Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
November 17, 2023

Location: All meeting participants were heard, viewed, captioned, and recorded for this advisory committee meeting via an online teleconferencing and/or video conferencing platform.

Topic: The Committee discussed new drug application 215010, for gefapixant oral tablets, submitted by Merck Sharp & Dohme Corp., for the proposed indication of treatment of adults with refractory or unexplained chronic cough.

These summary minutes for the November 17, 2023 meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration were approved on December 31, 2023.

I certify that I attended the November 17, 2023 meeting of the PADAC of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Takyiah Stevenson, PharmD	Paula Carvalho, MD, FCCP
Designated Federal Officer, PADAC	Acting Chairperson, PADAC

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
November 17, 2023

The Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 17, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing and/or video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Merck Sharp & Dohme Corp. The meeting was called to order by Paula Carvalho, MD, FCCP (Acting Chairperson). The conflict-of-interest statement was read into the record by Takyiah Stevenson, PharmD (Designated Federal Officer). There were approximately 544 people online. There were 18 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:
The Committee discussed new drug application 215010, for gefapixant oral tablets, submitted by Merck Sharp & Dohme Corp., for the proposed indication of treatment of adults with refractory or unexplained chronic cough.

Attendance:

Pulmonary-Allergy Drugs Advisory Committee Members (Voting):
Leonard B. Bacharier, MD; Emma H. D'Agostino, PhD (*Consumer Representative*); Scott E. Evans, MD, FCCP, ATSF; Brian T. Garibaldi, MD, PhD; Nicole Hamblett, PhD; Edwin H. Kim, MD, MS; Matthew A. Rank, MD

Pulmonary-Allergy Drugs Advisory Committee Member Not Present (Voting):
David H. Au, MD, MS (*Chairperson*); Fernando Holguin, MD, MPH; Janet S. Lee, MD, ATSF

Pulmonary-Allergy Advisory Committee Member (Non-Voting):
Dawn M. Carlson, MD, MPH (*Industry Representative*)

Temporary Members (Voting):
Paula Carvalho, MD, FCCP (*Acting Chairperson*); Cheryl D. Coon, PhD; Mark S. Courey, MD; Sally A. Hunsberger, PhD; John M. Kelso, MD; Jennifer Schwartzott, MS (*Patient Representative*)

FDA Participants (Non-Voting):
Sally Seymour, MD; Banu A. Karimi-Shah, MD; Stacy Chin, MD; Rachel Bean, MD; Weiya Zhang, PhD; Yongman Kim, PhD; Susan Mayo, MS

Designated Federal Officer (Non-Voting): Takyiah Stevenson, PharmD

Open Public Hearing Speakers: Gloria Kaplan-Seide; Anju T. Peters, MD, MSCI; Mary Oleksiuk; Gary Neil Gross, MD; Carol Shaw; Joan Saks; Mary Ellen McDonough; Marlene Bambrick; Suzanne Buchter; Danielle Schroer; Susan Coulombe; Nina Zeldes, PhD (Public Citizen's Health Research Group); Wendi Smith; Deborah L. Markel; Karen J. Moon; David Ferguson; April Adams; Rebecca Karger

The agenda was as follows:

Call to Order	**Paula Carvalho, MD, FCCP** Acting Chairperson, PADAC
Introduction of Committee and Conflict of Interest Statement	**Takyiah Stevenson, PharmD** Designated Federal Officer, PADAC
FDA Opening Remarks	**Stacy Chin, MD** Clinical Team Leader Division of Pulmonology, Allergy, and Critical Care (DPACC) Office of Immunology and Inflammation (OII) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Merck Sharp and Dohme LLC**
Introduction	**Lisa Bollinger, MD** Vice President, Regulatory Affairs Merck Sharp and Dohme LLC
Disease Background and Unmet Need	**Peter Dicpinigaitis, MD** Professor of Medicine Albert Einstein College of Medicine Director, Cough Center Montefiore Medical Center, New York
Program Overview and Efficacy Data	**George Philip, MD** Executive Director, Medical Affairs Merck Sharp and Dohme LLC
Patient Reported Outcomes	**Allison Martin Nguyen, MS** Executive Director, Epidemiology Patient-Centered Endpoints and Strategy (PaCES) Group Merck Sharp and Dohme LLC

APPLICANT PRESENTATIONS (cont.)

Clinical Safety	**English Willis, MD** Executive Director Clinical Safety and Risk Management Merck Sharp and Dohme LLC
Clinical Perspective on the Benefit-Risk Relationship	**Jaclyn Smith, MD, ChB, FRCP, PhD** Division of Infection, Immunity and Respiratory Medicine University of Manchester, United Kingdom
Closing Summary	**Lisa Bollinger, MD**

BREAK

FDA PRESENTATIONS

Overview of the Clinical Program and Review of Safety	**Rachel Bean, MD** Medical Officer DPACC, OII, OND, CDER, FDA
Statistical Review of Efficacy	**Susan Mayo, MS** Statistical Reviewer Division of Biometrics III Office of Biostatistics Office of Translational Sciences CDER, FDA
Clinical Considerations	**Rachel Bean, MD**

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Stacy Chin, MD**

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the evidence of effectiveness for gefapixant for the treatment of refractory or unexplained chronic cough in adults. Specifically address the following:

    a. The small reduction in cough frequency compared to placebo and the clinical meaningfulness of the reduction in cough frequency.

    b. The observed results from Patient-Reported Outcomes (PROs) and whether these results provide compelling evidence to inform the clinical meaningfulness of the reduction in cough frequency.

    c. Potential unblinding of patients due to taste disturbance and its impact on interpretation of cough frequency and PRO results.

    Committee Discussion*: There was a general consensus among the Committee members that the evidence of effectiveness for gefapixant for the treatment of refractory or unexplained chronic cough in adults was not adequately characterized based on the available data from the two pivotal trials, P030 and P027. Several members agreed that the small reduction in cough frequency compared to placebo demonstrates that the effectiveness of gefapixant was minimal and with little clinical meaningfulness. A Committee member recommended that more anchor-based methods and more analysis methods are needed to determine improvement in cough and the change in cough frequency. A few other members were not convinced that the endpoints chosen for the studies were adequate for establishing or analyzing efficacy. Possible endpoints recommended were coughing fits/clusters of coughing and incontinence.*

    Many Committee members also agreed that the observed results from PROs did not provide compelling evidence to inform the clinical meaningfulness of the reduction in cough frequency. One member expressed concerns on the limitations of each of the 3 PROs utilized in the studies (Leicester Cough Questionnaire, Cough Severity Diary Total Score, Cough Severity Visual Analog Scale) and concluded that the data from the PROs was unconvincing evidence of meaningful benefit.

    A few members expressed concerns regarding the potential unblinding of patients due to taste disturbance and mentioned how this impacted the interpretation of cough frequency and PRO results. One member noted that the patients in the gefapixant treatment arm could likely tell that they're taking the study drug due to the taste disturbance effect and this may have affected the reliability of the reported PRO results. Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION**: Discuss the overall benefit/risk assessment of gefapixant for the treatment of adults with refractory or unexplained chronic cough, a symptomatic condition.

    Committee Discussion*: Overall, the Committee members agreed that the risks of adverse events do not outweigh the benefits of gefapixant for the treatment of adults with refractory*

or unexplained chronic cough, a symptomatic condition. Members acknowledged that the adverse events reported, including taste disturbances, were minimal and reversible. As a result, Committee members concluded that there are minimal overall safety concerns. However, members were concerned that the efficacy data presented was unconvincing of a favorable benefit-risk profile. Members highlighted that the similarities in the data from the placebo and gefapixant treatment arms add to the uncertainty of whether benefit was demonstrated. A few Committee members commented that the risks of patients continuing to be untreated for refractory or unexplained chronic cough could outweigh the risks of being administered a possibly minimally effective drug, which has little safety concerns. One member recommended a longer period of monitoring patients for efficacy and safety as this is a chronic condition and patients may be taking gefapixant for longer than the duration of the studies discussed. Please see the transcript for details of the Committee's discussion.

3. **VOTE:** Does the evidence demonstrate that gefapixant provides a clinically meaningful benefit to adult patients with refractory or unexplained chronic cough, given the small reduction in cough frequency and results from PROs? Provide a rationale for your vote.

    a. If you conclude that there is insufficient evidence of a clinically meaningful benefit, describe the evidence that could be collected to show a benefit that is clinically meaningful.

    Vote Result: Yes: 1 No: 12 Abstain: 0

    Committee Discussion*: The majority of the Committee members voted "No" indicating the evidence does not demonstrate that gefapixant provides a clinically meaningful benefit to adult patients with refractory or unexplained chronic cough, given the small reduction in cough frequency and results from PROs. Several members who voted "No" agreed that though the small reduction in cough was statistically significant in one study, the clinical meaningfulness of that reduction was questionable. A few members expressed concerns over the possible unblinding due to the taste disturbance side effect, and the effect this had on the reliability of the PRO results. Other members mentioned the significant placebo effect reported made it difficult to assess the efficacy of gefapixant. Members reiterated concerns that the endpoints chosen may have not been suitable to analyze efficacy and recommended that future studies consider examining other endpoints such as bouts of coughing and incontinence. Other evidence, as recommended by one member, that could be collected to show a clinically meaningful benefit could be the patient's response to cough triggers while taking the study drug. The one member who voted "Yes" commented that any reduction in cough frequency and severity could be worthwhile to patients. The Committee were in agreement that there was little concern with the safety profile of gefapixant. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:30 p.m. ET.