issues where we agree with Galderma's conclusions and have no further recommendations or comments.

(b) (4)

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Table 4. Focused Analysis of Use Errors, Use Difficulties and Close Calls and DMEPA's Recommendations for Dual Chamber Autoinjector Study

UE = use error; CC = close call; D = use difficulty; URRA = use-related risk analysis; RCA = root cause analysis; IFU = instructions for use; HFVS = Human Factors Validation Study
Scenario Type: scenario 1 – deliver first simulated injection (all participant groups simulated one injection); scenario 2 – deliver second simulated injection (adult, caregiver, and HCPs: simulated two injections, adolescents: simulated one injection)
Participants ID: A = adult participant; T = adolescent participant; C = caregiver participant, H = healthcare provider participant
N = naïve user, X = experienced user

	Information Supplied by Applicant	DMEPA's Identified Areas of Dissent and Recommendations
1.	**Task: Activate the pen** **Errors:** D (n = 5); CC (n = 2) **Participant Type:** H = 1, TN = 2, TX - 2; CX = 1, TX = 1 **Scenario number:** 1; 2	
	Observed event(s): • Participants initially did not activate the AI. They shook the AI and began to wait before realizing they had not yet activated it and then proceeded to activate it. • Participants experienced difficulty knowing how to activate the AI. They attempted to remove the gray cap for a minute before activating the AI. Eventually, they noticed the activation knob and turned it.	
	Relevant RCA/Subjective Feedback/Observation • Negative transfer: Three participants assumed the AI would function similarly to an EpiPen, which does not require activation prior to injecting. • Activation knob appears somewhat inconspicuous due to similar color to AI's body: Participants initially overlooked the activation knob because it is the same color as the rest of the AI. They also assumed they had to remove the gray cap first because it was more noticeable due to its arrows, location at the top of the device, and different color from the rest of the AI. • Unexpected force required to turn activation knob: Participant initially attempted to twist the activation knob lightly because they thought the device seemed fragile. After attempting to twist the gray cap several times, they decided to try twisting the activation knob again with more force and succeeded.	
	Based on the Applicant's URRA, performing this task incorrectly or not at all may result in:	

<table>
<tr><td></td><td>Delayed injection: loaded spring may lead to potential eye injury; incomplete dose or single injection of low concentration; missed doses</td><td></td></tr>
<tr><td></td><td>Applicant Comment and Proposed Mitigations:
Based on these use issues related to activating the pen, Galderma updated the device overview image in the IFU to clarify the location of the activation knob, “Activation knob (arrow on unlocked icon)”. Galderma stated that this change does not have any impact on usability and no further validation is needed.</td><td>Based on subjective feedback, participants initially overlooked the activation knob because it is the same color as the rest of the AI. They also assumed they had to remove the gray cap first because it was more noticeable due to its arrows, location at the top of the device, and different color from the rest of the AI. Based on our overall assessment, we find that the dual chamber AI can be improved to emphasize the activation knob. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF data for Agency review.</td></tr>
<tr><td>2.</td><td>Task: Wait 5 minutes for bubbles to decrease
<table>
<tr><th>Errors:</th><th>Participant Type:</th><th>Scenario number</th></tr>
<tr><td>UE (n = 5)</td><td>TN = 2
TX = 3</td><td rowspan="2">1</td></tr>
<tr><td>CC (n = 3)</td><td>AN = 1
TX = 2</td></tr>
<tr><td>UE (n = 8)</td><td>CX = 1
TN = 3
TX = 4</td><td>2</td></tr>
</table></td><td></td></tr>
<tr><td></td><td>Observed event(s):
Participants activated the AI but did not wait for bubbles to decrease before injecting.
Participants activated the AI, then shook it, then attempted to inject without waiting for the bubbles to decrease.
Participant required assistance to remove gray cap.
Participants activated the AI and attempted to inject with the gray cap still attached to AI.</td><td></td></tr>
<tr><td></td><td>Relevant RCA/Subjective Feedback/Observation:
<u>Negative transfer:</u> Participants assumed the AI would function like an EpiPen or a typical AI that did not require mixing or waiting.
Participant thought the image in IFU Step 8 showing users what to inspect for depicted only bubbles and not particles.
<u>Relatively inconspicuous IFU Step 9a – located in between similarly formatted text:</u> Participant relied on Step 9 of IFU’s image which they considered depicted the medicine as neither obviously clear nor cloudy despite the image’s intention to depict clear medicine.</td><td></td></tr>
<tr><td></td><td>Based on the Applicant’s URRA, performing this task incorrectly or not at all may result in:
Undissolved drug may lead to local or systemic hypersensitivity reaction; underdose; air bubbles may lead to minor pain; degraded drug may lead to local or systemic hypersensitivity reaction; delayed injection.</td><td></td></tr>
<tr><td></td><td>Applicant Comment and Proposed Mitigations:
None</td><td>Based on subjective feedback, some participants thought the dual chamber AI did not require mixing or waiting for the medication to be dissolved, similar to their experience with other injection devices like EpiPen. Some</td></tr>
</table>

		participants thought the image in Steps 8 and 9 of IFU did not depict particles or dissolved medication, respectively. Based on our overall assessment, we find that the IFU image in Steps 8 and 9 can be improved to better depict undissolved and dissolved medication. **We provide our recommendation in Table A to address this concern.** We have determined that this change can be implemented without submitting additional HF data for Agency review.
3.	**Task: Throw away (dispose of) the pen and cap** **Errors:** / **Participant Type:** / **Scenario number** UE (n = 21) / AX = 3 CX = 2 TN = 12 TX = 4 / 1 D (n = 1) / TX = 1 / 1 UE (n = 19) / AX = 3 CX = 2 TN = 8 TX = 2 / 2	
	Observed Event(s): • Participants discarded the AI in the regular trash can.	
	Relevant RCA/Subjective Feedback/Observation: • IFU sharps container graphic appears similar to regular trash can: Participants thought the sharps container graphic in Step 17 of the IFU appeared to look like a regular trash can. • Vague IFU heading's *"throw away"* instruction: Participants assumed that they should discard into a regular trash can because *"throw away"* commonly refers to disposal into a regular trash can. One participant further noted that IFU Step 17's heading instructs users to discard the AI but does not specify where to do so. • Participant initially was unsure whether to dispose of used AI in the sharps container; however, after a while and upon referencing the IFU, they correctly disposed of the used AI in the sharps container. • Separate call to action and caution instruction – *"Do not"* heading separate from associated instructions: Participants did not see the *"Do not"* statement ahead of the bullet instructing users not to discard of the AI in household trash because they were skimming the IFU.	
	Based on the Applicant's URRA, performing this task incorrectly or not at all may result in: Needlestick injury that may lead to local or systemic infection, or infection by blood-borne pathogen.	
	Applicant Comment and Proposed Mitigations: Based on these use issues related to throwing away or disposing the pen and cap, Galderma updated Step 9 of the IFU to state, *"see Section C Throwing away (Disposing of) NEMLUVIO")"*. They note that adding the phrase *"throwing away"* improves readability, account for potential users with low literacy, and is more user friendly. They also updated Step 12 to align with commonly used terminology, from *"sharps container"* to *"sharps disposal container"*. Galderma stated that these changes do not require further validation.	Based on subjective feedback, some participants thought the sharps container graphic looked like a regular trash can in Step 17 of the IFU. Some participants assumed that they should discard into a regular trash can because *"throw away"* commonly refers to disposal into a regular trash can. One participant noticed the heading instructs users to discard the AI but does not specify where to do so in Step 17. Based on our overall assessment, we find that the disposal instructions can be improved in the IFU.

		We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF data for Agency review.

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3.1 ANALYSIS OF THE REMAINING IDENTIFIED ISSUES

The HF validation study reports showed issues with the tasks evaluated by simulated use and knowledge task assessments listed in Appendix D. However, based on our review of the available assessment of these identified issues, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), Galderma's root cause analysis, Galderma's post HF validation studies mitigation, and our evaluation of the residual risks, we did not identify recommendations to address the identified issues with the tasks in Appendix D.

3.2 LABELS AND LABELING

Table A below includes the identified medication error issues with the submitted instructions for use (IFU) based on the HF validation study results, our rationale for concern, and the proposed recommendations to minimize the risk for medication errors. Additionally, we note that the DMEPA 1 nomenclature and labeling review team evaluated product specific label and labeling under a separate cover.[13]

[13] Patel, M. Labeling Review. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 MAY 10. TTT.: 2023-7476.

Table 5. Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Full Prescribing Information – Section 2 Dosage and Administration- For the Atopic Dermatitis (AD) Indication			
1.	We note inconsistencies between the instructions for use (IFU) and section 2 dosage and administration section with regards to adolescents (aged ≥ 12 years) administering an initial dose of 60 mg (2 injections). Specifically, the IFU includes the statement, "*In adolescents (ages 12-17 years old), it is recommended that NEMLUVIO be given by or under supervision of a trained adults or caregiver*". However, the PI Section 2.4 Important administration instructions section does not include the aforementioned statement.	As designed, the Human Factors (HF) study was not reflective of actual use regarding adolescents (aged ≥ 12 years) administering an initial dose of 60 mg (2 injections). As such, we do not have data to support this task in this user group.	With respect to adolescents (aged ≥ 12 years) administering an initial dose of 60 mg (2 injections), we recommend that you consider the first dose be administered by a healthcare provider or caregiver for this user group and include the IFU statement, "*In adolescents (ages 12-17 years old), it is recommended that the first dose of NEMLUVIO be given by or under supervision of a trained adults or caregiver*", in the PI Section 2.4 Important administration instructions, since we do not have data to support this task in this user group.

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Dual Chamber Cartridge Autoinjector (DCC AI) Product Design			
1.	The activation knob on the DCC AI required for medication reconstitution lacks prominence as presented.	Per the URRA, if the user does not activate or activates the DCC AI in the incorrect order of steps, there is risk of delayed injection with negligible reduced efficacy or underdose with reduced or no efficacy. The human factors (HF) validation study results identified subjective feedback that indicated participants had difficulty knowing how to activate or initially did not	Increase the prominence of the activation knob. For example, consider using a color different from the body of the DCC AI and/or adding the number "1" on the activation knob and number "2" on the gray cap to indicate the correct order of operations.

		activate the DCC AI because they overlooked the activation knob as it was the same color as the rest of the DCC AI.	
Dual Chamber Cartridge Autoinjector (DCC AI) Instructions for Use (IFU)			
1.	The image in Step 8 and 9 of the IFU does not depict dissolved medication as presented. (See image below) (b) (4)	Per the use-related risk analysis (URRA), if the user does not wait 5 minutes for the bubbles to decrease, then there is a risk of undissolved medication, degraded drug, air bubbles, delayed injection or underdose, and they may experience local or systemic hypersensitivity reaction, minor pain, or negligible reduced efficacy. The human factors (HF) validation study results identified subjective feedback that indicated participants considered the image depicting the dissolved medicine as only bubbles and not particles, or neither obviously clear nor cloudy in Step 8 and 9 of the IFU, respectively.	Consider revising the image in Step 8 and 9 so that users can better identify the dissolved particles.

2.	The sharps container image in IFU Step 17 is not clearly depicted as presented. (See image below) (b) (4)	Per the use-related risk analysis (URRA), this results in needlestick injury that may lead to local or systemic infection, or infection by blood-borne pathogen. The human factors (HF) validation study results identified subjective feedback that indicated that participants thought the sharps container image appeared to look like a regular trash can or thought the IFU heading's *"throw away"* assumed they should discard in a regular trash can.	Consider changing the image for Step 17 to better portray the full image of the sharps container. Additionally, consider revising the title of Step 17 to read "*Throw away (dispose of) Nemluvio in a sharps disposal container*".

4 CONCLUSION AND RECOMMENDATIONS

(b) (4)

The results of the dual chamber prefilled autoinjector HF validation study demonstrated several use errors, close calls, and use difficulties with critical tasks. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors with labels and labeling. Above, we have provided recommendations in Table A for Galderma. We ask that the Division of Dermatology and Dentistry (DDD) convey Table A in its entirety to Galderma. These changes can be implemented without submitting additional HF validation testing data for Agency review.

4.1 RECOMMENDATIONS FOR GALDERMA LABORATORIES, L.P

(b) (4)

Dual Chambered Cartridge Autoinjector

The results of your human factors (HF) validation studies for Nemluvio 30 mg dual chamber cartridge autoinjector user interface indicate that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A. We recommend that you implement these recommendations and submit the revised instructions for use for our review, prior to the approval of this application. We have determined that in this instance, you may implement these revisions without submitting additional human factors testing data for Agency review.

[14] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[15] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. HUMAN FACTORS STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

(b) (4)

Dual Chamber Autoinjector:
\\CDSESUB1\EVSPROD\bla761390\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\prurigo-nodularis\5354-other-stud-rep\dcc-reports\report-body-dcc-ai-hfer.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On January 5, 2024, we issued an information request (IR) requesting Galderma to submit 5 placebo only-intend-to-market samples of the products. On January 10, 2024, Galderma provided a response that can be accessible in EDR via:
\\CDSESUB1\EVSPROD\bla761390\0003\m1\us\cover.pdf

On February 2, 2024, we issued an information request (IR) requesting Galderma to submit the following:

- Confirm that the HF validation study results for the proposed (b) (4) dual chamber autoinjector user interface you submitted on December 12, 2023, under BLA 761390 is the same as the HF validation study results you submitted on December 13, 2023, under BLA 761391.

(b) (4)

(b) (4)

On February 6, 2024, Galderma provided an acceptable response that can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761390\0006\m1\us\quality-info-resp-02feb2024.pdf and \\CDSESUB1\EVSPROD\bla761390\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\prurigo-nodularis\5354-other-stud-rep\dcc-reports\dcc-ai-urra-5feb24.pdf

On March 20, 2024, we issued an information request (IR) requesting Galderma to submit the moderator script. On March 21, 2024, Galderma provided a response that can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761390\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\prurigo-nodularis\5354-other-stud-rep\dcc-reports\dcc-ai-hf-val-mod-script.pdf

On April 18, 2024, we issued an information request (IR) requesting Galderma to clarify the steps they took to mitigate the use error of participants losing their grip on the dual chamber AI that resulted in the device slipping and their commercial intend- to- market labeling. On April 22, 2024, Galderma provided a response that can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761390\0021\m1\us\qual-cmc-ir6-18apr24.pdf

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[16] along with postmarket medication error data, we reviewed the following Nemluvio labels and labeling submitted by Galderma on December 12, 2023.

- Carton labeling
- Container labels
- Prescribing information (images not shown) is available from:
  \\CDSESUB1\EVSPROD\bla761390\0001\m1\us\annotated-draft-labeling-text.pdf
  \\CDSESUB1\EVSPROD\bla761391\0001\m1\us\annotated-draft-labeling-text.pdf
- (b) (4)
- Autoinjector IFU (image not shown):
  \\CDSESUB1\EVSPROD\bla761390\0001\m1\us\dcc-ai-ifu.pdf

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

[16] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Dual Chamber AI

- Use tasks:
  - Wash your hands
  - Hold AI
  - Check the pen
  - Check the medicine in the inspection window
  - Select one injection site
  - Clean the injection site
  - Twist the gray cap
  - Place the pen
  - Start injection and hold pen on the skin: There were eight use errors observed for this task. The root cause analysis indicated that the use errors were due to negative transfer and habit. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.

    - Inject for 15 seconds: There were 36 use errors observed for this task. The root cause analysis indicated that the use errors were due to negative transfer, high information density of the IFU, and the dual chamber AI's smooth body might not provide sufficient grip traction. We issued an information request (IR) to Galderma to clarify the steps they took to mitigate these use errors observed of participants losing their grip on the dual chamber AI that resulted in the device slipping and information regarding commercial intend- to- market labeling. Galderma provided a response indicated that the errors related to the dual chamber AI's smooth body were due to participant being distracted during injection, excessive pressure on the injection pad, nervousness, or holding the dual chamber AI with three fingers instead of holding it as shown in the IFU. Galderma indicated that the average injection time observed in dual chamber AI functional testing during the stability study was 2.96 seconds and the participants that repositioned their hands did so approximately 5 seconds after the start of the injection, which means all these participants received a complete dose. Additionally, we note that the intend- to- market label for the dual chamber AI includes raised lettering that may mitigate the slipperiness compared to the glossy label that was used for the validation study. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
    - Lift the pen up
    - Throw away (dispose of) the pen and cap
- Knowledge task assessments:
    - "Is there anyone who should not have access to this pen? If so, who?" Correct answer: "Keep DRUG NAME pen and all medicines out of the reach of children."
    - "Where should you keep the pen when you return from the pharmacy?" Correct answer: "Store DRUG NAME pen in the refrigerator between 36°F and 46°F (2°C and 8°C)."
    - [If participants state only that they would store it in the fridge] "How long can you store it at room temperature?" Correct answer: "DRUG NAME can be stored at room temperature up to 77°F (25°C) for a single period up to 90 days."
    - "Would you remove the pen from its box before storing it, or leave the pen in its box?" Correct answer: "Store DRUG NAME pen in the original carton to protect it from light."
    - "Should you freeze the medicine or not?" Correct answer: "Do not freeze the DRUG NAME pen."
    - "Is it OK if the pen gets wet, or not?" Correct answer: "Do not: directly expose the pen to liquids."
    - "What would you do after removing it from the refrigerator?" Correct answer: "Take the DRUG NAME carton out of the refrigerator and let it come to room temperature for 30-45 minutes before starting Step 2."

- "Is it OK or not OK to do something to warm up the pen?" Correct answer: "Do not heat the DRUG NAME pen."
- "How do you know if the pen is OK to use or not?" Correct answer: "Check the pen for the following: The pen has not been dropped and is not damaged or cracked. The lyophilized powder is white and not dissolved."
- "What should you check the mixed medicine for?" Correct answer: "Check to see if the dissolved medicine is clear and colorless to slightly yellow and does not contain particles."
- "How long after mixing the medicine do you need to use it?" Correct answer: "After the medicine has dissolved, it should be used within 4 hours. During this time, it should be kept at room temperature (up to 77°F (25°C)). If you have not used it within 4 hours, throw it away (dispose of it)."
- "Imagine you just pushed the pen down to start an injection, but the orange rod did not appear fully or at all. What does this mean?" Correct answer: "Check inspection window to make sure orange rod and gray rod have stopped. This means the injection has completed. After removing the pen, look for the orange rod in the window as a way to tell that the dose has not been given. If the orange rod does not appear, contact [helpline number]." There were 11 use errors observed in the knowledge check task. The root cause analysis indicated that the use errors were due to confusion and misinterpreting IFU Step 15's note because it first says, *"It is normal that the orange rod does not cover the whole inspection window…"* but then says, *"In case the orange rod is not visible throw away the pen and use a new one".* Based on the use errors and subjective feedback, Galderma changed the phrase, *"In case"* to *"If the"* in the abovementioned step 15 instruction to clarify the meaning and language. We acknowledge Galderma's mitigation strategies and based on review of the user interface, we did not identify any additional mitigations to address these use issues and have no recommendations at this time.
- "What should you avoid doing with your used sharps container?" Correct answer: "Do not: recycle your used sharps container."
- "Imagine you just injected your dose. How should you track when to take your next dose?" Correct answer: "Mark your calendar ahead of time to remember when to take DRUG NAME."
- "What is the product name?"

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/s/

OLUWAMUREWA OGUNTIMEIN on behalf of LISA HUANG
07/30/2024 10:19:35 AM

OLUWAMUREWA OGUNTIMEIN
07/30/2024 10:21:49 AM

JASON A FLINT on behalf of ARIANE O CONRAD
07/30/2024 11:45:33 AM

JASON A FLINT
07/30/2024 11:45:46 AM

MISHALE P MISTRY
07/30/2024 12:55:14 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7/12/2024

TO: Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761390
BLA 761391

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the sites listed below. The rationale for this decision is noted below.

Rationale

Celerion, Inc., Lincoln: The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in January 2024. The inspection was conducted under the following submission: NDA 218390.

The following items were discussed with the site:

- One subject left the study site mid-study and was allowed to continue in the study despite the protocol requirement for continuous confinement at the study site during the study.
- For one subject, the repeat ECGs were incorrectly entered in the electronic data capture (EDC) as the scheduled assessment.
- For one subject, the AE of urinary tract infection was incorrectly listed as "recovered/resolved" but urinalysis at the subject's discharge noted "positive for UTI".
- At Day-1 check-in, participants completed a questionnaire but were not interviewed individually to confirm compliance with specific restrictions, and there was no mechanism to assess truthfulness.

After review of the discussion items and the site's response, OSIS recommend excluding data from one subject and suggested that the review division consider evaluating data from another subject to determine whether the findings impact data integrity and subject safety.

Celerion, Inc., Tempe: ORA conducted an inspection for the clinical site in April 2024. The inspection was conducted under the following submission: NDA 219008.

OSIS concluded that data from the reviewed studies were reliable.

[redacted] OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in [redacted]. The RRA was conducted under the following submissions: NDAs [redacted].

OSIS concluded that data from the reviewed studies were reliable.

[redacted] OSIS conducted an RRA for the site in [redacted]. The RRA was conducted under the following submission: NDA [redacted].

OSIS concluded that data from the reviewed studies were reliable.

Sites

Facility Type	Facility Name	Facility Address
Clinical	Celerion, Inc.	621 Rose Street, Lincoln, NE
Clinical	Celerion, Inc.	2420 West Baseline Road, Tempe, AZ
Analytical	[redacted]	
Analytical		

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/s/

JAMES J LUMALCURI
07/12/2024 02:46:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: 6/5/2024 **Date consulted:** 3/26/24

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Dermatology and Dentistry (DDD)

Drug: Nemluvio (nemolizumab-ilto)

BLA: 761390 and 761391

Applicant: Galderma Laboratories

Subject: Pregnancy and Lactation Labeling and Postmarketing Requirements

Proposed Indication:

- BLA 761390: Treatment of adult patients with prurigo nodularis
- BLA 761391: Treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4)

Materials Reviewed:

- BLA 761390 submitted on 12/12/2023
- BLA 761391 submitted on 12/13/2023

- DPMH PLLR Review of Bimzelx (bimekizumab) BLA 761151 by Kristie Baisden, DO, dated 2/3/21, DARRTs Reference ID: 4741087.[1]
- Addendum DPMH PLLR and PMR Review of Bimzelx (bimekizumab) BLA 761151 resubmission by Kristie Baisden, DO, dated 4/25/23, DARRTs Reference ID: 5163918.[1]
- DPMH PLLR review of Dupixent (dupilumab) BLA 761055 by Christos Mastroyannis, MD, dated 1/13/17, DARRTs Reference ID: 4041992.[1]

Consult Question: "DDD requests Maternal Health Team review of subsections 8.1 and 8.2 of Nemluvio (nemolizumab-ilto) labeling"

INTRODUCTION

On December 12, 2023, the applicant, Galderma Laboratories, submitted an original BLA (761390) for nemolizumab-ilto for the treatment of adult patients with prurigo nodularis. On December 13, 2023, the applicant also submitted an original BLA (761391) for nemolizumab-ilto for the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4) . On January 30, 2024 and March 26, 2024, the Division of Dermatology and Dentistry (DDD) consulted the Division of Pediatrics and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections and to provide recommendations for postmarketing requirements (PMRs).

BACKGROUND

Drug Characteristics (based on currently proposed labeling)

- *Mechanism of action:* humanized IgG2 monoclonal antibody that inhibits IL-31 signaling by binding selectively to IL-31 RA. IL-31 is a cytokine that is involved in pruritis, inflammation, epidermal dysregulation, and fibrosis.
- *Dosage and administration:*
  - Prurigo Nodularis
    - Adult patients weighing less than 90 kg: initial dose of 60 mg followed by 30 mg every 4 weeks.
    - Adult patients weighing 90 kg or more: initial dose of 60 mg followed by 60 mg every 4 weeks.
  - Atopic Dermatitis
    - Initial dose of 60 mg followed by 30 mg given every 4 weeks.
    - After 16 weeks of treatment for patients who achieve clear or almost clear skin, a dose of 30 mg every (b) (4) 8 weeks may be considered at the prescriber's discretion.
- *Molecular weight:* 144,000 Daltons
- *Half-life:* 18.9 days

[1] DPMH consults for Bimzelx (bimekizumab) BLA (b) (4) and Dupixent (dupilumab) BLA 761055 were reviewed as background and are not being relied upon for any decisions regarding approval of Nemluvio, including its labeling. DPMH's recommendations for Nemluvio labeling discussed below are based on Nemluvio development program and information from the published literature that is not specific to a particular product.

Identified safety concerns (based on currently proposed labeling)

- *Contraindications:* known hypersensitivity to nemolizumab-ilto
- *Warnings and Precautions:* hypersensitivity reactions; complete all age-appropriate vaccinations and avoid use of live vaccines in patients treated with nemolizumab-ilto
- *Adverse reactions:* dermatitis atopic, eczema, eczema nummular, and headache.

Epidemiology of Atopic Dermatitis (AD) and Prurigo Nodularis (PN)[2]

- *Atopic Dermatitis*: In the US, two cross-sectional studies independently found that the prevalence of AD in adults was approximately 7 percent.[3,4]
- *Prurigo Nodularis*: In the US, the estimated prevalence of PN is 72 per 100,000 persons.[5] PN can occur in all age groups without sex predilection but primarily affects older adults.

REVIEW

PREGNANCY

Nonclinical Experience

In an enhanced pre- and postnatal development study, subcutaneous doses up to 25 mg/kg nemolizumab-ilto were administered to pregnant cynomolgus monkeys once every two weeks during organogenesis to parturition. No maternal or embryofetal toxicities were observed at doses up to 25 mg/kg (36 times the MRHD, based on AUC comparison). Early postnatal death occurred in the offspring of one control monkey and 3 monkeys at 25 mg/kg (36 times the MRHD, based on AUC comparison). The clinical significance of this nonclinical finding is unknown.

Nemolizumab-ilto was administered subcutaneously to the offspring at doses up to 25 mg/kg (122 times the MRHD, based on AUC comparison), once every 2 weeks for 6 months, starting from postnatal day 35. No adverse effects were noted in the remaining offspring. For additional details, refer to the Nonclinical Review by Jianyong Wang, PhD.

Clinical Trials

Pregnant women were excluded from clinical trials during the development program for nemolizumab-ilto. A total of 10 pregnancies have occurred in female participants during any nemolizumab-ilto study participation. Nemolizumab-ilto was discontinued at identification of pregnancy as per the study protocol. Pregnancy outcomes included: normal livebirth (n=3), unknown (n=3), spontaneous abortion (n=2), and pregnancy termination (n=2). No congenital anomalies were reported and the indications for the pregnancy terminations were not specified.

Review of Literature

Applicant's Review of Literature

The applicant did not perform a literature search related to nemolizumab-ilto use and pregnancy.

[2] UpToDate topics "Prurigo Nodularis" and "Atopic Dermatitis" accessed 5/15/2024.
[3] Chiesa Fuxench ZC, et al. Atopic Dermatitis in America Study: A Cross-sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol. 2019; 139(3). 2018.
[4] Hua T, et al. Atopic dermatitis in US adults: Epidemiology, association with marital status, and atopy. Ann Allergy Asthma Immunol. 2018;121(5):622. 2018.
[5] Huang AH, et al. Real-world Prevalence of Prurigo Nodularis and Burden of Associated Diseases. J Invest Dermatol. 202; 140(2). 2019.

DPMH Review of Literature
This Reviewer performed a search in PubMed, Embase, Micromedex[6], TERIS[7], Reprotox[8], and Briggs[9] to find relevant articles related to the use of nemolizumab-ilto during pregnancy. Search terms included "nemolizumab-ilto" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage." No relevant articles were identified.

LACTATION
Nonclinical Experience
Nemolizumab-ilto was detected in breast milk of monkeys in the enhanced pre- and postnatal development study mean nemolizumab-ilto concentrations in milk were approximately 0.3 – 0.5% of the maternal plasma levels from lactation day 7 to 63. For additional details, refer to the Nonclinical Review by Jianyong Wang, PhD.

Clinical Trials
Lactating women were excluded from clinical trials during the development program for nemolizumab-ilto. No lactation exposure cases were reported during clinical development.

Review of Literature
Applicant's Review of Literature
The applicant did not perform a literature searched related to nemolizumab-ilto use and lactation.

DPMH Review of Literature
This Reviewer performed a search in PubMed, Embase, Micromedex[6], TERIS[7], Reprotox[8], and Briggs[9], *Medications and Mothers' Milk*[10], and LactMed[11] to find relevant articles related to the use of nemolizumab-ilto during lactation. Search terms included "nemolizumab-ilto" AND "breastfeeding" or "lactation." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of nemolizumab-ilto. No effects on fertility parameters as reproductive organ morphology, menstrual cycle length, or sperm/testicular analysis were observed in male or female sexually mature cynomolgus monkeys that were administered nemolizumab-ilto at subcutaneous doses up to 25 mg/kg once every two weeks for 6 months (53 times the MRHD, based on AUC comparison). The

[6] Truven Health Analytics information, http://www.micromedexsolutions.com/ Accessed 4/17/24.
[7] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 4/17/24.
[8] Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 4/17/24.
[9] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[10] Hale, Thomas (2020) Medications and Mothers' Milk online. Accessed 4/17/24.
[11] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 4/17/24.

monkeys were not mated to evaluate fertility. For additional details, refer to the Nonclinical Review by Jianyong Wang, PhD.

Review of Literature

Applicant's Review of Literature

The applicant did not perform a literature search related to nemolizumab-ilto use and fertility.

DPMH Review of Literature

This Reviewer performed a search in PubMed, Embase, Reprotox[8] to find relevant articles related to the use of nemolizumab-ilto and effects on fertility. Search terms included "nemolizumab-ilto" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant articles were identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

Pregnant women were excluded from clinical trials with nemolizumab-ilto during the clinical development program. A total of 10 pregnancy exposure cases were reported with outcomes including: normal livebirth n=3, unknown n=3, pregnancy termination n=2, and spontaneous abortion n=2. Overall, these limited available human data are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Therefore, DPMH recommends subsection 8.1 of Nemluvio labeling include a Risk Summary statement to summarize the limited available human pregnancy exposure data from case reports during the clinical development program.

There are no available pregnancy pharmacokinetic (PK) data for nemolizumab-ilto to inform evidence-based dosing recommendations during pregnancy. There are also no available human data regarding the amount of nemolizumab-ilto placental transfer, nemolizumab-ilto levels at birth in infants exposed in utero, or the duration of persistence of nemolizumab-ilto in infant serum after delivery. Considering nemolizumab-ilto is an IgG2 monoclonal antibody, placental transfer is presumed based on published literature for other monoclonal antibodies.[12] Published literature for other monoclonal antibodies indicate the amount of placental transfer varies widely and the half-life observed in adults may not be predictive of the half-life or the duration of pharmacodynamic effects in the in utero exposed infant.[12]

Given the lack of available human PK and placental transfer data specific to nemolizumab-ilto use in pregnancy, DPMH recommends including language in subsection 8.1 similar to the Agency's approach to PLLR labeling for other monoclonal antibodies. Pregnancy labeling should include information under Risk Summary and Clinical Considerations about the active transport of monoclonal antibodies across the placenta, the potential for immunosuppression in the *in utero* exposed infant, and the risks and benefits that should be considered prior to administration of live vaccines. The labeling should include a statement that a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, however, a minimum of 3 months after birth should be considered based on the half-life of the product. DPMH confirmed with the DDD Clinical Team the appropriateness of including this language in

[12] Soh MC, et al. The Use of Biologics for Autoimmune Rheumatic Diseases in Fertility and Pregnancy. Obstetric Medicine 2020, Vol. 13 (1) 5-13.

labeling for nemolizumab-ilto considering the related Warning and Precaution regarding live vaccine administration in adults prior to treatment.[13]

Nemolizumab-ilto is proposed for treatment of conditions that affect females of reproductive potential (including during pregnancy), and current data are insufficient to inform women regarding nemolizumab-ilto use during pregnancy. There is a potential safety risk in fetuses exposed to nemolizumab-ilto because fetuses would not otherwise be exposed to this product except through maternal exposure. Data in animal studies are unclear about the risk to human fetuses. Therefore, DPMH recommends a postmarketing requirement (PMR) for the applicant to conduct a pregnancy exposure registry and a complementary study of a different design (such as a claims database study). Refer to the FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies, published May 2019. DPMH also recommends including language regarding the planned postapproval pregnancy exposure registry in subsection 8.1 and section 17 of labeling along with the applicant's pharmacovigilance contact information. After the pregnancy registry study protocol has been finalized, the applicant should submit a prior approval supplement (PAS) to update PLLR labeling with the established pregnancy registry contact information.

Lactation

Lactating women were excluded from clinical trials with nemolizumab-ilto and no lactation exposure cases were reported during clinical development. There are no available data on the presence of nemolizumab-ilto in human milk, the effects on the breastfed infant, or the effects on milk production. The molecular weight for nemolizumab-ilto is 144,000 Daltons, and according to breastfeeding experts, the amount of monoclonal antibody in human milk, if any, is expected to be low. Considering nemolizumab-ilto is an IgG2 monoclonal antibody, DPMH recommends including language in subsection 8.2 of Nemluvio labeling similar to the Agency's approach to PLLR labeling for other monoclonal antibodies. Lactation labeling should include information under Risk Summary that "maternal IgG and monoclonal antibodies are known to be present in human milk" as well as the "the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to nemolizumab-ilto are unknown." The following risk/benefit statement should also be included: "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Nemluvio and any potential adverse effects on the breastfed infant from Nemluvio or from the underlying maternal condition."

Nemolizumab-ilto is proposed for treatment of conditions that would be expected to be seen in females of reproductive potential (including during lactation), and there are no available data to inform women regarding nemolizumab-ilto use during lactation. Therefore, DPMH recommends issuing a PMR for the applicant to conduct a clinical lactation study with nemolizumab-ilto to inform labeling. Refer to the FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design, published May 2019.

Females and Males of Reproductive Potential

There are no available human data on the effects of nemolizumab-ilto on male or female fertility. Animal fertility studies do not indicate any adverse effects. Therefore, DPMH recommends omitting subsection 8.3 from labeling for Nemluvio.

[13] DPMH personal communication with DDD Clinical Team Leader, David Kettl, MD, dated 6/5/24.

PMR RECOMMENDATIONS

(b) (4)

Reviewer's Comment
Regarding issuing PMRs for transplacental transfer studies, DPMH is planning a workshop and aims to establish a policy which will be developed based on the results of the workshop.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 and section 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Nemluvio (nemolizumab-ilto) Pregnancy and Lactation Labeling
FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

(b) (4)

Risk Summary

Available data on nemolizumab-ilto use in pregnant women exposed during clinical trials are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Transport of human IgG antibody across the placenta increases as pregnancy progresses and peaks during the third trimester; therefore, Nemluvio may be transferred from the mother to the developing fetus *(see Clinical Considerations).* In an enhanced pre- and postnatal development study in cynomolgus monkeys, when nemolizumab-ilto was administered subcutaneously during organogenesis to parturition, an increase in early postnatal death was observed at a dose 36 times the maximum recommended human dose (MRHD) *(see Data)*. The clinical significance of this nonclinical finding is unknown.

The background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20% respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Because nemolizumab-ilto may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to Nemluvio in utero. There are no data regarding infant serum levels of nemolizumab-ilto at birth and the duration of persistence of nemolizumab-ilto in infant serum after birth. Although a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, a minimum of 3 months after birth should be considered because of the half-life of the product.

Data

Animal Data

In an enhanced pre- and postnatal development study, subcutaneous doses up to 25 mg/kg nemolizumab-ilto were administered to pregnant cynomolgus monkeys once every two weeks during organogenesis to parturition. No maternal or embryofetal toxicities were observed at doses up to 25 mg/kg (36 times the MRHD, based on AUC comparison). Early postnatal death occurred in the offspring of one control monkey and 3 monkeys at 25 mg/kg (36 times the MRHD, based on AUC comparison). The clinical significance of this nonclinical finding is unknown. Nemolizumab-ilto was administered subcutaneously to the offspring at doses up to 25 mg/kg (122 times the MRHD, based on AUC comparison), once every 2 weeks for 6 months, starting from postnatal day 35. No adverse effects were noted in the remaining offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of nemolizumab-ilto in human milk, the effects on the breastfed infant, or the effects on milk production. Nemolizumab-ilto was detected in breast milk of monkeys *(see Data).* Endogenous maternal IgG and monoclonal antibodies are transferred in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to nemolizumab-ilto are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Nemluvio and any potential adverse effects on the breastfed infant from Nemluvio or from the underlying maternal condition.

Data

Nemolizumab-ilto was detected in breast milk of monkeys in the enhanced pre- and postnatal development study following subcutaneous doses of up to 25 mg/kg once every two weeks during organogenesis to parturition. The mean nemolizumab-ilto concentrations in milk were approximately 0.3 – 0.5% of the maternal plasma levels from lactation day 7 to 63. The concentration of nemolizumab-ilto in animal milk does not necessarily predict the concentration of drug in human milk.

17 PATIENT COUNSELING INFORMATION

(b) (4)

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/s/

KRISTIE W BAISDEN
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TAMARA N JOHNSON
06/06/2024 10:33:51 AM

LYNNE P YAO
06/06/2024 10:43:42 AM