CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213976Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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:	April 19, 2024
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 213976/S-001
Product Name, Dosage Form, and Strength:	Eohilia (budesonide) oral suspension, 2 mg/10 mL
Applicant/Sponsor Name:	Takeda Development Center Americas, Inc. (Takeda)
TTT ID #:	2024-8737
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 28, 2024 for Eohilia. The Division of Gastroenterology (DG) requested that we review the revised container labels, carton labeling, prescribing information, patient information, and Instructions for Use for Eohilia (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

[a] Abraham, S. Label and Labeling Review for Eohilia (NDA 213976/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 NOV 7. TTT ID No.: 2023-6152.

2 BACKGROUND

NDA 213976 is a 505(b)(2) NDA, and the listed drug product is Entocort EC, NDA 021324. NDA 213796 was approved on February 9, 2024. Prior to approval, Takeda committed to submit a prior approval supplement to update all labels and labeling within one month post approval (i.e., March 9, 2024).[b]

The following is a list of our outstanding recommendations from our previous label and labeling reviews[a,c]:

1. Revise the route of administration statement so that it reads, "For oral use" on the container labels.
2. Remove the statement, "Individual pack not for resale" from the trade container label.
3. Remove bold font from the "Rx only" statement on the container labels.
4. Add the statement of dosage "Recommended Dosage: see Prescribing Information" to the back panel in accordance with 21 CFR 201.55 on the container labels.

3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[b] Chung M. NDA Approval for Eohilia (NDA 213796). Silver Spring (MD): FDA, CDER, OND, DG (US); 2024 FEB 9. Available from: darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80724e3d.

[c] Abraham S. Label and Labeling Review Memo for Eohilia (NDA 213796). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 FEB 2. TTT ID No.: 2023-6152-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 28, 2024

- Prescribing Information and Patient Information received on February 28, 2024
  \\CDSESUB1\EVSPROD\nda213976\0094\m1\us\uspi-tracked.docx
  \\CDSESUB1\EVSPROD\nda213976\0094\m1\us\ppi-tracked.docx
- Instructions for Use received on February 28, 2024, available from
  \\CDSESUB1\EVSPROD\nda213976\0094\m1\us\ifu-tracked.docx

(b) (4)

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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:	February 2, 2024
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 213976
Product Name, Dosage Form, and Strength:	Eohilia (budesonide) oral suspension, 2 mg/10 mL
Applicant/Sponsor Name:	Takeda Development Center Americas, Inc. (Takeda)
TTT ID #:	2023-6152-1
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader (Acting):	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 23, 2024 for Eohilia. The Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for Eohilia (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Per Takeda's submission received on January 23, 2024, some of our recommendations (b) (4) (b) (4) (b) (4) Thus, Takeda requested to defer implementing some of our container label and carton labeling recommendations "*to ensure availability of EOHILIA to patients as soon as*

[a] Abraham, S. Label and Labeling Review for Eohilia (NDA 213976). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 NOV 15. TTT ID No.: 2023-6152.

[b] 1.11.4. Response to Packaging Artwork Comments (NDA 213976 Eohilia). Lexington (MA): Takeda Pharmaceuticals, Inc; 2024 JAN 23. Available from: \\CDSESUB1\EVSPROD\nda213976\0080\m1\us\multiple-module-information-amendment.pdf

possible after the approval."[b] On January 24, 2024, Takeda stated that (b) (4) On January 29, 2024, Takeda agreed to implement some of our recommendations and update the container label and carton labeling within one month of approval of the product through a prior approval supplement (PAS):[d]

1. Revise the route of administration statement so that it reads, "For oral use" on the container labels.
2. Remove the statement, "Individual pack not for resale" from the trade container label.
3. Remove bold font from the "Rx only" statement on the container labels.
4. Add the statement of dosage "Recommended Dosage: see Prescribing Information" to the back panel in accordance with 21 CFR 201.55 on the container labels.

We agree to Takeda's proposal to implement the above recommendations in a post-product approval PAS.

Additionally, in their January 23, 2024 submission, Takeda stated that they (b) (4) We find these changes acceptable from a medication error perspective.

We previously recommended to "*Move the barcode that does not contain the NDC number to away from the barcode containing the NDC number and present it in a size that does not compete with, distract from the presentation of other required or recommended information on the label.*" However, Takeda stated that they believe *"there is sufficient blank space surrounding the barcode so that it can be scanned correctly and is compliant with all aspects of 21CFR Section 201.25 Bar code label requirements* (b) (4) we find the Applicant's rationale acceptable at this time.

We also recommended to "*add the flavoring of the product, e.g., "cherry flavored", to the container label.*" However, Takeda stated that, *"EOHILIA does not contain any dye and there is no data demonstrating that the inactive ingredient of cherry flavor has an increased risk of hypersensitivity reactions as compared to the other inactive ingredients for EOHILIA. The reference to the flavor/ingredient is located on both the proposed EOHILIA carton and PPI."*

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[c] 1.11.4. Information Request Response (NDA 213976 Eohilia). Lexington (MA): Takeda Pharmaceuticals, Inc; 2024 JAN 24. Available from: \\CDSESUB1\EVSPROD\nda213976\0081\m1\us\multiple-module-information-amendments.pdf

[d] 1.11.4. Postmarketing Commitment (PMC) and Packaging Response (NDA 213976 Eohilia). Lexington (MA): Takeda Pharmaceuticals, Inc; 2024 JAN 29. Available from: \\CDSESUB1\EVSPROD\nda213976\0082\m1\us\multiple-module-information-amendments.pdf

Given that that the flavoring information is included in the carton labeling and PPI, we find the Applicant's rationale acceptable at this time.

As noted above, Takeda implemented some of our recommendations and agreed to implement some of our other recommendations in a future PAS post-product approval. We find this proposal acceptable and have no additional recommendations at this time.

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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:	January 9, 2024
To:	Mary Chung Senior Regulatory Project Manager Division of Gastroenterology (DG)
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Meeta Patel, 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):	EOHILIA (budesonide)
Dosage Form and Route:	suspension, for oral use
Application Type/Number:	NDA 213976
Applicant:	Takeda Pharmaceuticals U.S.A., Inc.

1 INTRODUCTION

On August 22, 2023, Takeda Pharmaceuticals U.S.A., Inc. submitted for the Agency's review a resubmission to their 505(b)(2) New Drug Application (NDA) 213976. The former application received a Complete Response (CR) on December 17, 2021. The proposed indication for EOHILIA (budesonide) is for the treatment of Eosiniophilic Esophagitis (EoE), (b) (4) (b) (4) in patients 11 years and older. The purpose of this resubmission is to address the deficiencies and propose changes outlined in the CR.

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 Gastroenterology (DG) on September 1, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for EOHILIA (budesonide) suspension, for oral use.

2 MATERIAL REVIEWED

- Draft EOHILIA (budesonide) PPI and IFU received on August 22, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 19, 2023.
- Draft EOHILIA (budesonide) Prescribing Information (PI) received on August 22, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 19, 2023.
- Approved ENTOCORT EC (budesonide) comparator labeling dated July 15, 2020.

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%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

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 is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- 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 is 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/

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

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

Memorandum

Date: January 8, 2024

To: Mary Chung, Project Manager, DG

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for **Eohilia™ (budesonide oral suspension)**

NDA: 213976

In response to DG's consult request dated September 1, 2023, OPDP has reviewed the proposed product labeling (PI), Prescribing Patient Information (PPI), and Instructions for Use (IFU) for Eohilia.

Labeling: OPDP has four comments on the proposed labeling based on the draft labeling received by electronic mail from DG on December 19, 2023.

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

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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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 Pediatric and Maternal Health Addendum

Date: 12/18/23 **Date Consulted:** 8/22/23

From: Jane Liedtka, M.D., Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, Director, DPMH

To: Mary Chung, Regulatory Project Manager (RPM)
Division of Gastroenterology (DG)

Drug: Eohilia (budesonide) oral suspension

NDA: 213976

Indication: For 12 weeks of treatment in adult and pediatric patients 11 years of age and older with eosinophilic esophagitis (EoE).

Applicant: Takeda Pharmaceuticals U.S.A. Inc.

Subject: Pregnancy and Lactation Labeling [Class 2 resubmission of New Drug Application (NDA), 505(b)(2)]

Materials Reviewed:

- Applicant's submission dated 3/10/22.
- Original DPMH review of Eohilia (budesonide) oral suspension, NDA 213976. Jane Liedtka, MD. 3/10/21. DARRTS Reference ID # 4760638.[1]

[1] DPMH consult reviews of budesonide, NDAs 121920 and 21324 were part of the materials reviewed but were not relied upon for the purposes of the recommendations.

- DPMH review of Budesonide, NDA 121920. Christos Mastroyannis, MD. 12/19/18. DARRTS Reference ID # 4366204.[1]
- DPMH review of Entocort EC (budesonide). NDA 21324. Miriam Dinatale, D.O. 1/25/16. DARRTS Reference ID # 3875179.[1]

Consult Question: DG requests DPMH maternal health teams' support with the review of the label.

INTRODUCTION

- A previous review by DPMH[1] for Eohilia was placed in DARRTS on 3/10/21. Please see this review for "Introduction and Background", "Drug Characteristics", "EoE and Pregnancy", "Reviews of the Literature", "Pharmacovigilance Review", "Discussion and Conclusions".
- The Complete Response (CR) to the first cycle review for Eohilia was issued on 12/17/21.
- On 8/22/23, the Applicant submitted their resubmission for the short-term treatment of EoE in adults and adolescents. DG reconsulted DPMH on 9/1/23 for review of the Pregnancy and Lactation Labeling Rule (PLLR) subsections of the labeling.

REVIEW

- The recommended labeling for the Highlights of Prescribing Information (HPI), subsection 8.1 and section 17 have not changed since the previous review but is repeated below for ease of reference.
- The recommended labeling for subsection 8.2 was still being discussed between the Clinical Pharmacology team and DPMH at the time of the previous review so recommendations for labeling for subsection 8.2 were postponed till the second cycle. An IR was sent to the applicant asking for further information about a publication by Fält et al.,[2] which described a lactation study in 8 mothers receiving inhalational budesonide. Despite contacting the investigators, the applicant was unable to obtain any additional information.

Reviewer's Comments

After further discussion between the Clinical Pharmacology team and DPMH Maternal Health team, the decision was made to keep most of the current labeling language regarding the Fält et al., publication except for correcting the dosage and calculated relative infant dose (RID) for use of Eohilia compared to the inhaled budesonide dose. See clinical pharmacology section of the review for NDA 213976 for details.

In addition, there was discussion with the division regarding issuance of a post-marketing requirement (PMR) for a clinical lactation study with the oral formulation of budesonide in order to obtain more accurate estimation of the exposure to the infant. The lack of a new safety signal precluded this so the decision was reached to request a post-marketing commitment (PMC) for a clinical lactation study.

[2] Fält A, Bengtsson T, Kennedy BM, Gyllenberg A, Lindberg B, Thorsson L, Stråndgarden K. Exposure of infants to budesonide through breast milk of asthmatic mothers. J Allergy Clin Immunol. 2007 Oct;120(4):798-802.

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LYNNE P YAO
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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:	November 7, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 213976
Product Name, Dosage Form, and Strength:	Eohilia (budesonide) oral suspension, 2 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Takeda Development Center Americas, Inc. (Takeda)
FDA Received Date:	August 22, 2023
TTT ID #:	2023-6152
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Eohilia (budesonide) oral suspension, the Division of Gastroenterology (DG) requested that we review the proposed Eohilia prescribing information (PI), patient information, instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 213976 is a 505(b)(2) NDA and the listed drug product is Entocort EC, NDA 021324.

Takeda previously submitted NDA 213976 for Eohilia on October 15, 2020. The application received a complete response (CR) on December 17, 2021, due to clinical and statistical deficiencies.[a] DMEPA did not complete a label and labeling review for the application during the previous review cycle.

Takeda responded to the CR for NDA 213796 and re-submitted the Eohilia NDA for our review on August 22, 2023.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, patient information, IFU, container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We

[a] Chung M. Complete Response Letter for Eohilia (NDA 213976). Silver Spring (MD): FDA, CDER, OND, DG (US); 2021 DEC 17 https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806345c1

provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Takeda.

4 RECOMMEDATIONS FOR DIVISION OF GASTROENTEROLOGY (DG)

A. Prescribing Information

1. Prescribing Information-General issues

   a. The statement, (b) (4) (b) (4) with the statement, "Do not eat or drink for 30 minutes after taking EOHILIA" in the IFU step 4 under: Taking Eohilia. The definition of (b) (4) The sentence lacks consistency as to how to properly administer the medication in reference to a meal. We defer to the review team to determine the accurate administration information and to ensure alignment across all labels and labeling.

   b. The container-closure term is referred to as "stick pack" and the package-type terminology is referred to as "single dose". We defer to OPQ team for the correct container-closure term and package-type terminology across all label and labeling.

2. Highlights (HL) of Prescribing Information

   a. Recommendations to increase the readability of important product information for Highlights are noted in track changes below:

   (b) (4)

   b.

3. Full Prescribing Information: Section 2 Dosage and Administration

   a. Recommendations to increase the readability and prominence of important dosage and administration within Section 2 are noted in track changes below:

4. Full Prescribing Information: Section 16 How supplied/Storage and Handling
    a. Recommendations for Section 16 are noted in track changes below:

    b.

5. Full Prescribing Information: Section 17 Patient Counseling Section
    a. Recommendations for Section 17 are noted in track changes below:

(b) (4)

b. Sections 3, 11, and 16 mention the product is cherry flavored, but section 17 is missing this information. Typically, the Prescribing Information (PI) is intended for healthcare providers and not for patients. If important information about flavoring is missing in Section 17, it might not get communicated to the patients. Consider adding to Section 17 that Eohilia is cherry flavored so that patients are informed of this important information to avoid hypersensitivity reactions.

6. Instructions for Use (IFU)

   a. Recommendations to increase the readability of important product information for IFU are noted in track changes below:

(b) (4)

b. The container-closure term is referred to as "stick pack" and the package-type terminology is referred to as "single dose". We defer to OPQ team for the correct container-closure term and package-type terminology across all label and labeling.

c. IFU is missing important information that product has cherry flavoring. Consider adding to the IFU that product is cherry flavored so that patients are informed of this important information to avoid hypersensitivity reactions.

7. Patient Information

a. Recommendations to increase the readability of important product information for patient information are noted in track changes below:

5 RECOMMENDATIONS FOR TAKEDA DEVELOPMENT CENTER AMERICAS, INC. (TAKEDA)

Table 2. Identified Issues and Recommendations for Takeda (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The route of administration statement contains the word "only".	We reserve the use of the word "only" when there is a safety concern or data that supports the product must be given by a specific route.	We recommend revising the route of administration statement so that it reads, "For oral use".
Container Label(s)			
1.	Per the product samples received on 9/28/23, we note that the strength statement is not on the Principal Display Panel	Prominence and readability of the strength presentation is required per 21 CFR 201.15(a)(6).	Ensure that the strength statement is present on the PDP.

Table 2. Identified Issues and Recommendations for Takeda (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(PDP). (b) (4)		
2.	The trade container label includes the statement, "Individual pack not for resale".	This is an error, as the trade container is intended for retail sale, not for use as a sample.	Remove the statement, "Individual pack not for resale" from the container label.
3.	The "Rx only" statement is bolded.	Overuse of bold font may diminish its effect on prominence for other important product information.	Reserve the use of bolded font only for the most important product information on the label and labeling; remove bold font from the "Rx only" statement.
4.	The statement of dosage is missing from container label.	Requirement per 21 CFR 201.55 that labels for prescription drugs bear a statement of the recommended dosage.	Add the statement of dosage "Recommended Dosage: see Prescribing Information" to the back panel in accordance with 21 CFR 201.55.
5.	As currently presented, there are two types of barcodes on the container located near each other.	The drug barcode is often used as an additional verification during the medication use process. The presence of barcodes near one another could lead to scan errors.	We recommend moving the barcode that does not contain the NDC number to away from the barcode containing the NDC number and present it in a size that does not compete with, distract from the presentation of other required or recommended information on the label.
6.	The flavoring of the product, "cherry flavoring", is not mentioned on the container label.	Absence of flavoring can contribute to potential hypersensitivity adverse events.	Add the flavoring of the product, e.g., "cherry flavored", to the container label.

Table 2. Identified Issues and Recommendations for Takeda (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	The terminology within the statement of dosage is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage to read, "Recommended Dosage: see Prescribing Information."
2.	(b) (4) are found on the carton labeling.	(b) (4)	Remove (b) (4) in the IFU by relocating the statement, "Before use, please read the enclosed Instructions for Use for detailed administration instructions." into that space. Alternatively, add instructions to carton labeling that (b) (4) Increase the prominence of the step numbers.
3.	The duplicated statement, (b) (4) is found on the PDP and on the back panel.	The PDP should be reserved for important product information. Duplicative statement located on the PDP takes readers' attention away from more important information such as proprietary and established names, strength, and dosage form.	Delete the duplicated statement, (b) (4) n the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION
Table 3 presents relevant product information for Eohilia that Takeda submitted on August 22, 2023, and the listed drug (LD).

Table 3. Relevant Product Information for Entocort EC and Eohilia

Product Name	Entocort EC (NDA 021324)	Eohilia
Initial Approval Date	10/02/2001	N/A
Active Ingredient	budesonide	
Indication	ENTOCORT EC is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.	Treatment (b) (4) in patients 11 years and older with eosinophilic esophagitis (EoE).
Route of Administration	oral	
Dosage Form	capsules	oral suspension
Strength	3 mg	2 mg/10 mL
Dose and Frequency	9 mg taken once daily in the morning for up to 8 weeks.	2 mg twice daily; max dose 4 mg/day
How Supplied	Bottle of 100	60 single dose stick pack
Storage	Store at 25°C (77°F); excursions permitted to 15-30° (59-86°F) [See USP Controlled Room Temperature].	Store at 25°C (77°F); excursions permitted to (b) (4) 30° ((b) (4) -86°F) (b) (4)

APPENDIX F. LABELS AND LABELING

F.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 experiences with similar products, we reviewed the following Eohilia labels and labeling submitted by Takeda.

- Container label(s) received on August 22, 2023
- Carton labeling received on August 22, 2023
- Professional sample container label received on August 22, 2023
- Professional sample carton labeling received on August 22, 2023
- Instructions for Use received on August 22, 203, available from \\CDSESUB1\EVSPROD\nda213976\0064\m1\us\ifu-clean.docx
- Prescribing Information and Patient Information (Images not shown) received on August 22, 2023, available from \\CDSESUB1\EVSPROD\nda213976\0064\m1\us\patient-information-clean.docx \\CDSESUB1\EVSPROD\nda213976\0064\m1\us\draft-labeling-clean.docx

F.2 Label and Labeling Images

Container label(s)

\\CDSESUB1\EVSPROD\nda213976\0064\m1\us\draft-2mg-10ml-trade-foil-clean.pdf

(b) (4)

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

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

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

Memorandum

Date: March 30, 2021

To: Benjamin Vali, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology (DG)

From: Adewale Adeleye, Pharm.D., MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for EOHILIA (budesonide)

NDA: 213976

This memo is in response to Division of Gastroenterology (DG) labeling consult request dated December 3, 2020. Due to outstanding clinical deficiencies, DG plans to issue a Complete Response (CR) letter. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DG submits a new consult request during the subsequent review cycle. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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/s/

ADEWALE A ADELEYE
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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 Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	March 29, 2021
To:	Benjamin Vali, MS, RAC Regulatory Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	EOHILIA (budesonide)
Dosage Form and Route:	oral suspension
Application Type/Number:	NDA 213976
Applicant:	Takeda Pharmaceuticals U.S.A. Inc.

1 INTRODUCTION

On October 15, 2020, Takeda Pharmaceuticals U.S.A Inc. submitted for the Agency's review an original New Drug Application (NDA) for EOHILIA (budesonide) oral suspension. The proposed indication is for the treatment of eosinophilic esophagitis (b) (4) in adult and adolescent patients 11 years and older. On December 3, 2020, the Division of Gastroenterology (DG) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for EOHILIA (budesonide).

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for EOHILIA (budesonide).

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DG plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

KELLY D JACKSON
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03/29/2021 01:03:17 PM

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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2020505
NDA#:	NDA 213976 (referencing IND 103173)
Sponsor:	Takeda
Established Name/Trade Name:	Budesonide oral suspension (BOS; Eohilia)
Indication:	Treatment of eosinophilic esophagitis (EoE), (b) (4) (b) (4) in adult and adolescent patients 11 years and older ☒Rare Disease/Orphan Designation ☒Pediatrics
Meeting Type:	NDA review
Review Division:	Division of Gastroenterology (DG)
Clinical Reviewer	Sarrit Kovacs, PhD
Clinical Team Leader (TL)	Erica Lyons, MD
Regulatory Project Manager:	Benjamin Vali, MS
COA Reviewer:	Christopher St. Clair, PharmD
COA TL:	Onyeka Illoh, OD, MPH
COA Director:	David Reasner, PhD
Date Consult Request Received:	November 22, 2020
Date COA Briefing Package/Submission Received:	October 15, 2020
Instruments reviewed:	Dysphagia Symptom Questionnaire version 5 (DSQv5) ☒ Patient-reported outcome (PRO)

1. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 213976 for budesonide oral suspension (BOS; Eohilia). The proposed indication is treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older.

The Applicant used the following patient-reported outcome (PRO) assessments in their phase 3 randomized, double-blind, placebo-controlled study (Study SHP621-301) and extension study (Study SHP621-302) in adolescent and adult (aged 11 to 55 years) EoE patients with dysphagia:

- Co-Primary Endpoint: Dysphagia Symptom Questionnaire version 5 (DSQv5; Appendix A)
- Exploratory: Patient Global Impression of Severity (PGIS; Appendix B)
- Exploratory: Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A; adults only)
- Exploratory: Pediatric Quality of Life Inventory – EoE (PedsQL-EoE; adolescents only)
- Exploratory: EQ-5D-3L (adults) or EQ-5D-3Y (adolescents)

This NDA submission included a COA evidence dossier for the DSQv5. DG seeks input from the Division of Clinical Outcome Assessment (DCOA) on adequacy of the DSQv5 to support regulatory decision-making and labeling claims.

This COA review concludes the following:

- The evidence submitted by the applicant is sufficient to demonstrate that the DSQv5 is fit-for-purpose[1] to measure dysphagia in the context of use of this drug development program.

- However, the interpretation of clinically meaningful within-patient change in DSQ scores is unclear, as the Patient Global Impression of Severity (PGIS) anchor scale included in phase 3 (SHP621-301 and SHP621-302) used a recall period ("the past 7 days") that did not match the assessment period for the DSQ (14 days). Furthermore, the 30% responder definition used for the primary endpoint definition was based on phase 2 (MPI 101-06) data using a different anchor, the Patient Global Impression of Change (PGIC), which is not comparable to the PGIS scale included in phase 3.

DCOA has the following recommendations for future drug development:

- We recommend adding a follow-up question for patients who answer "No" to DSQ Question 1 ("Since you woke up this morning, did you eat solid food?") to assess whether these patients did not eat solid food because of their EoE.

- We recommend using Patient Global Impression of Severity (PGIS) scales with recall periods that match the assessment period for the DSQ (e.g., "the past 14 days").

- We recommend multiple anchors when applying an anchor-based approach and, specifically, including overlapping anchors in phase 2 and phase 3 clinical trials (e.g., a PGIS assessment in both phase 2 and phase 3).

[1] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www.ncbi.nlm.nih.gov/books/NBK338448/)

3 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

- 2010: A ClinRO called the Physician-Administered EoE Symptom Score was proposed for use in children and adolescents with EoE. SEALD was consulted and recommended development of a PRO for children and adolescents who are able to reliably self-report, and an ObsRO for children who are unable to reliably self-report (e.g., young children). (Refer to previous COA review AT2010-80; DARRTS Reference ID: 2865790.)

- 2012: The Dysphagia Symptom Questionnaire (DSQ) version 3 (DSQv3) was proposed as a PRO for use in clinical trials for patients (b) (4) with EoE. SEALD did not agree that content validity of the proposed DSQ had been established, as the instrument appeared to (b) (4) Furthermore, the proposed (b) (4) (b) (4) which SEALD did not agree was acceptable. (Refer to previous COA review AT2012-049; DARRTS Reference ID: 3158289.)

- 2013: SEALD noted that previous concerns regarding content validity of the DSQ had still not been addressed. The Sponsor proposed a responder analysis based on a 30% change on the DSQ, but SEALD noted that the Sponsor had not provided data to support a 30% reduction in DSQ score as a clinically meaningful change. SEALD noted that the incremental change that is meaningful is expected to differ based on baseline severity. (Refer to previous COA review AT2013-079; DARRTS Reference ID: 3361414.) FDA conveyed the following comments to the Sponsor at that time (refer to Meeting Minutes dated 9/25/2013; DARRTS Reference ID: 3379192):

> *We remind you that we have not concurred with the content validity of the DSQ that was submitted in the 2012 submission. For a trial to support registration, the PRO instrument upon which you assess efficacy must be well-defined and reliable. You should submit your revised PRO dossier for review. Once you have developed a well-defined and reliable Reference ID: 3379192 IND 103173 Meeting Minutes Type C Page 3 instrument, you must establish and justify a patient-level clinically meaningful change in score.*
>
> ***You have proposed a responder analysis based on a ≥ 30% change in DSQ score but have not provided data to support that this is a clinically meaningful change.*** *What is considered a meaningful % change may depend on the severity of baseline score.* ***You may want to consider using the actual DSQ score (as a continuous variable) as a co-primary endpoint rather than a responder definition. However, you will still need to provide information about what would define a clinically meaningful change for a patient*** *as well as what a meaningful effect size (compared to placebo) would be.*

- 2014: SEALD noted that the Sponsor was progressing in the right direction with the DSQ version 5 (DSQv5). SEALD recommend clarifying the recall period for Question 4 (pain while swallowing), which the Sponsor agreed to by adding a recall period of "today." (Refer to COA review AT2014-115; DARRTS Reference ID: 3659806.) Regarding the proposed responder definition of ≥ 30% reduction in DSQ score from baseline, FDA conveyed the following comments to the Sponsor at that time (refer to Meeting Minutes dated 11/30/2014; DARRTS Reference ID: 3665494):

  > *We agree that the study should be designed to show statistically significant differences vs. placebo in the proportion of responders based on both the DSQ score and number of eosinophils on histology.* ***However, given the new phase 2 data presented and revisions to the DSQ during development, please provide your rationale that a ≥30% reduction in DSQ from baseline (e.g., as opposed to ≥50%) is still clinically meaningful for a phase 3 trial.*** *We note that the proportion of responders who had a ≥50% reduction in DSQ from baseline was similar to those who had a ≥30% reduction compared to placebo.*

- 2015: COA Staff (formerly SEALD) noted that the Sponsor followed FDA's advice from November 2014 regarding the DSQv5 (refer to COA review AT2015-096; DARRTS Reference ID: 3832615). FDA conveyed the following comments to the Sponsor at that time and issued a post-meeting comment (refer to Meeting Minutes dated 7/15/2015; DARRTS Reference ID: 3792696):

  > *We agree with the overall study design of the Induction study (12-week, randomized, double-blind, multicenter, parallel-group, placebo-controlled study), as well as the use of a co-primary endpoint for the phase 3 study assessing both histology and DSQ score****. It is not clear, however, that a statistically significant difference in change from baseline vs placebo in DSQ score would be clinically meaningful to individual patients. You should define a responder a priori based on the data from your phase 2 studies.*** *Please address how the patient global impression of change data from phase 2 might be leveraged to help establish a responder definition for phase 3.* ***You should also include a patient global impression of disease severity score in phase 3 to support the clinical relevance of the responder definition selected.***
  >
  > *[...]* ***Post-Meeting Comment: Please provide a summary of the results of the anchor-based and distribution-based analyses that support a*** (b) (4) ***change in the DSQ as a clinically meaningful responder definition.***

- 2015: COA Staff reviewed the Sponsor's response to an information request that included anchor-based analyses of phase 2 DSQv4 scores using PGIC (refer to COA review AT2015-096; DARRTS Reference ID: 3832615). The Sponsor provided the following table as justification for a responder definition of 30% change in DSQ score:

Measure used to classify: PGI-C	N OBS (n=87, mITT)	N	Mean	Median	Std Dev	Minimum	Maximum
Worse	2	2	-2.82	-2.82	8.03	-8.49	2.86
A little worse	6	6	-12.71	-7.92	49.72	-100	54.29
No change	12	12	-18.23	-13.80	40.16	-100	53.95
A little better	23	23	-28.19	-19.23	44.38	-100	79.53
Better	23	23	-55.40	-59.13	41.15	-100	37.25
Much better	20	20	-75.42	-74.50	25.14	-100	-4.02

(Source: \\CDSESUB1\evsprod\ind103173\0059\m1\us\efficacy-information-amendment.pdf))

FDA responded with the following comment (refer to Advice/Information Request dated 9/15/2015; DARRTS Reference ID: 3819768):

> ***Your proposal to use a 30% change in the DSQ as a responder definition for one of the components of the co-primary endpoints is acceptable, however it should be supported by sensitivity analyses looking at absolute point changes.*** *There are differences between "percent reduction" vs. "score/point reduction." For example, it may be mathematically easier to be classified as a responder in subjects with certain disease severity subgroups (e.g., mild subgroup with low baseline score) using a percent reduction responder definition.* ***From your phase 3 data, please provide the following as supportive analyses:***
>
> - *Descriptive statistics of DSQ scores (including frequency distribution tables and histograms of the DSQ score) at baseline and end-of-study.*
> - *Descriptive statistics of DSQ change scores (including frequency distribution tables and histograms of the DSQ change score) from baseline to end-of-study.*
> - *Cumulative distribution function curves for the DSQ change scores (absolute change and percent change) by patient global impression scale response options. We recommend that you consider using a global measure of severity that asks about the patient's current symptom experience in a non-comparative way (at different time points) rather than requiring patients to make a comparison to some period in the past (i.e., patient global impression of change as you used in your phase 2 study).*
> - *A table with DSQ change score statistics and patient responder numbers and percentages using the ≥30% responder definition, split into baseline DSQ severity level subgroups (i.e., 0-21, 22-42, 43-63, 64-84) or into baseline patient global measure of severity.*

- 2018: FDA sent an information request reminding the Sponsor of the supportive analyses requested in the Advice/Information Request dated 9/15/2015 (DARRTS Reference ID: 3819768). The Sponsor responded by confirming that the requested supportive analyses had been incorporated in the final draft SAP for SHP621-301 (source: \\CDSESUB1\evsprod\ind103173\0124\m1\us\response.pdf).

- 2018: FDA sent a follow-up information request seeking clarification on analyses of DSQ change scores in the final draft SAP and requesting inclusion of shell tables for 1-point and 2-point PGIS changes in the final SAP (refer to Advice/Information Request dated 9/17/2018; DARRTS Reference ID: 4321984).

- 2019: FDA sent a follow-up information request regarding inclusion of 10th, 25th, 50th, 75th, and 90th percentile change scores and sample sizes for each curve in all anchor-based eCDF figures, and also requesting these percentiles in the shell tables (refer to Advice/Information Request dated 2/7/2019; DARRTS Reference ID: 4387185).

- 2020: FDA communicated the following comments to the Sponsor at the pre-NDA meeting requesting anchor-based analyses of phase 3 data to confirm the clinically meaningful within-patient change threshold for DSQ score (refer to Additional Comments in the Meeting Minutes dated 6/2/2020; DARRTS Reference ID: 4618512):

    - ***Submit a patient-reported outcome (PRO) evidence dossier that includes all the evidence to support the content validity and psychometric measurement properties and performance of the latest version of the Dysphagia Symptom Questionnaire (DSQ) used in your phase 3 program.*** *You may refer to the Appendix of the 2009 FDA Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf) for the PRO-related information that should be included in an evidence dossier for review by the FDA.*

    - ***Please conduct anchor-based analyses using your phase 3 data to confirm the clinically meaningful within-patient change threshold for DSQ score (absolute change and percent change).*** *We refer you to the recommendations conveyed in our September 15, 2015 'Advice/Information Request' letter, February 15, 2018 email, September 17, 2018 'Advice/Information Request' letter, and February 07, 2019 'Advice/Information Request' letter.*

Previous COA Reviews:

- C2019406 (DARRTS Reference ID: 4522464)
- C2019159 (DARRTS Reference ID: 4466624)
- C2019003 (DARRTS Reference ID: 4386311)
- C2018259 (DARRTS Reference ID: 4320755)
- C2017186 (DARRTS Reference ID: 4320700)
- AT2015-096 (DARRTS Reference ID: 3832615)
- AT2014-115 (DARRTS Reference ID: 3659806)

- AT2013-079 (DARRTS Reference ID: 3361414)
- AT2012-049 (DARRTS Reference ID: 3158289)
- AT2010-096 (DARRTS Reference ID: 2865831)
- AT2010-080 (DARRTS Reference ID: 2865790)

Disease Background: EoE is a chronic disease. Adolescents and adults with EoE are reported to present clinically with dysphagia and food impaction. Refer to Section 2.1 of the integrated review for additional information.

Investigational Product: Budesonide is an anti-inflammatory corticosteroid with high glucocorticoid and weak mineralocorticoid activity. The investigational product is an oral suspension. Refer to Section 3 of the integrated review for additional information.

4 CLINICAL OUTCOME ASSESSMENT REVIEW

4.1 Clinical Trial Population

The target population for Studies SHP621-301 and SHP621-302 were adolescent and adult (aged 11 to 55 years) EoE patients with dysphagia.

Study SHP621-301 consisted of 318 patients, randomized 2:1 to treatment vs. placebo. Study SHP621-302 (the extension study) consisted of 219 subjects who had completed SHP621-301, with randomization based on treatment assignment and treatment response in SHP621-301.

Refer to Section 6.2.2.2 of the integrated review for additional information on inclusion and exclusion criteria.

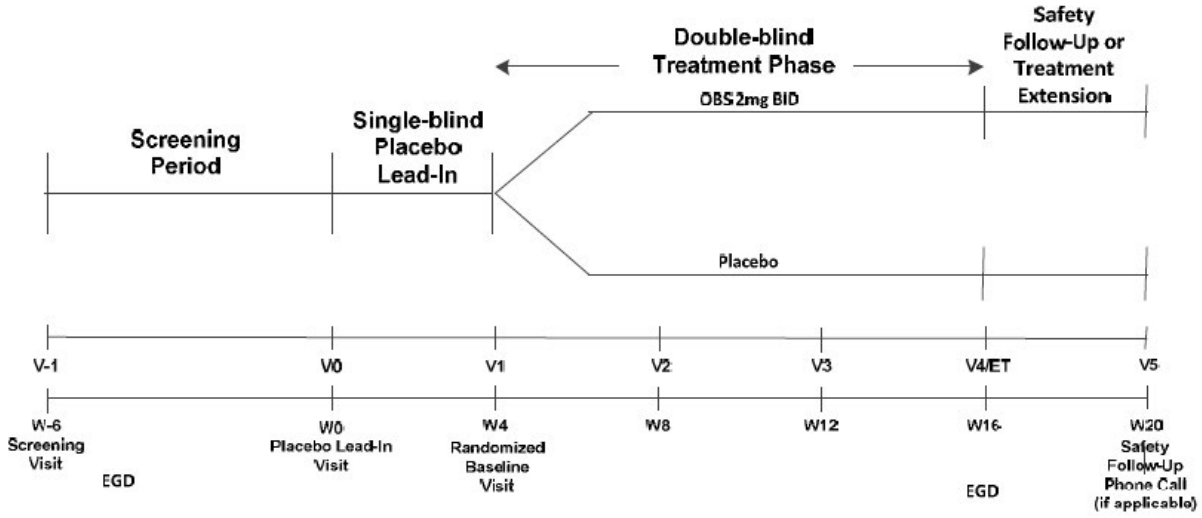
4.2 Clinical Trial Design

Study SHP621-301 was a phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of BOS treatment administered twice daily for 12 weeks in adolescents and adults, aged 11 to 55 years, inclusive, with EoE and symptoms of dysphagia.

Study SHP621-302 was a phase 3, double-blind extension study to evaluate the efficacy, safety, and tolerability of BOS treatment administered twice daily for 36 weeks. The study was conducted in adolescents and adults with EoE and dysphagia who completed the SHP621-301 induction study.

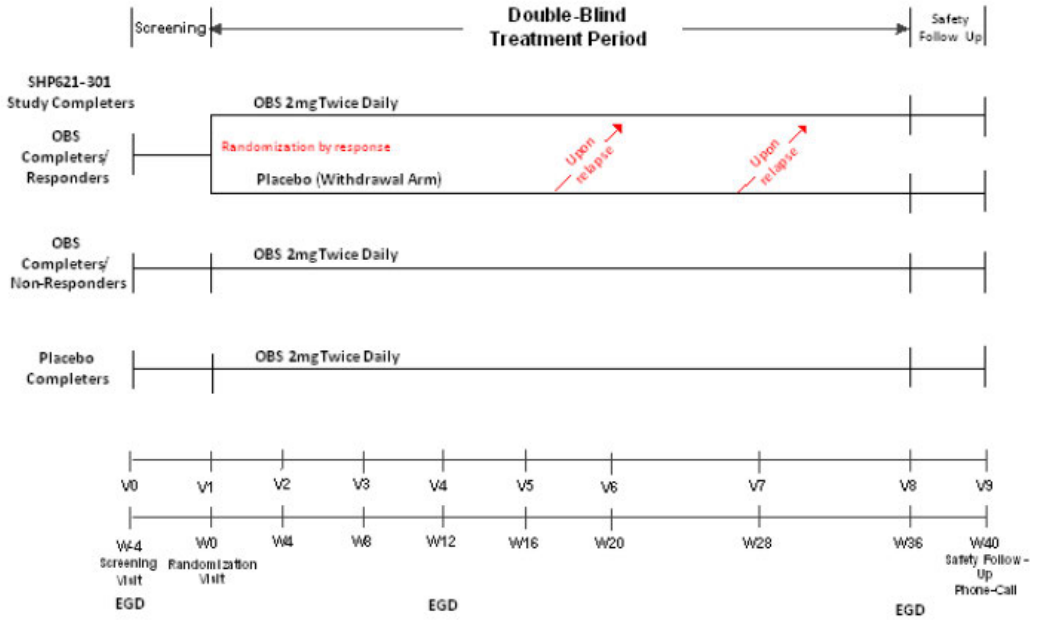
Figures 1 and 2 describe the clinical trial designs of Study SHP621-301 and SHP621-302, respectively.

Figure 1. *SHP621-301 Study Design*



BID=twice daily; EGD=esophagogastroduodenoscopy; ET=end of treatment; BOS=oral budesonide suspension

Figure 2. *SHP621-302 Study Design*



EGD=esophagogastroduodenoscopy; BOS (BOS)=oral budesonide suspension
Note: The IP was originally referred to as oral budesonide suspension (OBS) and is now referred to as budesonide oral suspension (BOS).
Note 2: The nonresponder group also includes partial responders.

Refer to Section 6.2.2.1 of the integrated review for additional information on clinical trial design.

4.3 Endpoint Position, Definition, and Assessment Schedule

Table 1 describes the placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for Studies SHP621-301 and SHP621-302. Refer to Section 6.2.2.1 of the integrated review for additional information on clinical trial design.

Table 1. *Endpoint Position, Definition, and Assessment Schedule for SHP621-301*

Endpoint Position	Assessment	Endpoint Definition	Assessment Frequency
Co-Primary	Dysphagia Symptom Questionnaire version 5 (DSQv5; PRO)	Co-Primary: ≥30% reduction in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)	☒ Daily
Co-Primary	Histologic response	Peak eosinophil count of ≤6/HPF across all available esophageal levels at the final treatment period evaluation (Visit 4)	☒ Other
Key Secondary	DSQv5 (PRO)	Change in DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation (Visit 4)	☒ Daily
Exploratory	Patient Global Impression of Severity (PGIS; PRO)	Change in PGIS from baseline to the final treatment period evaluation (Visit 4)	☒ Monthly

ClinRO= Clinician-reported outcome; **ObsRO**= Observer-reported outcome;
PerfO= Performance outcome; **PRO=** Patient-reported outcome

5 CLINICAL OUTCOME ASSESSMENTS

5.1.1 Dysphagia Symptom Questionnaire version 5 (DSQv5)

The DSQv5 is a 4-item PRO assessment of dysphagia and painful swallowing. **Table 2** describes the instrument's items, response options, and item-level scores.

Table 2. *DSQv5 Items, Response Options, and Response Scoring*

DSQ Questions (Version 5)	Response Options	Scoring
1. Since you woke up this morning, did you eat solid food?	▪ Yes	▪ Patient continues ▪ Not scored
	▪ No	▪ Patient stops ▪ Questions 2 through 4 are set to missing
2. Since you woke up this morning, has food gone down slowly or been stuck in your throat or chest?	▪ Yes	▪ 2 points
	▪ No	▪ 0 points
3. For the most difficult time you had while swallowing food today, did you have to do anything to make the food go down or to get relief?	▪ No, it got better or cleared up on its own	▪ 0 points
	▪ Yes, I had to drink liquid to get relief	▪ 1 point
	▪ Yes, I had to cough and/or gag to get relief	▪ 2 points
	▪ Yes, I had to vomit to get relief	▪ 3 points
	▪ Yes, I had to seek medical attention to get relief	▪ 4 points
4. The following question concerns the amount of pain you have experienced when swallowing food: What was the worst pain you had while swallowing food today?	▪ None, I had no pain	▪ 0 points
	▪ Mild	▪ 1 point
	▪ Moderate	▪ 2 points
	▪ Severe	▪ 3 points
	▪ Very Severe	▪ 4 points

DSQ = Dysphagia Symptom Questionnaire.

Screenshots of the exact DSQv5 instrument used in Studies SHP621-301 and SHP621-302 are provided in **Appendix A** of this review.

5.1.2 Conceptual Framework

Table 3 describes the conceptual framework for the DSQv5.

Table 3. *DSQv5 Conceptual Framework*

DSQ Version 5 Question	Domain	Concept
1. Since you woke up this morning, did you eat solid food?	(Not scored)	Coping Behavior
2. Since you woke up this morning, has food gone down slowly or been stuck in your throat or chest?	Food passing slowly	Dysphagia
3. For the most difficult time you had while swallowing food today, did you have to do anything to make the food go down or to get relief?	Difficulty swallowing	
4. The following question concerns the amount of pain you have experienced when swallowing food: What was the worst pain you had while swallowing food today?	Pain on swallowing	Odynophagia

5.1.3 Scoring Algorithm

The DSQ scoring method used to support the co-primary endpoint is described as the "Combined Score." The DSQ combined score is based on the sum of scores of Question 2 and Question 3, prorated for a 14-day period. The calculation is as follows:

> *DSQ combined score = (Sum of daily DSQv5 Question 2 and Question 3 responses) × 14 days/(Number of daily diaries with non-missing data in the selected 14-day period)*

The possible range of daily scores for Question 2 + Question 3 is 0 to 6. Therefore, over a 14-day period, the range of possible DSQ combined scores is 0 to 84.

5.1.4 Content Validity

Overall, development of the DSQ involved:

- Hybrid concept elicitation and cognitive interviews using DSQ version 1 (DSQv1) in 20 patients (10 adults and 10 adolescents);
- Additional cognitive interviews using DSQ version 2 (DSQv2) in 20 patients (10 adults and 10 adolescents);
- A 30-day field test using DSQ version 3 (DSQv3) in 37 patients (19 adults and 18 adolescents);
- Addition of Question 4 (assessing worst pain while swallowing) in DSQv4 based on FDA feedback; and

- Revisions to recall periods for Question 3 (i.e., from "today (during the past 24 hours)" to "today") and Question 4 (i.e., from "over the past 24 hours" to "today") in DSQv5 based on FDA feedback.

The first version of the DSQ (DSQv1) was developed (b) (4)

(b) (4)

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(b) (4)

5.1.5 Other Measurement Properties

5.1.5.1 Test-Retest Reliability

Table 11 describes the results of test-retest reliability analyses from phase 3 data. Overall, intra-class correlation coefficients (ICCs) ranged from 0.69-0.97 in adolescents and 0.85 to 0.90 in adults, which is acceptable. ICCs were calculated based on patients who had no change in PGIS scores from Baseline to Week 8, Week 8 to Week 12, or Week 12 to Week 16 in SHP621-301, and from Baseline to Week 12 or Week 12 to Week 36 in SHP621-302. Test-retest reliability is acceptable based on analysis results from Week 8 to Week 12 (0.89; 95% CI: 0.75, 0.95) and Week 12 to Week 16 (0.89; 95% CI: 0.67, 0.96). However, it should be noted that the Baseline to Week 8 analysis for adolescents showed a notably lower ICC with a wide 95% CI (0.69; 95% CI: 0.25, 0.89).

Table 11. *Test–Retest Reliability for the DSQv5 Summary Scores: Studies SHP621-301 and SHP621-302*

				Subsample = No Change in PGIS Intraclass Correlation Coefficient (95% CI), n	
Age Group	**Study**	**Test**	**Retest**	**DSQ Combined**	**DSQ + Pain**
Adolescents	SHP621-301	Baseline	Week 8	0.69 (0.25, 0.89), 16	0.72 (0.32, 0.90), 16
		Week 8	Week 12	0.89 (0.75, 0.95), 22	0.86 (0.69, 0.94), 22
		Week 12	Week 16	0.89 (0.67, 0.96), 24	0.88 (0.57, 0.96), 24
	SHP621-302	Baseline	Week 12	–[a], 13	–[a], 13
		Week 12	Week 36	0.97 (0.92, 0.99), 16	0.98 (0.94, 0.99), 16
Adults	SHP621-301	Baseline	Week 8	0.85 (0.79, 0.89), 152	0.87 (0.82, 0.90), 152
		Week 8	Week 12	0.89 (0.85, 0.92), 166	0.91 (0.88, 0.94), 166
		Week 12	Week 16	0.90 (0.87, 0.93), 167	0.91 (0.87, 0.93), 167
	SHP621-302	Baseline	Week 12	0.89 (0.83, 0.93), 86	0.89 (0.84, 0.93), 86
		Week 12	Week 36	0.88 (0.82, 0.92), 76	0.89 (0.84, 0.93), 76

DSQv5 = Dysphagia Symptom Questionnaire (Version 5); ICC = intraclass correlation coefficient; PGIS = patient global impression of severity.

[a] ICC not computed due to sample size < 15.

Notes: Table used data from participants included in the psychometric analysis sample.

5.1.5.2 Convergent Validity

Table 12 describes the results of convergent validity analyses from phase 3 data. Correlations with the PGIS were moderate to strong as expected at Week 16 for both adults (0.76; $p < 0.05$) and adolescents (0.77; $p < 0.05$). The correlation between DSQ combined score and PGIS at baseline was notably lower for adolescents (0.36; $p < 0.05$) than adults (0.61; $p < 0.05$). In the

adolescent group, correlation between DSQ combined score and the PedsQL-EoE Symptoms II domain score (which measures trouble swallowing, feeling like food gets stuck in throat or chest, needing to drink to help swallow food, and needing "more time to eat than other kids my age") was around -0.40 ($p < 0.05$) at Baseline and Week 16. In the adult group, correlation between DSQ combined score and the EoE-QoL-A eating/diet impact domain score (which assesses fear, worry, and embarrassment related to eating because of EoE) were also around -0.40 ($p < 0.05$).

Table 12. *Construct Validity Correlations for the Key DSQv5 Summary Scores: Study SHP621-301*

	Correlation Coefficient, n			
	Correlation with DSQ Combined		Correlation with DSQ + Pain	
Supportive Measures	**Baseline**	**Week 16/ET**	**Baseline**	**Week 16/ET**
Adolescents				
PGIS	0.36*, 40	**0.77*, 39**	0.49*, 40	**0.79*, 39**
Peak eos/HPF	-	−0.14, 39	-	−0.18, 39
PedsQL-EoE				
Total score	−0.18, 38	−0.21, 37	−0.25, 38	−0.22, 37
Symptoms I	−0.25, 38	−0.32, 37	−0.35*, 38	−0.38*, 37
Symptoms II	**−0.39*, 38**	**−0.43*, 37**	**−0.34*, 38**	**−0.41*, 37**
Treatment	0.06, 38	−0.10, 37	0.03, 38	−0.08, 37
Worry	−0.00, 38	−0.04, 37	−0.07, 38	−0.04, 37
Communication	−0.07, 38	0.16, 37	−0.15, 38	0.15, 37
Food and eating	−0.26, 24	−0.11, 23	−0.28, 24	−0.14, 23
Food feelings	−0.11, 24	0.19, 23	−0.14, 24	0.18, 23
Adults				
PGIS	**0.61*, 274**	**0.76*, 248**	**0.66*, 274**	**0.77*, 248**
Peak eos/HPF	-	0.14*, 245	-	0.16*, 245
EoE-QoL-A				
Total Score	−0.29*, 273	−0.38*, 248	−0.33*, 273	−0.39*, 248
Eating/diet impact	**−0.33*, 273**	**−0.40*, 248**	**−0.35*, 273**	**−0.41*, 248**
Social impact	−0.12, 273	−0.27*, 248	−0.14*, 273	−0.27*, 248
Emotional impact	−0.35*, 273	−0.40*, 248	−0.41*, 273	−0.42*, 248
Disease anxiety	**−0.13*, 273**	**−0.26*, 248**	**−0.16*, 273**	**−0.27*, 248**
Swallowing anxiety	**−0.19*, 273**	**−0.28*, 248**	**−0.22*, 273**	**−0.28*, 248**

* $P < 0.05$; '-' = Not assessed.

DSQv5 = Dysphagia Symptom Questionnaire (Version 5); EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life Questionnaire; EOS/HPF = esophageal peak eosinophil counts/high power field; ET = early termination; PedsQL-EoE = Pediatric Quality of Life–EoE Questionnaire; PGIS = Patient Global Impression of Severity.

Notes: Table used data from participants included in the psychometric analysis sample. **Bold** font indicates hypothesized correlations; blue-shaded cells indicate support for convergent validity. Pearson correlations were computed, except for polyserial correlations, which were computed with PGIS.

Convergent validity was also assessed using phase 2 data by correlating DSQv4 scores to peak eosinophil count and scores from a Physician Global Assessment (PGA) visual analogue scale. Peak eosinophil count and the PGA are not PRO measures and are not adequate comparators for assessment of convergent validity, and a PGIS scale was not included in phase 2. Nonetheless, Pearson and Spearman correlations were both low (0.0250 and 0.0337, respectively, for peak eosinophil count; 0.2658 and 0.2587, respectively, for PGA). It was observed that some physicians were reporting low disease activity despite the patient reporting higher DSQ scores.

5.1.5.3 Known-Groups Validity

Figures 3 and 4 describe the results of known-groups validity analyses from phase 3 data. DSQ combined scores were significantly lower for patients who reported no or mild severity on the PGIS versus patients who responded moderate, severe, or very severe on the PGIS. A notable limitation is that most patients in phase 3 were mild or moderate on the PGIS at baseline, and therefore, there is limited data on patients who reported severe or very severe on the PGIS.

Figure 3. *Box Plot of DSQ Combined Scores by PGIS at Week 16/ET: Study SHP621-301*

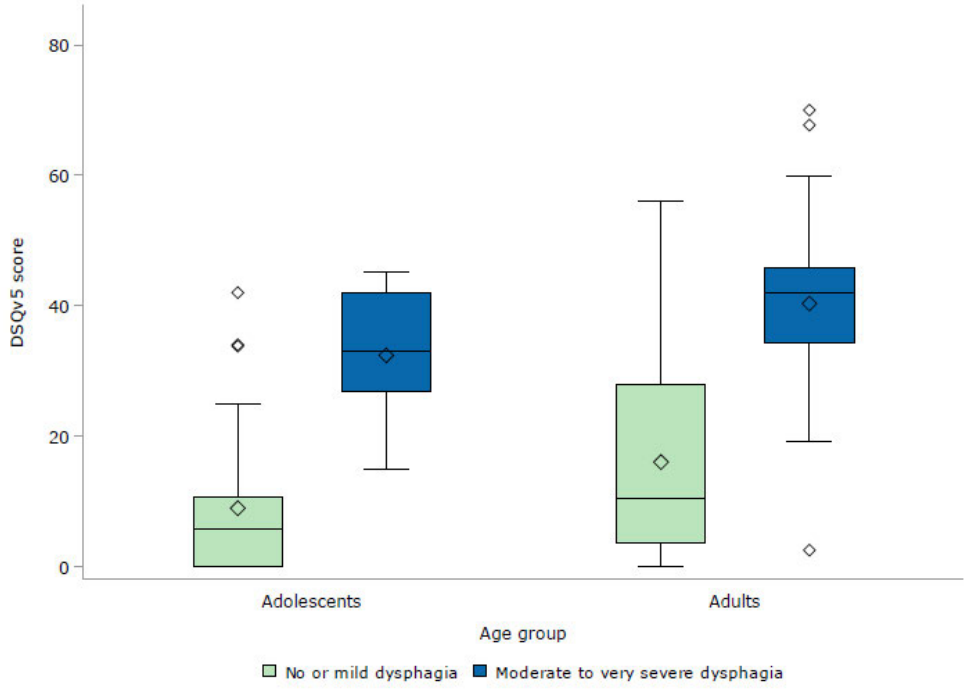
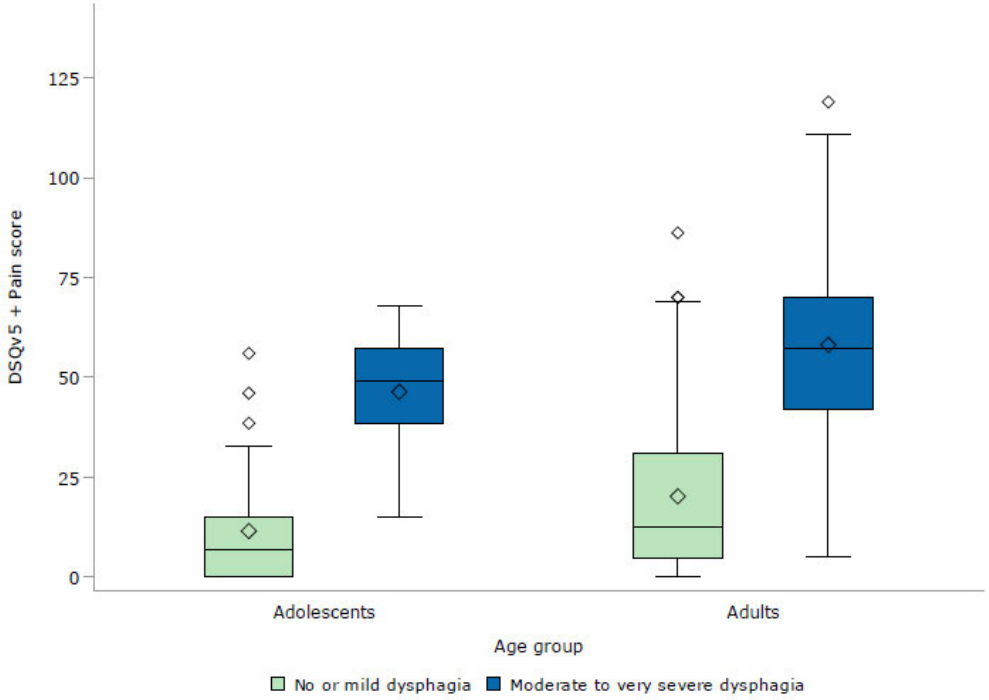


Figure 4. *Box Plot of DSQ + Pain Scores by PGIS at Week 16/ET: Study SHP621-301*



Phase 2 analyses of known-groups validity categorized patients based on PGA data and a patient-reported EoE Symptom Survey. The PGA analysis is of limited utility, given that the convergent validity analysis previously described showed poor correlations between PGA and DSQ scores. The EoE Symptom Survey analysis is of limited utility because the survey did not assess symptom severity (it only assessed presence of symptoms) and did not assess dysphagia symptoms (it assessed heartburn, chest pain, regurgitation, abdominal pain, nausea, and vomiting). Nonetheless, statistically significant differences in mean DSQ scores were observed at baseline between patients who did or did not report heartburn ($p = 0.0140$), chest pain ($p = 0.0448$), regurgitation ($p = 0.0092$), nausea ($p = 0.0325$), and vomiting (<0.0001) on the EoE Symptom Survey, and a trend towards a significant difference in mean scores was observed between DSQ and PGA scores, but it was not statistically significant ($p = 0.0709$).

5.1.5.4 Ability to Detect Change

Figures 5 and 6 describe the results of analyses of ability to detect change from phase 3 data. Improvements in PGIS were correlated with improvements (i.e., decrease) in DSQ scores, but statistically significant differences were only found for adults ($p < 0.05$) and not adolescents.

Figure 5. *Box Plot of DSQ Combined Scores by PGIS at Week 16/ET: Study SHP621-301*

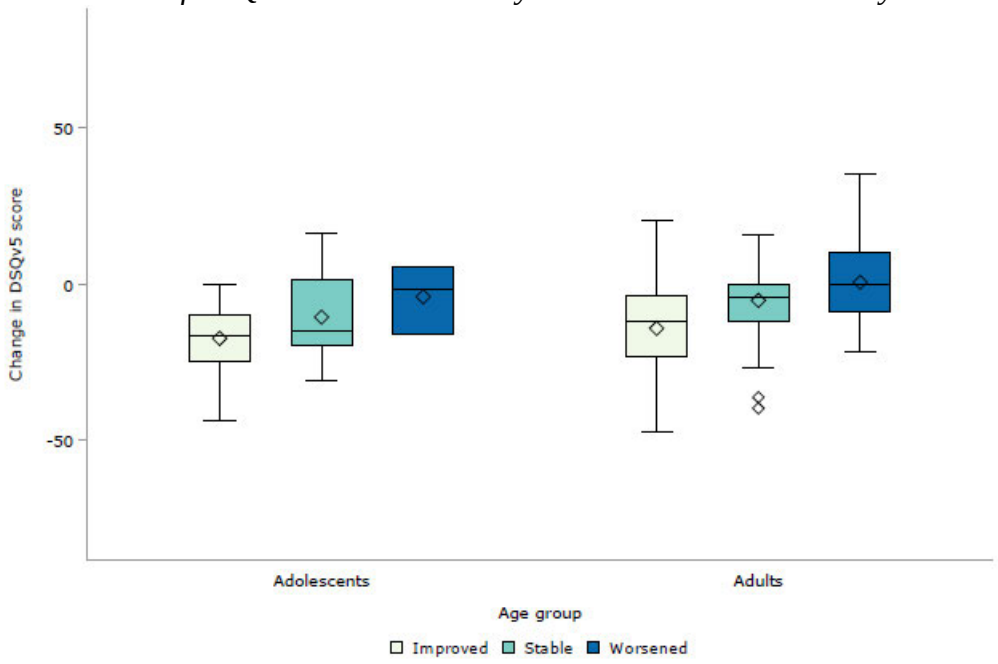
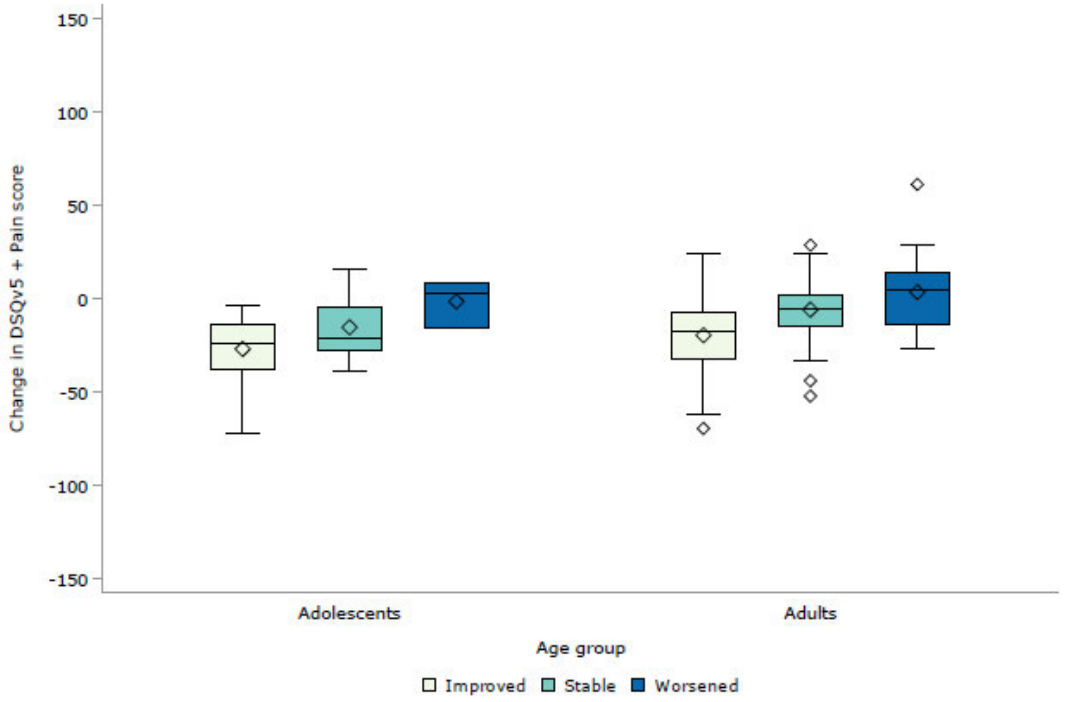


Figure 6. *Box Plot of DSQ + Pain Scores by PGIS at Week 16/ET: Study SHP621-301*



5.1.5.5 Floor and Ceiling Effects

Table 13 describes floor and ceiling effects for Questions 3 and 4 in both the phase 2 study (MPI 101-06) using the DSQv4 and phase 3 study (SHP621-301) using the DSQv5.

DSQ Questions	n	% Floor (Lowest Score)	% Ceiling (Highest Score)
Study MPI 101-06			
Question 3. For the most difficult time you had while swallowing food today, did you have to do anything to make the food go	93	8.6	6.5
Question 4. What was the worst pain you had while swallowing food today?	93	17.4	5.4
Study SHP621-301			
Question 3. For the most difficult time you had while swallowing food today, did you have to do anything to make the food go	316	7.0	0.0
Question 4. What was the worst pain you had while swallowing food today?	316	15.5	0.0

DSQ = Dysphagia Symptom Questionnaire; SD = standard deviation.
Notes: Table used data from participants included in the psychometric analysis sample. Questions 3 and 4: Floor = 0 and Ceiling = 56.

5.1.5.6 Missing Data

A review of the daily item-level DSQ responses during baseline in phase 3 showed a low frequency of missing responses to Question 1 (Did you eat solid food?). The frequency of reporting "No" to Question 1 (Did you eat solid food?) on any of the 14 days was considerably lower than the frequency of missing responses, indicating missing responses to Questions 2 through 4 during the baseline period, and in turn the DSQv5 summary scores, could not be accounted for by patients' avoidance of solid food (i.e., responding "No" to Question 1). Only a single adolescent reported "No" on 5 out of the 14 days and the number of adults who reported "No" ranged from 0 (day 7) to 8 (2.9%; day 14). Similar patterns of missingness were observed at Week 16/ET, with more daily missing (unreported causes) than "No" responses to Question 1 (Did you eat solid food?) during the 14-day period.

Analysis of missing data during the baseline period in phase 2 was consistent across the DSQ questions: 15.1% for Question 1 (Did you eat solid food?), 15.1% for Question 2 (Since you woke up this morning, has food gone down slowly or been stuck in your throat or chest?), and 16.4% for Question 3 (For the most difficult time you had swallowing food today, did you have to do anything to make the food go down or to get relief?). The percentage of missing data increased to 33.6% for all three questions by Week 12.

5.1.6 Interpretation of Meaningful Within-Patient Score Changes

5.1.6.1 Anchor Scales

The only anchor scale included in phase 3 was a Patient Global Impression of Severity (PGIS) scale with a 7-day recall period, which did not match the 14-day assessment period used for scoring the DSQ.

The only anchor scale included in phase 2 was a Patient Global Impression of Change (PGIC). The PGIC is not ideal as the sole anchor because it requires patients to recall back to their disease status before beginning treatment. The endpoint in phase 2 was at 12 weeks, making the PGIC effectively require a 12-week recall period. Furthermore, the version of the DSQ used in phase 2 (DSQv4) was different than the version used in phase 3 (DSQv5), and the extent to which any differences between the two versions of the DSQ may limit their comparability is currently unknown.

5.1.6.2 Anchor-Based Analyses

Table 14 below describes the PGIS response distributions for adolescents and adults. Almost half of patients in both age groups reported having mild symptoms at baseline.

Table 14. *PGIS Response Distributions by Age Group*

	Study SHP621-301		Study SHP621-302 (Extension)	
PGIS	**Baseline**	**Week 16/ET**	**Week 0**	**Week 36/ET**
Adolescents, n (%)	**40 (97.6)**	**41 (100.0)**	**30 (100.0)**	**30 (100.0)**
No dysphagia	1 (2.5)	13 (31.7)	8 (26.7)	15 (50.0)
Mild dysphagia	19 (47.5)	16 (39.0)	17 (56.7)	9 (30.0)
Moderate dysphagia	17 (42.5)	12 (29.3)	5 (16.7)	5 (16.7)
Severe dysphagia	3 (7.5)	0 (0.0)	0 (0.0)	1 (3.3)
Very severe dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1	0	0	0
Adults, n (%)	**276 (99.6)**	**265 (95.7)**	**187 (98.9)**	**181 (95.8)**
No dysphagia	9 (3.3)	66 (24.9)	57 (30.5)	80 (44.2)
Mild dysphagia	149 (54.0)	140 (52.8)	90 (48.1)	70 (38.7)
Moderate dysphagia	97 (35.1)	44 (16.6)	33 (17.6)	24 (13.3)
Severe dysphagia	18 (6.5)	10 (3.8)	6 (3.2)	7 (3.9)
Very severe dysphagia	3 (1.1)	5 (1.9)	1 (0.5)	0 (0.0)
Missing	1	12	2	8
Overall, n (%)	**316 (99.4)**	**306 (96.2)**	**217 (99.1)**	**211 (96.3)**
No dysphagia	10 (3.2)	79 (25.8)	65 (30.0)	95 (45.0)
Mild dysphagia	168 (53.2)	156 (51.0)	107 (49.3)	79 (37.4)
Moderate dysphagia	114 (36.1)	56 (18.3)	38 (17.5)	29 (13.7)
Severe dysphagia	21 (6.6)	10 (3.3)	6 (2.8)	8 (3.8)
Very severe dysphagia	3 (0.9)	5 (1.6)	1 (0.5)	0 (0.0)
Missing	2	12	2	8

ET = early termination; PGIS = Patient Global Impression of Severity.

Notes: Table used data from participants included in the psychometric analysis sample.

Anchor-based analyses were conducted using phase 2 data (MPI 101-06, using DSQv4 and PGIC) and phase 3 (SHP621-301, using DSQv5 and the 7-day recall PGIS). Note that, as stated previously, the 7-day recall period of the PGIS did not match the 14-day assessment period of the DSQ. Nonetheless, **Table 15** describes the results of anchor-based analyses from phase 2 and phase 3 data.

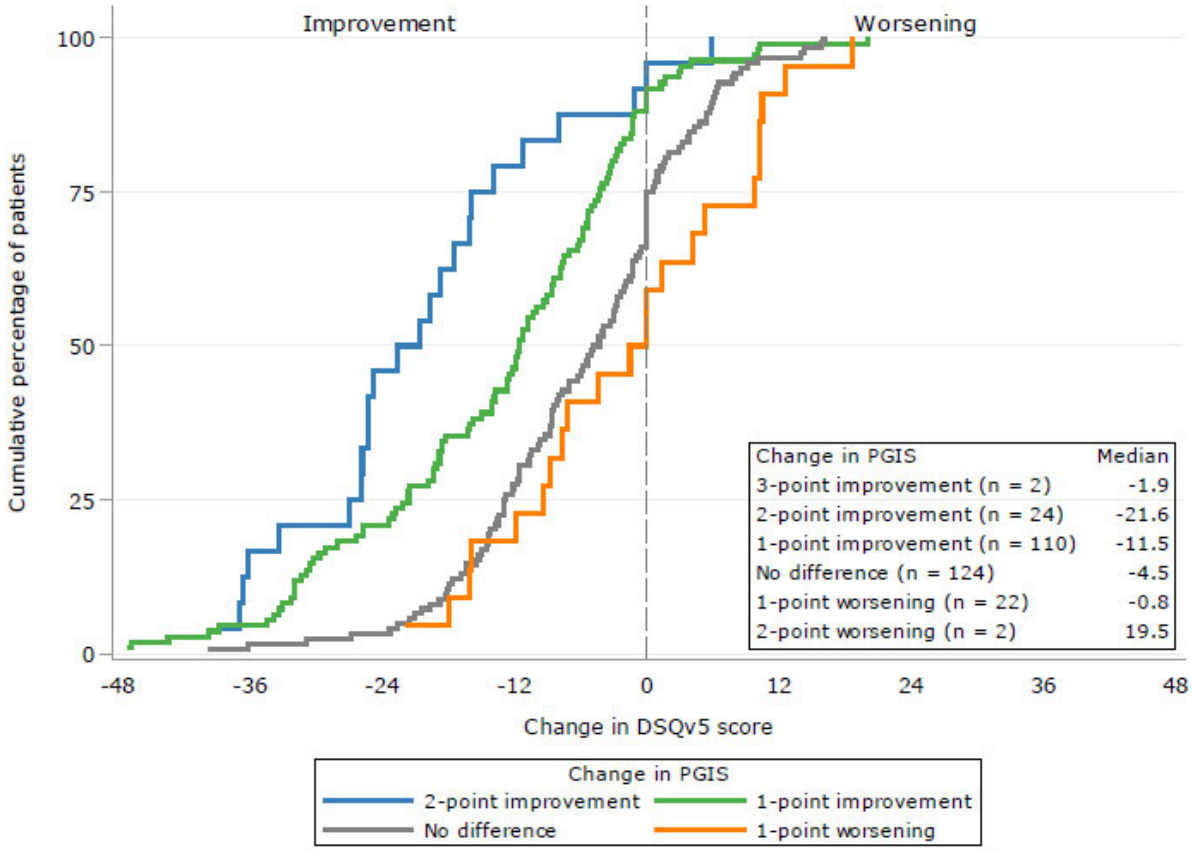
Table 15. *Summary of Thresholds of Meaningful Within-Patient Change*

	DSQ Combined	
Method	**Absolute Change**	**Percentage Change**
Based on Study MPI 101-06[b]		
Anchor-based		
PGIC "a little better" (n = 24)	-6.5	-27.4
PGIC "better" (n = 23)	-13.5	-55.4
Distribution-based		
Half-SD	7.4	
SEM	9.8	
Based on Study SHP621-301 Data		
Anchor-based[a]		
Improvement of 1-point in PGIS (n = 110)		
Mean	-13.6	-49.9
Median	-11.5	-56.6
Improvement of 2-point in PGIS (n = 24)		
Mean	-20.6	-68.4
Median	-21.6	-80.4
Distribution-based		
Half-SD	6.82	
SEM range	4.54, 7.60	

DSQv5 = Dysphagia Symptom Questionnaire (Version 5); PGIC = patient global impression of change; PGIS = patient global impression of severity; SD = standard deviation; SEM = standard error of measurement.
'-' = Not assessed.
[a] The remaining a priori selected anchor measure, eos/HPF, did not meet the recommended magnitude of the correlation between DSQv5 scores and eos/HPF (i.e., 0.371) or did not exhibit the expected linear relationship in DSQ change scores across the levels of the anchor measure. Such findings suggest that eos/HPF is not a suitable anchor for estimating the threshold of meaningful within-person change in DSQv5 scores.
[b] Thresholds included in Hudgens et al. and Takeda's DSQ (Version 4) estimates estimated using Phase 2 Clinical Study MPI 101-06 (PRO Dossier, September 26, 2014).

Figure 7 below shows the empirical cumulative distribution function (eCDF) curves for anchor-based analyses of DSQ combined scores by PGIS categories.

Figure 7. *Empirical CDF Plot of Change from Baseline to Week 16/ET in DSQ Combined Score by Change in PGIS: Study SHP621-301 (Overall)*



CDF = cumulative distribution function; DSQv5 = Dysphagia Symptom Questionnaire (Version 5); ET = early termination; PDF = probability density function; PGIS = patient global impression of severity.
Notes: Figure used data from participants included in the psychometric analysis sample.

Due to the inconsistency between assessment period for the DSQ (14 days) and recall period for the PGIS (7 days), additional anchor-based analyses were conducted using 7-day DSQ scores with the PGIS. **Figures 8 and 9** below show the results of analysis of change from baseline to Week 16 in prorated and un-prorated 7-day DSQ scores, which appeared to show minimal to no separation between treatment and placebo groups in the range of scores that could be considered meaningful (indicated by dashed vertical lines in the figures). Therefore, it was concluded that no difference between BOS and placebo was identified in the range that patients considered to be a meaningful improvement.

Figure 8. *eCDF plot of Change from Baseline to Week 16 in DSQ Prorated 7-day Combined Score by Treatment Group: Study SHP621-301*

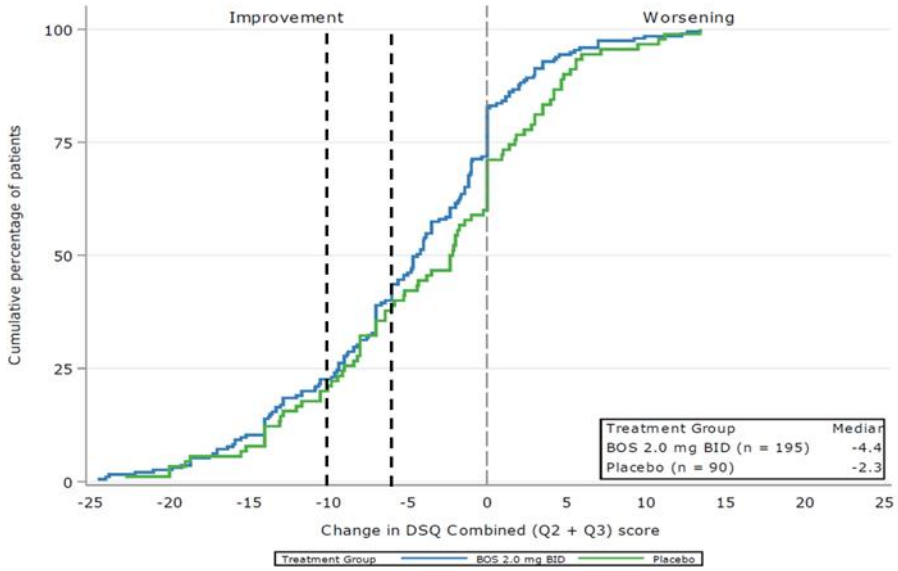
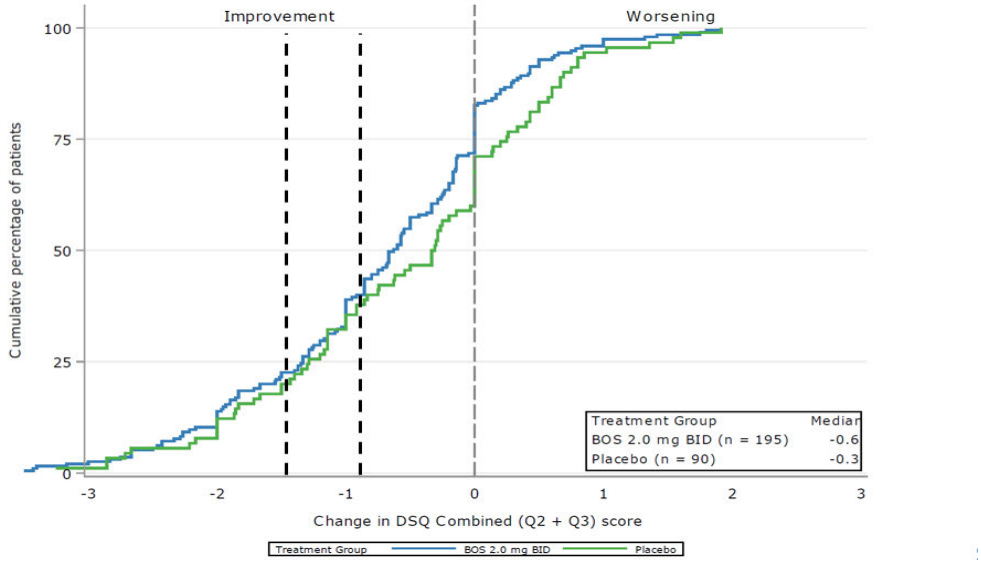


Figure 9. *eCDF plot of Change from Baseline to Week 16 in DSQ Unprorated 7-day Combined Score by Treatment Group: Study SHP621-301*



Refer to Section 6.3.2 of the integrated review for detailed assessment of the anchor-based analyses, documented by members of the review team from Biostatistics and Patient-Focused Statistical Support.

5.1.6.3 Responder Definition

The co-primary DSQ endpoint was based on a responder definition of ≥ 30% reduction in DSQ combined score. This 30% threshold was based on phase 2 anchor-based analyses using PGIC, as shown in **Table 15** above. A threshold closer to 50% appears to be more appropriate based on

PGIC responses of "better" in phase 2 (corresponding to a -55.4% change in DSQ combined scores) and 1-point improvements in PGIS in phase 3 (corresponding to a -49.9% mean change and -56.6% median change in DSQ combined scores). Refer to Section 6.3.1 of the integrated review for detailed assessment of the issues with the 30% responder threshold, documented by members of the review team from Biostatistics and Patient-Focused Statistical Support.

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8. Appendix B: Patient Global Impression of Severity (PGIS)

How would you rate the overall severity of your dysphagia (difficulty swallowing) over the past 7 days?

Rating	Description
0	No dysphagia
1	Mild dysphagia
2	Moderate dysphagia
3	Severe dysphagia
4	Very severe dysphagia

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CHRISTOPHER ST. CLAIR
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DAVID S REASNER
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Clinical Inspection Summary Report

Date	March 18, 2021
From	Zana Marks, M.D., M.P.H. Karen Bleich, M.D. Kassa Ayalew, M.D., M.P.H. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sarrit Kovacs, Ph.D. Erica Lyons, M.D. Benjamin Vali, M.S., RAC, RPM Division of Gastroenterology
NDA#	213976
Applicant	Takeda Pharmaceuticals U.S.A., Inc.
Drug	Budesonide (suspension)
NME (Yes/No)	No
Therapeutic Classification	Anti-inflammatory corticosteroid
Proposed Indication	For the treatment of eosinophilic esophagitis (EoE), (b) (4) in patients 11 years and older.
Consultation Date	December 1, 2020
Review Priority	Priority
Summary Goal Date	April 9, 2021
Action Goal Date	April 15, 2021
PDUFA Date	April 15, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies SHP621-301 and SHP621-302 were submitted to the Agency in support of a New Drug Application (NDA 213976) for budesonide oral suspension for the treatment of eosinophilic esophagitis. Three participating clinical investigators, Dr. Curtis Baum (Site 148), Dr. Evan Dellon (Site 101), and Dr. Daniel Soteres (Site 168), were selected for clinical inspection.

The primary endpoints of the studies were based on centrally-read esophageal biopsy results and subject diary data. Some of the endpoint data was available at the clinical sites for verification during the inspections, as provided to the sites by the sponsor. Endpoint data that could not be verified during inspections was verified by OSI after the inspection based on source documents submitted to the NDA by the study sponsor on March 2, 20121, as requested. The endpoint data was verified for all the subjects in the two studies at the three inspected sites.

There were no regulatory violations at the inspected sites. There was no under reporting of adverse events or protocol deviations. Based on the results of these inspections, the clinical data generated by the investigators appear reliable and are supportive of this NDA.

II. BACKGROUND

Budesonide oral suspension (BOS) consists of budesonide formulated in a viscous suspension (b) (4). Budesonide is a corticosteroid that is present in several FDA-approved drug products. Takada Pharmaceuticals submitted data from two clinical trials (SHP621-301 and SHP621-302) in support of the proposed indication for BOS for the treatment of eosinophilic esophagitis.

Study SHP621-301

Study SHP621-301 is a phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy, tolerability and safety of twice daily administration of budesonide oral suspension in adolescents and adults aged 11-55 years with eosinophilic esophagitis and dysphagia. Key eligibility criteria of the study include the presence of eosinophilic inflammation defined as ≥15 eosinophils/high power field (HPF) from at least two levels of the esophagus and the presence of moderate dysphagia defined as at least four days of dysphagia as measured by the Dysphagia Symptom Questionnaire (DSQ) over a two-week period prior to enrollment. Additionally, subjects were to have been non-responsive to a minimum of six weeks of high dose proton-pump inhibitor therapy.

All subjects were to complete a 4-week single-blind placebo lead-in prior to randomization. Eligible subjects were then to be randomized (2:1) to receive either BOS or placebo orally for 12 weeks of double-blind treatment, with randomization stratified by age group (<18 years or ≥18 years) and diet restriction for EoE or other health-related conditions (no diet restrictions or any diet restrictions). Efficacy and safety evaluations were to occur at weeks 8, 12, and 16.

The co-primary endpoints for the study are the histologic response (defined as a peak eosinophil count of ≤6/HPF across all available esophageal levels at the final treatment period evaluation) and dysphagia symptom response (defined as ≥30% reduction in the DSQ combined score (questions 2+3) from baseline to the final treatment period evaluation after 12 weeks of double-blind treatment).

At the end of the 12-week double-blind treatment phase, subjects who completed the study had the opportunity to participate in the extension study (SHP 621-302).

The study was conducted from 12/7/2015 – 2/15/2019. 450 subjects were enrolled in the placebo lead-in phase. 322 subjects were randomized in the double-blind treatment phase (215 in the BOS group and 107 in the placebo group). The study was conducted at 72 sites in the US.

Study SHP621-302

Study SHP621-302 is a phase 3 multicenter, double-blind extension study to evaluate the long-term treatment effect of BOS in subjects who completed Study SHP621-301.

Subjects were to continue their assigned double-blind treatment from SHP621-301 for up to 4 weeks, and were then to be assigned to BOS or placebo for up to 36 weeks based on their treatment group and clinical response in Study SHP621-301 as follows:

- Subjects who had received BOS in SHP621-301:
  - Full-responders at the final treatment evaluation were to be randomized (1:1) to either remain on BOS or change to placebo
  - Partial or non-responders were to remain on BOS
- Subjects who had received placebo in SHP621-301 were to receive BOS in SHP621-302

The primary endpoint of the study is relapse and is specific to the population of subjects who had received BOS and were full responders in Study SHP621-301. The relapse endpoint is defined as having both of the following:

- Histological relapse (eosinophil count of ≥15/HPF from at least 2 of 3 levels of the esophagus), and
- Dysphagia relapse (minimum of 4 days of dysphagia, measured by the DSQ in the 2-week period prior to study visit)

The key secondary endpoint of the study is long-term response and is specific to subjects who had received BOS and were non-responders in SHP621-301. The long-term response endpoint is defined as having both of the following:

- Histological response (peak eosinophil count of ≤6 eosinophils/HPF across all available esophageal levels at the final treatment period evaluation), and
- Dysphagia response (≥30% reduction in the DSQ combined score from baseline of SHP621-301 to the final treatment period evaluation in SHP621-302)

The study was conducted 4/1/2016 – 11/12/2019. 219 subjects were enrolled in the double-blind treatment period and received at least 1 dose of study drug in SHP621-302. The study was conducted at 70 sites in the US.

The Division of Gastroenterology and OSI selected three domestic investigators for clinical inspection who participated in both Study SHP621-301 and Study SHP621-302. They were selected based on relatively high enrollment, efficacy, and risk ranking by the Clinical Investigator Site Selection Tool (CISST).

III. RESULTS

1. Daniel Soteres, M.D. [Site 168]
2709 North Tejon Street
Colorado Springs, CO 80907

Dr. Soteres was inspected from January 12 through January 25, 2021 as a data audit for Studies SHP621-301 and SHP621-302. This was the second FDA clinical inspection of the investigator. The last inspection was conducted 2018, with no regulatory violations.

For both studies records for all enrolled subjects were reviewed, including informed consent forms, randomization assignments, eligibility criteria, study assessments, adverse events, laboratory test results, and electronic case report forms. Regulatory documentation was also examined, including the Institutional Review Board approvals of the study protocol and amendments, signed investigator agreements (Form FDA 1572s), delegation of tasks log, financial disclosures, training records, investigator's reporting to sponsor, sponsor's monitoring, and investigational drug storage and accountability records.

Study SHP621-301
Dr. Soteres enrolled 16 subjects into Study SHP621-301, including 11 randomly assigned to the budesonide oral suspension (BOS) arm and 5 to the placebo arm. All 16 subjects completed the study.

There was one major protocol violation at the site. Subject # (b) (6) was enrolled into the study (placebo arm) despite not having met the inclusion criteria for dysphagia in the screening period (inclusion criteria #5). The subject was randomized into the placebo arm of the trial on (b) (6). The eligibility error was identified shortly thereafter, and the study monitor and the sponsor were notified. The cause of the error was that the eligibility report from the eDiary had been performed incorrectly (user error). Dr. Soteres requested approval for the continued participation of the study subject, which was granted by the sponsor on (b) (6).

Reviewer comment: Subject # (b) (6) did not meet the dysphagia inclusion criteria and should not have been enrolled in the study. Documents at the site show that the study coordinator was provided with instructions in order to avoid repeating the error. Although this is a regulatory violation, there is no evidence of recurrence of the error at the site with other subjects. The protocol violation is appropriately reported in the data listings provided by the sponsor. There is no evidence of harm to the subject related to study participation.

There were 9 instances in which the morning cortisol blood draw was not collected during the specified timeframe of 6am – 9am, including study assessments for Subjects # (b) (6) (b) (6) These were not reported as protocol deviations. No other unreported protocol deviations were identified.

Reviewer comment: Eight of the 9 blood draws performed outside of the 6am – 9am timeframe occurred prior to 9:30am. There was one instance in which the cortisol blood draw was obtained at 11:02am. The protocol states that the 6am – 9am timeframe is a target. The delays in blood draws were mostly minimal. The delays were not reported as protocol deviations given that the protocol specified a timeframe target, not a required timeframe.

The combined Dysphagia Symptom Questionnaire (DSQ) results at baseline and at Week 16 were available at the site, provided by the sponsor. The baseline and Week 16 results were reviewed for all subjects. There were no discrepancies between the data at the site and the submitted data listings for the combined DSQ score endpoint.

The esophageal biopsy results and peak eosinophil counts were not available for verification at the site. After the close of the inspection, an information request was sent to the sponsor requesting source documents for verification of the primary endpoints of the study for the subjects enrolled by the inspected clinical investigators. The source records for the Week 16 histology results for all 16 subjects at the site were submitted to the NDA on March 2, 2021.

Reviewer comment: OSI reviewed the Week 16 esophageal biopsy results including the peak eosinophil counts for the proximal, mid, and distal esophageal biopsies for all study subjects at the site. There are no discrepancies between the source records and the data listings.

Study SHP621-302

Dr. Soteres enrolled 9 subjects into Study SHP621-302. Of the four subjects who had been full responders in Study SHP621-301, two were randomized to continue to receive BOS (Subjects # (b) (6), and two were randomized to the placebo arm (Subjects # (b) (6) Three subjects had been non-responders in Study SHP621-301 and they were assigned to continue BOS treatment in Study SHP621-302 (Subjects # (b) (6) Two subjects had been in the placebo arm of SHP621-301 and they were assigned to the BOS arm of SHP621-302 (Subjects # (b) (6) (b) (6) Two of the study subjects withdrew from the study prior to the endpoint assessments (Subjects # (b) (6) Treatment assignments and subject disposition were verified with the source records at the site.

There were 4 instances in which the morning cortisol blood draw was not collected during the specified timeframe of 6am – 9am, including study assessments for Subjects # (b) (6) (b) (6) These were not reported as protocol deviations. No other unreported protocol deviations were identified.

Reviewer comment: As with Study SHP621-301, the delays in morning cortisol blood draws were minimal (in this case, all recorded prior to 9:30am). Given the protocol instructions, the delays were not reported as protocol deviations.

Three subjects (Subjects # (b) (6) were in the full analysis set for the primary endpoint of the study (the full analysis set included subjects who had received BOS in Study 301 and achieved a full response) and were evaluated for the endpoint of relapse. The esophageal biopsy results for the histologic portion of the endpoint were not available at the site. Additionally, the evening diary scores for the dysphagia portion of the endpoint were not available at the site. As noted previously, after the close of the inspection, the source records for the endpoint data was uploaded to the submission by the sponsor.

Reviewer comment: OSI reviewed the Week 36 esophageal biopsy source reports for all subjects in the full-responder analysis set (Subjects # (b) (6) There were no discrepancies between the biopsy reports and the peak eosinophil counts in the submitted data listings. None of the three subjects had an eosinophil count ≥15/HPF. Since the definition of the relapse endpoint required the presence of ≥15 eosinophils per HPF, the co-primary endpoint result regarding Question 2 on the DSQ would not impact the relapse endpoint for these three subjects. The primary endpoint (no relapse) was thus verified for the three subjects at this site by verification of the histology results.

The secondary efficacy endpoint of the study was the long-term treatment response, assessed only for subjects who had not responded to treatment with BOS during Study SHP621-301, specifically Subjects # (b) (6) The data for the dysphagia portion of the endpoint (DSQ combined score for Week 36) was available and verified for Subject # (b) (6) at the site during the inspection. The DSQ combined score was not available at the site for Subject # (b) (6) No peak eosinophil data from esophageal biopsies was available at the site.

Reviewer comment: OSI reviewed the DSQ evening diary scores submitted by the sponsor including the two weeks used to calculate the combined DSQ score for Subject # (b) (6) (b) (6) at Week 36. OSI additionally reviewed the source esophageal biopsy records for Subjects # (b) (6) There were no discrepancies between the source records and the submitted data listings. The endpoint of long-term treatment response from baseline was confirmed to be present for Subject # (b) (6) and confirmed to be absent for Subject # (b) (6)

There were no significant study conduct concerns and there were no regulatory violations at the site. No Form FDA 483 Inspectional Observations was issued to Dr. Soteres at the conclusion of this inspection.

2. Evan Dellon, M.D. [Site 101]
130 Mason Farm Road
4140 Bioinformatics Building
Campus Box 7080
Chapel Hill, NC 27599

Dr. Dellon was inspected from February 8-12, 2021 as a data audit for Studies SHP621-301 and SHP621-302. This was the first FDA clinical inspection of the investigator.

For both studies, all subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included the informed consent forms, inclusion/exclusion criteria, randomization scheme, primary endpoint data, adverse events, laboratory tests, and electronic case report forms (CRFs). Regulatory documentation was also examined, including the Institutional Review Board approvals of the study protocol and amendments, signed investigator agreements (Form FDA 1572s), delegation of duties log, financial disclosures, training records, investigator's reporting to sponsor, sponsor's monitoring, and investigational drug storage and accountability records.

Study SHP621-301

Dr. Dellon enrolled 8 subjects into Study SHP621-301, including 7 randomly assigned to the budesonide oral suspension (BOS) arm and one to the placebo arm. All 8 subjects completed the study.

The combined Dysphagia Symptom Questionnaire (DSQ) results at baseline and at Week 16 were available at the site provided by the sponsor but were not reviewed for verification of the primary endpoint data during the inspection. The esophageal biopsy results and peak eosinophil counts were not available for verification at the site. After the close of the inspection, an information request was sent to the sponsor requesting source documents for verification of the primary endpoints of the study.

Reviewer comment: OSI reviewed the Week 16 esophageal biopsy results including the peak eosinophil counts for the proximal, mid, and distal esophageal biopsies for all 8 study subjects enrolled at the site. OSI additionally reviewed the DSQ evening diary data for all subjects for the two weeks prior to baseline and the two weeks prior to Week 16. There were no discrepancies between the source records provided by the sponsor and the data listings.

Study SHP621-302

Dr. Dellon enrolled 6 subjects into Study SHP621-302, all into the BOS treatment arm of the study. Two subjects (Subjects # (b) (6) withdrew from the study prior to completion. Four subjects completed the study. Of the four completers, one subject (Subject # (b) (6)) had been a full responder in Study 301 and was evaluated for the relapse endpoint; three subjects (Subjects # (b) (6) (b) (6) had been non-responders in Study SHP621-301 and were evaluated for the long-term response endpoint. Treatment assignments and subject disposition were verified with the source records at the site.

As in Study SHP621-301, the esophageal biopsy results were not available at the site and the DSQ diary data were not reviewed during the inspection. Both were obtained from the sponsor after the inspection.

Reviewer comment: OSI reviewed the Week 36 esophageal biopsy results for the proximal, mid, and distal esophageal biopsies and the DSQ diary data as follows:

- *For Subject # (b) (6) in the full-responder analysis set, the primary endpoint (no relapse) was verified by reviewing source DSQ evening diary entries and confirming the responses to question 2 throughout the two weeks prior to the Week 36 assessment and by verifying the Week 36 biopsy results.*

- *For Subjects # (b) (6) the secondary endpoint (no long-term response) was verified by the Week 36 esophageal biopsy results which did not meet criteria for response (the long-term response endpoint required the presence of histological response).*

- *For Subject # (b) (6) the secondary endpoint (response) was verified by both the Week 36 esophageal biopsy results and the DSQ combined scores in the two weeks prior to the Week 36 assessment.*

There were no significant study conduct concerns and there were no regulatory violations at the site. No Form FDA 483 Inspectional Observations was issued to Dr. Dellon at the conclusion of this inspection.

3. Curtis Baum, M.D. [Site 148]
720 Southwest Lane
Topeka, Kansas, 66606

Dr. Baum was inspected from February 22-26, 2021 as a data audit for Studies SHP621-301 and SHP621-302. This was the first FDA clinical inspection of the investigator.

For both studies, reviewed records included IRB approval letters and correspondence, monitoring reports, informed consent forms, subject medical records, financial disclosure reports, case report forms, subject questionnaires and electronic diaries, dosing records, responsibility logs, and site training documentation.

Study SHP621-301

Dr. Baum enrolled 14 subjects into Study SHP621-301. 13 subjects completed the study. Subject # (b) (6) was lost to follow-up after signing consent, prior to randomization. There were no discrepancies between the enrollment logs at the site and the site data listings.

One subject (Subject # (b) (6) enrolled at the site did not meet inclusion criteria #3 (peak eosinophil count of ≥15/HPF from 2 of 3 levels of the esophagus at screening endoscopy). According to the entries in the CRF reviewed at the site, the peak eosinophils from the esophageal biopsies obtained on (b) (6) were 0 (proximal), 1 (mid), and 6 (distal). Despite not having a peak eosinophil count of ≥15/HPF for any of the esophageal biopsies, the central reader entered "yes" in the eCRF indicating that the subject met

histologic criteria for the study. According to email communications reviewed at the site, the site monitor confirmed to the research coordinator that the subject did meet eligibility criteria on (b) (6) The subject was randomized to the BOS arm of the study on (b) (6) The protocol deviation was identified on (b) (6) (after the subject had completed the study) by the study monitor and is included as a protocol deviation in the data listings.

Reviewer comment: The subject did not meet the histological entry criteria for the diagnosis of eosinophilic esophagitis and should not have been enrolled in the study. Dr. Baum should have checked the results for the peak eosinophil counts to confirm eligibility. While the protocol violation is appropriately reported in the submitted data listings, we note that the subject is included in the full analysis set and thus contributes to the efficacy endpoint histological response (achieved for 113/213 subjects in the treatment arm of the trial) despite not having had histological disease at baseline. There is no evidence of harm to the subject related to study participation.

There was no evidence of under reporting of adverse events. The histological and DSQ endpoint data was available verified at the site with no discrepancies with the site data listings.

Study SHP621-302

Dr. Baum enrolled 11 subjects into Study SHP621-302, all of whom were either randomized or assigned (depending on treatment assignment and response status in SHP621-301) to receive treatment with BOS in the extension study. Subject # (b) (6) (b) (6) withdrew from the study prior to completion. Ten subjects completed the study. There were no discrepancies between the enrollment logs at the site and the site data listings.

The relapse primary endpoint was verified for the two subjects (Subjects # (b) (6) (b) (6) who had been full responders in Study SHP621-301 by verifying histologic and DSQ data (responses to evening diary question #2) available at the site as compared to the data listings.

The long-term response secondary endpoint was verified for the five subjects (Subjects # (b) (6) who had been non-responders in Study SHP621-301 using histologic and DSQ data (DSQ combined scores) available at the site as compared to the data listings.

There was no evidence of under reporting of adverse events or protocol deviations.

There were no significant study conduct concerns and there were no regulatory violations at the site. No Form FDA 483 Inspectional Observations was issued to Dr. Baum at the conclusion of this inspection.

{See appended electronic signature page}

Zana H. Marks, M.D., M.P.H.
Good Clinical Practice Assessment Branch
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cc:

Central Documentation
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Review Division/Medical Officer
Review Division /Medical Team Leader
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OSI/DCCE/GCPAB Team Leader
OSI/ GCP Program Analysts
OSI/Database Project Manager

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Maternal Health Labeling Review

Date: March 10, 2021 **Date consulted:** December 2, 2020

From: Jane Liedtka, M.D., Medical Officer, Maternal Health Team (MHT), Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, D.O., Team Leader, MHT, DPMH

Lynne Yao, MD, Division Director, MHT, DPMH

To: Benjamin Vali, Regulatory Project Manager
Division of Gastroenterology (DG)

Drug/ NDA#: Eohilia (budesonide) oral suspension, NDA 213976

Applicant: Takeda Pharmaceuticals U.S.A. Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Language
[Original 505(b)(2) NDA, Orphan Drug Designation, Breakthrough Therapy Designation, Priority Review]

Indication: For the treatment of eosinophilic esophagitis (EoE), (b) (4) (b) (4) in adult and adolescent patients 11 years and older

Materials Reviewed:

- 10/15/2020, initial submission for budesonide, NDA 213976
- DPMH Review of Budesonide. NDA 121920. Christos Mastroyannis, MD. 12/19/2018. DARRTS Reference ID# 4366204[1],[2].
- DPMH Review of Entocort EC (budesonide). NDA 21324. Miriam Dinatale, D.O.

[1] DPMH Review of Budesonide). NDA 121920. Christos Mastroyannis, MD. 12/19/2018. DARRTS Reference ID# 4366204.

[2] DPMH consult reviews of budesonide, NDAs 121920 and 21324 were part of the materials reviewed, but were not relied upon for the purposes of the recommendations.

1/25/2016. DARRTS Reference ID #3875179[2,3.]

Consult Question: Assist with Pregnancy and Lactation Labeling Rule (PLLR)

INTRODUCTION AND BACKGROUND

- On 10/15/20, the applicant, Takeda Pharmaceuticals U.S.A. Inc., submitted an original New Drug Application (NDA 213976) for Eohilia (budesonide) oral suspension under the 505(b)(2) pathway with reliance on public literature and information related to budesonide, including the listed drug, Entocort EC (NDA 021324, approved on 10/2/01). Entocort EC is approved for the treatment of mild to moderate Crohn's disease in patients 8 years and older and for maintenance of clinical remission of mild to moderate Crohn's disease for up to 3 months.
- DG consulted DPMH on 12/2/20, to provide input for appropriate labeling of the *Pregnancy* and *Lactation* subsections of Eohilia to comply with the PLLR. Eohilia is a synthetic corticosteroid and has qualified for orphan drug designation, breakthrough therapy designation and a priority review. The proposed indication is for the treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older.
- DPMH has completed two previous budesonide reviews (DPMH reviews' cited above under "Materials Reviewed" dated 12/19/2018[1] and 1/25/2016[3]). For details regarding previously reviewed literature (through December of 2018) see the above DPMH reviews.

Eohilia Drug Characteristics[4]

- Molecular weight of 430.5 Daltons
- Half-life of 3.30 hours after repeated administration of a 2 mg twice daily dose, which is the proposed dose for the indication of EoE.
    - The oral bioavailability of budesonide is estimated to be 14.2% in the fasting state of healthy adults, indicating high first pass metabolism.
    - Protein-binding of 85-90%
    - Eohilia is a white to yellow thixotropic, viscous suspension intended (b) (4) (b) (4).

Current Approved Budesonide Labeling[5]

See Appendix A for currently approved labeling for Entocort EC.

REVIEW

For a detailed review of Entocort (budesonide) use in Pregnancy and Lactation with summaries of published literature, the reader is referred to the DPMH consult review by Miriam Dinatale, DO, in DARRTS, Reference ID: 3875179, and dated January 25, 2016[3].

Eosinophillic esophagitis (EoE) And Pregnancy

EoE is a chronic disorder of unknown etiology, characterized by symptoms of esophageal dysfunction and esophageal inflammation with intraepithelial eosinophils[6]. EoE is estimated to

[3] DPMH Review of Entocort EC (budesonide). NDA 21324. Miriam Dinatale, D.O. 1/25/2016. DARRTS Reference ID #3875179.
[4] Eohilia proposed labeling-confirmed by divisional team as accurate
[5] Entocort EC (budesonide) delayed-release capsules, for oral use approved 7/15/20
[6] Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras C, Katzka DA. ACG clinical guideline: evidence-based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. Am J Gastroenterol. 2013;108:679–692.

affect 57/100,000 Americans[7] and its incidence and prevalence have dramatically increased in recent years[8]. Animal models, genetic studies, comorbid allergic disorders, and the efficacy of elimination diets suggest that EoE is an atopic condition[9]. EoE is more common in cold and arid climates, and in rural areas[10], and most frequently affects those younger than 50[7], men, and Caucasians[11].

Several treatments, including topical steroids[12] and dietary therapy, are currently used as first-line modalities[13]. The first-line pharmacologic therapy for EoE is a topical corticosteroid, typically either a fluticasone metered-dose inhaler that is dispensed into the mouth and swallowed or an oral viscous slurry of budesonide[6,14] Fluticasone is poorly absorbed from the GI tract[15], and budesonide undergoes extensive first-pass metabolism and has low systemic bioavailability when taken orally[16], though a recent study has suggested that active EoE may impair some elimination of budesonide.

There are currently limited data on the management of EoE during pregnancy. A contributing factor to the limited available data is that approximately two-thirds of EoE patients are male[6].

PREGNANCY

Animal Data

In animal reproduction studies, subcutaneous administration of budesonide during organogenesis in pregnant rats (at doses up to approximately the maximum recommended human dose [MRHD], based on body surface area [BSA]) or pregnant rabbits (at doses approximately 0.14 times the MRHD, based on body surface area [BSA]) resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels.

Review of Literature

Applicant's and DPMH's Review

Few published studies report on the use of budesonide in pregnant women. The majority of

[7] Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol. 2014;12:589.e581–596.e581.

[8] Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. Clin Gastroenterol Hepatol. 2009;7:1055–1061.

[9] O'Shea K, Aceves S, Dellon E, et al. Pathophysiology of Eosinophilic Esophagitis. Gastroenterology. 2018; 154(2):333-45.

[10] Jensen ET, Hoffman K, Shaheen NJ, et al. Esophageal eosinophilia is increased in rural areas with low population density: results from a national pathology data-base. Am J Gastroenterol 2014;109(5):668–75.

[11] Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology. 2017; 154(2):319-32.

[12] Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. Gastroenterology. 2012;143:e321.

[13]Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology. 2012;142:e1451.

[14] Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128:e26

[15] Holliday SM, Faulds D, Sorkin EM. Inhaled fluticasone propionate. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in asthma. Drugs. 1994;47: 318–331.

[16] Edsbacker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. Clin Pharmacokinet. 2004;43:803–821.

these are in women with inflammatory bowel disease (most commonly Crohn's Disease) or in women with asthma using inhaled formulations of budesonide. For a table of summaries of published literature from earlier DPMH budesonide reviews, see Appendix B, Table 1. For several newly identified publications that are relevant, see Appendix B Table 2. None of the newly identified publications change the recommended labeling for budesonide.

Pharmacovigilance Review

A search of the applicant's pharmacovigilance databases for comprehensive safety information from product development to present was performed. Three subjects reported a pregnancy in the Eohilia clinical development program but only one was actually exposed to the investigational product (IP) during pregnancy. That case is summarized below.

- Subject (b) (6) (18-year-old female; BOS-BOS Group) had a nonserious treatment emergent adverse event (TEAE) of pregnancy on Day 236. The event led to the discontinuation of IP and the subject being withdrawn from the study. Pregnancy was the reason for study discontinuation. The subject delivered a healthy baby on (b) (6)

Reviewer Comments:

The published experience (clinical trial, retrospective review of case series, epidemiological studies and review publications) with oral and inhaled budesonide do not show an increased risk of congenital malformations when budesonide is taken during pregnancy. Limitations of these studies include limited number of patients exposed to budesonide and the retrospective nature of the reports. Although the low dose inhaled budesonide (400mcg/day) does not appear to be associated with adverse effects in the fetus or neonate, different effects (adrenal insufficiency/crisis, bone fracture, short stature) may be seen in offspring of women who use higher dose of oral budesonide. In addition, current glucocorticoid labeling, including budesonide, states that hypoadrenalism may occur in infants of mothers who have taken corticosteroid during pregnancy. This statement will be included in the "Clinical Considerations" section of Budesonide labeling.

LACTATION

Animal Data

No studies have been performed on budesonide use in lactating animals.

Review of Literature

Applicant's Review

The applicant identified one study with use of inhaled budesonide during lactation.

- Fält et al.[17] collected milk and plasma samples up to 8 hours after dosing from 8 mothers receiving inhaled budesonide maintenance treatment (200 or 400 mcg twice daily) for asthma. Infant exposure was estimated based on average milk budesonide concentrations. Budesonide concentrations in milk reflected those in maternal plasma and were always lower than that in maternal plasma. The authors propose passive diffusion of budesonide between plasma and milk. The mean milk/plasma ratio was 0.46. The estimated daily infant dose was 0.3% of the daily maternal dose. The average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma. Budesonide concentrations in infant

[17] Fält A, Bengtsson T, Kennedy BM, Gyllenberg A, Lindberg B, Thorsson L, Stråndgarden K. Exposure of infants to budesonide through breast milk of asthmatic mothers. J Allergy Clin Immunol. 2007 Oct;120(4):798-802.

plasma samples were all less than the limit of quantification. The authors recommend continued use of inhaled budesonide during breastfeeding. There were no adverse events noted in the infants.

DPMH Review

No additional publications were identified in addition to the Fält article. DPMH conducted a search of Dr. Hale's *Medications and Mother's Milk*[18], the Drugs and Lactation Database (LactMed)[19], Micromedex[20], and of published literature in PubMed and EMBASE using the search terms "budesonide AND lactation" and "budesonide AND breastfeeding."

In Medications and Mother's Milk[18], Thomas Hale, a breastfeeding expert, states the following regarding budesonide and lactation:

> Approximately 10% of oral budesonide dose is bioavailable in the mother and the milk/plasma ratio is approximately 0.5. Thus, the dose in maternal milk could provide a therapeutic dose to a small infant. Due to its potency, caution is recommended for prolonged use of oral budesonide in breastfeeding mothers. If used, observe the infant for linear growth rate.

Budesonide is referenced in LactMed[19]. The authors describe the results of the Fält[17] et al. study and the summary of use during lactation states:

> The amounts of inhaled budesonide excreted into breastmilk are minute and infant exposure is negligible. When taken by mouth, budesonide is only about 9% bioavailable; bioavailability in the infant is likely to be similarly low for any budesonide that enters the breastmilk. Expert opinion considers inhaled, nasal and oral corticosteroids acceptable to use during breastfeeding[21, 22].

Pharmacovigilance Review

The applicant did not identify any cases of exposure to budesonide during lactation in their pharmacovigilance database.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Animal Data

In fertility studies in rats given subcutaneous budesonide at doses 0.07 times the MRHD, there was no evidence of impaired fertility.

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[18] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.

[19] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database 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.

[20] Truven Health Analytics information, http://www.micromedexsolutions.com/.

[21] National Heart, Lung, and Blood, Institute, et al. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. 2004:1-57

[22] Middleton PG, Gade EJ, Aguilera C, et al. ERS/TSANZ Task Force Statement on the management of reproduction and pregnancy in women with airways diseases. Eur Respir J. 2020;55:1901208.

Applicant's and DPMH Review of literature
The applicant performed a search of published literature for available human fertility data for budesonide. DPMH also conducted a review of published literature in PubMed and Embase to evaluate the use of budesonide and its effects on fertility. No published data were found. The applicant did not report any cases from the pharmacovigilance database.

DISCUSSION AND CONCLUSIONS
Pregnancy
There is evidence of embryofetal toxicity in animal reproduction studies performed with budesonide. Human data from the applicant's pharmacovigilance database are scant. Published data for budesonide and other corticosteroids are inconsistent in their conclusions. There are studies that suggest that corticosteroid use in pregnancy may increase the risk of congenital malformations, in particular cleft palate, but other studies that have not demonstrated an increased risk of congenital malformations with corticosteroid use during pregnancy. There were no increased rates of congenital malformations with low and moderate doses of inhaled budesonide use during pregnancy, however, different effects may be seen in women who use oral budesonide during pregnancy. DPMH agrees that information about the potential for hypoadrenalism in infants born to mothers receiving corticosteroids in pregnancy is important and this will be included under the "Clinical Considerations" section of labeling.

Lactation
Budesonide is present in human milk. One lactation study with inhaled budesonide is currently in labeling and DPMH recommends retaining this in the Data section. Discussion with clinical pharmacology is ongoing regarding how this correlates with the proposed doses for use for EoE. The risk/benefit statement regarding lactation is appropriate for this label and will be included.

Reviewer's Comments
The division decided to give this submission a complete response (CR). Clinical pharmacology will provide updated labeling for the lactation section in the next cycle when the sponsor resubmits. For that reason, for the purposes of this review, the proposed lactation labeling will be draft.

Females and Males of Reproductive Potential
There are no human data on the effects of budesonide on fertility and no evidence of infertility in animal studies. There are no recommendations for pregnancy testing or contraception. Therefore, subsection 8.3, Females and Males of Reproductive Potential will not be included in Budesonide labeling.

CONCLUSIONS AND RECOMMENDATIONS
Budesonide labeling has been revised to comply with the PLLR. DPMH has the following recommendations for the Budesonide labeling. DPMH met with DG on 2/23/21 to discuss the labeling recommendations but will plan to make additional revisions to the lactation section in the next review cycle. At that time, an addendum to this review will be filed.

Appendix A

Current Approved Budesonide Labeling[23]

The current labeling for the listed drug, Entocort EC states:

- "Pregnancy: Based on animal data, may cause fetal harm" under "Use in Specific Populations" under "Highlights of Prescribing Information".
- Contraindications include "Hypersensitivity to budesonide or any of the ingredients in Entocort EC".
- Warnings and Precautions include "Hypercorticism and Adrenal Axis Suppression", "Symptoms of Steroid Withdrawal in Patients Transferred from Other Systemic Corticosteroids", "Increased Risk of Infection, including Serious and Fatal Chicken Pox and Measles" and "Other Corticosteroid Effects" [Monitor patients with concomitant conditions where corticosteroids may have unwanted effects (e.g., hypertension, diabetes mellitus)].
- In subsection **8.1 Pregnancy** under "Risk Summary" the labeling states:

  Limited published studies report on the use of budesonide in pregnant women; however, the data are insufficient to inform a drug-associated risk for major birth defects and miscarriage. There are clinical considerations *[see Clinical Considerations]*. In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during organogenesis at doses approximately 0.5 times or 0.05 times, respectively, the maximum recommended human dose (MRHD), resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

  The estimated background risk of major birth defects and miscarriage of the indicated population is 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.

- In subsection **8.1 Pregnancy** under "Clinical Considerations" with the subheading " Disease-Associated Maternal and/or Embryo/Fetal Risk" labeling states:

  Some published epidemiological studies show an association of adverse pregnancy outcomes in women with Crohn's disease, including preterm birth and low birth weight infants, during periods of increased disease activity (including increased stool frequency and abdominal pain). Pregnant women with Crohn's disease should be counseled regarding the importance of controlling disease.

- In subsection **8.1 Pregnancy** under "Clinical Considerations" with the subheading "Fetal/Neonatal adverse reactions" labeling states

  Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Infants should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly *[see Warnings and Precautions (5.1)]*.

- In subsection **8.1 Pregnancy** under "Data" with the subheading "Animal Data" labeling states

  Budesonide was teratogenic and embryolethal in rabbits and rats. In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis from gestation days 6-15 there were effects on fetal

[23] Entocort EC (budesonide) delayed-release capsules, for oral use approved 7/15/20

development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.5 times the MRHD on a body surface area basis). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6-18, increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses up to approximately 25 mcg/kg in rabbits (approximately 0.05 times the MRHD on a body surface area basis). Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.01 times the MRHD on a body surface area basis) and 500 mcg/kg in rats (approximately 0.5 times the MRHD on a body surface area basis).

In a peri-and post-natal development study, rats dosed subcutaneously with budesonide during the period of Day 15 post coitum to Day 21 postpartum, budesonide had no effects on delivery but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures 0.02 times the MRHD (on a mg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

- In subsection **8.2 Lactation, under "**Risk Summary" labeling states:

  Lactation studies have not been conducted with oral budesonide, including ENTOCORT EC, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENTOCORT EC and any potential adverse effects on the breastfed infant from ENTOCORT EC, or from the underlying maternal condition.

- In subsection **8.2 Lactation**, under "Data" labeling states

  One published study reports that budesonide is present in human milk following maternal inhalation of budesonide which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.4 and 0.5. Budesonide plasma concentrations were not detected and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide. The recommended daily dose of ENTOCORT EC capsules is higher (up to 9 mg daily) compared with inhaled budesonide (up to 800 mcg daily) given to mothers in the above described study. The maximum budesonide plasma concentration following a 9 mg daily dose (in both single-and repeated-dose pharmacokinetic studies) of oral budesonide is approximately 5 to 10 nmol/L which is up to 10 times higher than the 1 to 2 nmol/L for a 800 mcg daily dose of inhaled budesonide at steady state in the above inhalation study. Assuming the coefficient of extrapolation between the inhaled and oral doses is constant across all dose levels, at therapeutic doses of ENTOCORT EC, budesonide exposure to the nursing child may be up to 10 times higher than that by budesonide inhalation.

- In Section **13 NONCLINICAL TOXICOLOGY** under subsection 13.1 "Carcinogenesis, Mutagenesis, Impairment of Fertility" labeling states

  In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.023 times the

maximum recommended human dose on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). Budesonide was not genotoxic in the Ames test, In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.07 times the maximum recommended human dose on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg (approximately 0.02 times the maximum recommended human dose on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.005 times the maximum recommended human dose on a body surface area basis).

- **In Section 17 PATIENT COUNSELING INFORMATION** under subheading **"**Pregnancy" labeling states

  Advise female patients that ENTOCORT EC may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy

Appendix B
Table 1 Publications Reporting on Use of Budesonide in Pregnancy[1]

Author/ Year	Study Design	Time of Exposure	Amount/Duration	Outcome/Conclusion
Silverman et al., 2005[24]	Clinical Trial, a randomized, double-blind, placebo-controlled. 7241 patients aged 5 to 66 years (2473 females aged 15 to 50 years) with mild-to moderate persistent asthma (Pregnancy was not an exclusion criterion).	Throughout pregnancy	Once daily, budesonide (400 mcg) for adults or placebo via dry powder inhaler in addition to their usual asthma medication for 3 years	313 pregnancies all together reported (196 to Budesonide and 117 to placebo). Healthy children were delivered in 81% and 77% in the budesonide and placebo groups, respectively. Adverse outcomes: Budesonide: 38 (19%) Placebo: 27 (23%) Budesonide Placebo Miscarriage: 23 (12%) 11 (9%) Cong. Malfor: 3 (2%) 4 (3%) Other: 12 (6%) 12 (10%)
Beaulieu et al., 2009[25]	Retrospective review of a case series of 8 mothers with Inflammatory Bowel Disease (IBD) and Crohn's Disease (CD) and their infants	During pregnancy	Budesonide was used at the 6 mg/day dose in 6 patients and 9 mg/day dose in 2 patients. The average treatment duration ranges from 1-8 months.	There were no cases of maternal adrenal suppression, glucose intolerance, ocular side effects, hypertension or fetal congenital abnormalities. The authors concluded, Budesonide may be a safe option for treatment of Crohn's disease (CD) during pregnancy.
Gluck et al., 2005[26]	Review of Clinical and epidemiological studies (5 publications and 3 abstracts). 6600 infants whose mothers were exposed to orally inhaled budesonide.	Either during early pregnancy only or throughout pregnancy	Maternal exposure to orally inhaled or intranasal budesonide (dosage and duration not stated)	Normal gestational age, birth weight, and length, with no increased rate of stillbirths, multiple births, or congenital malformations or cardiovascular defects.
Källén et al., 1999[27]	Case study using the Swedish Medical Birth Registry; congenital malformations were studied in 2014 infants.	Mothers had used inhaled budesonide for asthma in early pregnancy.	Not reported	No increase in the general rate of congenital malformations was observed: 3.8% (95% confidence interval [CI] 2.9, 4.6) of the infants had a congenital malformation diagnosed, which is similar to the population rate (3.5%).
Alhussien et al.,	Review of 3 publications	During pregnancy	Intranasal use of different steroids including	No significant association with congenital malformations. Budesonide is safe, if used at the

[24] Silverman M, Sheffer A, Diaz PV, Lindmark B, Radner F, Broddene M, de Verdier MG, Pedersen S, Pauwels RA. START Investigators Group. Outcome of pregnancy in a randomized controlled study of patients. with asthma exposed to budesonide. Ann Allergy Asthma Immunol. 2005 Dec;95(6):566-70.
[25] Beaulieu DB, Ananthakrishnan AN, Issa M, Rosenbaum L, Skaros S, Newcomer JR, Kuhlmann RS, Otterson MF, Emmons J, Knox J, Binion DG. Budesonide induction and maintenance therapy for Crohn's disease during pregnancy. Inflamm Bowel Dis. 2009 Jan;15(1):25-8.
[26] Gluck PA, Gluck JC. A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide. Curr Med Res Opin. 2005 Jul;21(7):1075-84
[27] Källén B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol. 1999 Mar;93(3):392-5.

Author/ Year	Study Design	Time of Exposure	Amount/Duration	Outcome/Conclusion
2018[28]			budesonide. Dosage was not identified.	recommended therapeutic dose after a proper medical evaluation. Risk/benefit ratio should always be considered before prescribing any intranasal corticosteroid sprays during pregnancy.
Norjavaara et al., 2003[29]	Population based study from the Swedish Medical Birth Register, which includes 99% of births in Sweden. During 1995 to 1998, 293,948 newborn infants were identified. Pregnancy outcomes were compared for mothers in Sweden reporting asthma medication usage (2,968 mothers) with those reporting no asthma medication usage.	During early pregnancy	Inhaled budesonide (no dosage is reported)	Infants born to mothers who used budesonide during their pregnancy had normal gestational age, birth weight, and length, with no increased rate of stillbirths or multiple births. The rate of cesarean births was higher among mothers who used asthma medication during their pregnancy. The use of inhaled budesonide in Sweden is not linked with any clinically relevant effects associated with pregnancy outcome.
Källén et al., 2003[30]	Case control study with cases (cardiovascular defects without known chromosome anomalies) being identified from three Swedish health registers (n=5015) (2230 used budesonide nasal spray) and controls being all infants born in Sweden during the period 1 July 1995-2001 (n=577,730).	Interview on drug exposure in early pregnancy	Budesonide in nasal preparations and use of other drugs.	Some observed associations with any of the medications identified are probably due to confounding from underlying disease, some may be due to multiple testing, and some may be true drug effects. Budesonide used as an inhaled anti-asthmatic drug showed no statistically significant association with cardiovascular defects, with odds ratio for the inhaled drug (OR=1.12)
Christensson et al., 2008 [31]	Clinical review of scientific literature. Four studies using data from the Swedish birth and health registries	During pregnancy	Inhaled budesonide	No increased risk for congenital malformations, cardiovascular defects, decreased gestational age, birth weight or birth length among infants born to women using inhaled budesonide during pregnancy compared with the general population.

From DPMH review of Budesonide. NDA 121920. Christos Mastroyannis, MD. 12/19/2018. DARRTS Reference ID# 4366204

[28] Alhussien AH, Alhedaithy RA, Alsaleh SA. Safety of intranasal corticosteroid sprays during pregnancy: an updated review. Eur Arch Otorhinolaryngol. 2018 Feb;275(2):325-333.

[29] Norjavaara E, de Verdier MG. Normal pregnancy outcomes in a population-based study including 2,968 pregnant women exposed to budesonide. J Allergy Clin Immunol. 2003 Apr;111(4):736-42.

[30] Källén BA, Otterblad Olausson P. Maternal drug use in early pregnancy and infant cardiovascular defect. Reprod Toxicol. 2003 May-Jun;17(3):255-61

[31] Christensson C, Thorén A, Lindberg B. Safety of inhaled budesonide: clinical manifestations of systemic corticosteroid-related adverse effects. Drug Saf. 2008;31(11):965-88.

Table 2: Additional Publications Regarding Budesonide Exposure during Pregnancy

Author/ Year	Study Design	Time of Exposure	Amount/ Duration	Outcome/Conclusion
Tegethoff[32] et al. 2012	Cohort study based on prospective data from the Danish National Birth Cohort (1996 – 2003) in all pregnancies with asthma with live singleton birth outcome (65,085 mother-child pairs) to estimate the associations between use of glucocorticoid inhalants for asthma treatment during pregnancy and the offspring's disease risk.	followed-up in real time from early pregnancy into childhood	Variable	In women with asthma during pregnancy, use (vs. no use) of glucocorticoid inhalants was associated with a significantly increased risk for the first diagnosis of endocrine and metabolic disorders but not of diseases in any other category. With adjusted regression analyses stratifying them for propensity score strata, the hazard ratio [HR], 1.84; 95% confidence interval [CI], 1.13–2.99). The findings were stable when repeating analyses with budesonide inhalation only, the most common type of glucocorticoid inhalation in this sample.
Rahimi[33] et al. 2006	Data from 4 clinical studies (1997 to 2005) that evaluated the pregnancy and perinatal outcomes in women exposed to inhaled corticosteroids (ICs) [fluticasone, beclomethasone, budesonide, triamcinolone and flunisolide] during pregnancy by the meta-analytic technique.	Variable	Variable	ICs do not increase the risk of major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension.
Burke[34] et al. 2016	Case Reports (total of 4 women pregnant with EoE but none exposed to steroids during pregnancy) and literature review	No exposure	No exposure	Corticosteroids are among the medications currently used to treat inflammatory bowel disease (IBD) in pregnant women, when needed based on disease severity. By extension, budesonide is likely to be relatively safe for use in pregnant EoE patients, particularly because the doses tend to be lower than in IBD, though data specifically in EoE and pregnancy are needed to test this hypothesis.
McConnell and Mahadevan[35] 2016	Review of risks to pregnancy of various treatments for IBD	Not applicable (NA)	NA	Budesonide has a low risk to pregnancy and is compatible with breastfeeding, with clinically insignificant concentrations entering breast milk.

[32] Tegethoff M et al. Inhaled Glucocorticoids during Pregnancy and Offspring Pediatric Diseases A National Cohort Study. Am J Respir Crit Care Med .2012; 185, Iss. 5, pp 557–563.

[33] Rahimi R et al. Meta-analysis (MA) finds use of inhaled corticosteroids during pregnancy safe: a systematic MA review. Human & Experimental Toxicology. 2006; 25: 447-452.

[34] Burke CM et al. Management of Eosinophilic Esophagitis During Pregnancy. Dig Dis Sci (2016) 61:1819–1825.

[35] McConnell RA and Mahadevan U. Pregnancy and the Patient with Inflammatory Bowel Disease. Gastroenterology Clinics of North America. 2016; 45(2): 285-301.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ORPURM
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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MEMORANDUM TO FILE

Version Date:	March 11, 2021
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Shetarra Walker, MD, MSCR, Clinical Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director DPMH
NDA Number:	213,976
Sponsor:	Takeda
Drug:	Eohilia (budesonide), oral suspension, 2mg/10mL
Indication:	Treatment of eosinophilic esophagitis (EoE) (b) (4) in patients 11 years and older.
Dosage Form and Route of Administration:	Suspension for oral (PO) administration
Proposed Dosing Regimen:	2 mg PO, twice daily (BID)
Division Consult Request:	The Division of Gastroenterology (DG) products requests DPMH assistance with labeling this new product.

Background

The Applicant submits an application for an oral budesonide suspension (OBS), a corticosteroid, for treatment of patients with EoE, 11 years and older. On December 20, 2006, the Sponsor received orphan designation for use of OBS for treatment of EoE.

EoE is a chronic allergic/immune disorder characterized by esophageal inflammation with elevated eosinophilic granulocytes (Eos). By definition, patients are symptomatic and have greater than 15 Eos per high power field (hpf) on light microscopy (commonly defined as 400 to 500 x magnification);[1,2] however, some sources recommend a diagnostic cut-off of 20 Eos per hpf to help distinguish from esophageal neutrophilic infiltrates in patients with gastroesophageal reflux disorder (GERD).[3] The drug development plan for EoE has used the 15 Eos per hpf definition, which is reasonable.

Potential etiologies/contributing factors include food allergies, acid reflux, and other ill-defined allergic/immunologic disturbances. Untreated patients may develop heartburn, dysphagia, and achalasia. EoE is currently thought to be distinct from other allergic enteropathies (e.g., eosinophilic gastritis, or celiac disease). There are no approved drug or biologic treatments for patients with EoE.

If offending food allergens are identified, a selective elimination diet may be attempted; however, lack of response is common. Clinicians commonly prescribe proton-pump inhibitors (PPI) and oral steroids in off-label fashion. Curiously, chronic use of PPIs for other reasons such as GERD has been associated with eosinophilic mucosal infiltration of the esophagus which may not resolve upon discontinuation of PPIs. Whether some patients with PPI-associated EoE represent nascent cases of non-PPI associated EoE or whether PPIs are a causative factor for EoE is a matter of academic debate. Disease recrudescence is thought to be common in patients who initially respond to PPI or corticosteroids.

DG has requested DPMH assistance in reviewing proposed labeling.

<u>Reviewer comment</u>: Communication with the DG reviewer on February 4, 2021 indicates that the DG will likely not accept the Applicant's description of the studies intended to

(b) (4)

however, the Sponsor's clinical summary of efficacy suggests that all non-responders were ultimately offered OBS.

<u>Reviewer comments</u>: The proposed commercial product name "Eohilia" could be perceived as promotional depending on the Applicants proposed pronunciation or how professional or lay consumers interpret the spelling (that is Eo-heal-ya; or 'heal you').

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[1] Dellon ES. Eosinophilic esophagitis: Diagnostic test and criteria. Curr Opin Gastroenterol. 2012 July ; 28(4): 382–388.
[2]Kim D, Pantanowitz L, Schuffler P, et al. (Re) Defining the high-power field for digital pathology. J Pathol Inform 2020; 11:33;
[3] Rodrigo S, Abboud G, Oh D, et al. High intraepithelial eosinophil counts in esophageal squamous epithelium are not specific for eosinophilic esophagitis in adults. Am J Gastroenterol. 2008 Feb;103(2):435-42

This concern was communicated to DG on February 6, 2021 for further discussion. The agreed upon commercial product name will be found in final approved labeling.

Approvability issue: Review of the data by the DG and Statistics teams revealed that the clinical studies do not support approval. For acute treatment, FDA analyses showed that prespecified change in biopsy eosinophil count was met; however, while the change (improvement) in the symptom scoring instrument (a co-primary endpoint) was met, FDA concluded that the applicant's prespecified change threshold had not been agreed upon with FDA prior to the study and was subsequently deemed as not being clinically meaningful upon review and analysis by FDA during the NDA review cycle. For chronic treatment, both of the applicant's prespecified co-primary endpoints (i.e., pertaining to eosinophil count and symptoms) were not met, and the DG and Statistics teams concluded that this study failed to meet any clinically meaningful change in either co-primary endpoint.

DG presented the data to the medical policy and program review council (MPPRC) on March 10, 2010. The MPPRC agreed the studies failed to support efficacy and agreed with issuing a complete response (CR).

Recommendations for pediatric labeling are being deferred at this time. If the applicant decides to pursue development, DG should reconsult DPMH for input into the pediatric aspects of the development plan.

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/s/

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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: 12/18/2020

TO: Division of Gastroenterology (DG)
Office of Immunology and Inflammation (OII)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

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

RE: NDA 213976

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The clinical inspection was conducted in February 2018 and the analytical inspection was conducted in (b) (4) which falls within the surveillance interval. The inspections were conducted under the following submissions: NON-RESPONSIVE

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the rationale provided above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Clinical Pharmacology of Miami, LLC.	550 West 84th Street, Miami, FL
Analytical	(b) (4)	

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/s/

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