Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
May 8, 2019

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Ave, Silver Spring, Maryland.

Topic: The committee discussed new drug application (NDA) 202049, for mannitol inhalation powder, for oral inhalation submitted by Chiesi USA, Inc., for the proposed indication of management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies.

These summary minutes for the May 8, 2019 Pulmonary-Allergy Drugs Advisory Committee meeting of the Food and Drug Administration were approved on_9/17/19___.

I certify that I attended the May 8, 2019 Pulmonary-Allergy Drugs Advisory Committee meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	/s/
Cindy Chee, PharmD	David Au, MD, MS
Designated Federal Officer, PADAC	Chairperson, PADAC

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
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The Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on May 8, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Chiesi USA, Inc. The meeting was called to order by David H. Au, MD, MS (Chairperson). The conflict of interest statement was read into the record by Cindy Chee, PharmD (Designated Federal Officer). There were approximately 100 people in attendance. There were eleven Open Public Hearing 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 (NDA) 202049, for mannitol inhalation powder, for oral inhalation submitted by Chiesi USA, Inc., for the proposed indication of management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies.

Attendance:

Pulmonary-Allergy Drugs Advisory Committee Members Present (Voting): David H. Au, MD, MS (Chairperson); John M. Kelso, MD; David J. Lederer, MD, MS; Gailen D. Marshall Jr, MD, PhD, FACP; Loretta G. Que, MD; Carrie A. Redlich, MD, MPH; Richard W. Weber, MD

Pulmonary-Allergy Drugs Advisory Committee Member Present (Non-Voting): Stuart Green, MD (Industry Representative)

Pulmonary-Allergy Drugs Advisory Committee Members Not Present (Voting): Emma H. D'Agostino, BS (Consumer Representative); Brian T. Garibaldi, MD, PhD; Susanne May, PhD

Temporary Members (Voting): Kathryn Blake, PharmD, BCPS, FCCP, CIP; Erica Brittain, PhD; Mary Cataletto, MD, MMM; Scott S. Emerson, MD, PhD; Daniel L. Gillen, PhD; Erin Moore, BS (Patient Representative); Richard B. Parad, MD, MPH; Karen S. Schell, DHSc, RRT-NPS, RRT-SDS, RPFT, RPSGT, AE-C, CTTS (Acting Consumer Representative); James M. Tracy, DO

FDA Participants (Non-Voting): Sally Seymour, MD; Robert H. Lim, MD; Yongman Kim, PhD; Khalid Puthawala, MD; Cesar Torres, PhD

Designated Federal Officer (Non-Voting): Cindy Chee, PharmD

Open Public Hearing Speakers: Brian Callanan; Veronica Wetmore; Nicholas Kelly, MS, RD, LD; Henry A. Wojtczak, MD; Stephanie Fox-Rawlings, PhD (National Center for Health

Research); Zoë Hurley; Emily Grumbine *(via video introduced by Zoë Hurley)*; Michael Boyle, MD (Cystic Fibrosis Foundation); Mary Beth and Angelica Rock; Tess Dunn *(via video introduced by Angelica Rock)*; Emily Schaller (Rock CF Foundation) *(via video introduced by Mary Beth Rock)*

The agenda was as follows:

Call to Order and Introduction of Committee	**David Au, MD** Chairperson, PADAC
Conflict of Interest Statement	**Cindy Chee, PharmD** Designated Federal Officer, PADAC
FDA Introductory Remarks	**Robert H. Lim, MD** Clinical Team Leader Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Office of Drug Evaluation II (ODE II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Chiesi USA, Inc.**
Introduction to Bronchitol for Adult Patients with Cystic Fibrosis	**Mark Parry-Billings, PhD** Head of Corporate Drug Development Chiesi Farmaceutici S.p.A.
Unmet Need and Disease Background	**Scott H. Donaldson, MD** Professor of Medicine University of North Carolina at Chapel Hill School of Medicine; Division of Pulmonary and Critical Care Director, Adult Cystic Fibrosis Center
Efficacy in Adult Patients with Cystic Fibrosis	**Carmen Dell'Anna, MD** Vice President, Medical Affairs Chiesi USA, Inc.
Safety of Bronchitol	**W. James Alexander, MD, MPH** Senior Medical Affairs Consultant Chiesi USA, Inc.
Bronchitol: A Clinician's Perspective	**Patrick A. Flume, MD** Medical University of South Carolina The Powers-Huggins Endowed Chair for Cystic Fibrosis Professor of Medicine and Pediatrics Associate Provost for Research Compliance and Regulatory Affairs

Clarifying Questions	
BREAK	
FDA PRESENTATIONS	
Overview of Clinical Program	**Khalid Puthawala, MD** Clinical Reviewer DPARP, ODE II, OND, CDER, FDA
Statistical Review of Efficacy	**Cesar Torres, PhD** Statistical Reviewer Division of Biometrics II (DBII) Office of Biostatistics (OB) Office of Translational Sciences (OTS) CDER, FDA
Clinical Review of Efficacy, Safety, and Benefit-Risk Assessment	**Khalid Puthawala, MD**
Clarifying Questions	
LUNCH	
Open Public Hearing	
Charge to the Committee	**Robert H. Lim, MD**
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Discuss the efficacy of dry powder mannitol (DPM) for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. Include the following topics in your discussion:
    a. Effect on FEV_1, including effect size and durability of effect
    b. Secondary endpoints, particularly exacerbations and the Cystic Fibrosis Questionnaire – Revised respiratory domain score
    c. Statistical persuasiveness

***Committee Discussion**: The committee members noted that the increase in FEV_1 is minimal, but the small increase in FEV_1 may still represent a clinically meaningful improvement for some patients with CF. It was noted by a committee member that if 100 ml on a patient level was clinically meaningful, then the number needed to treat would be ~ 10. Thus, it was suggested that the decision to use DPM would be best left to the clinicians treating patients with CF. The committee members also commented on the questionable durability of effect, how missing data were addressed, ambiguity in the data presented, and the null secondary exacerbation endpoint. Please see the transcript for details of the Committee discussion.*

2. **DISCUSSION**: Discuss the safety data for DPM for the proposed use in patients with cystic fibrosis 18 years of age and older, particularly exacerbation and hemoptysis.

***Committee Discussion**: The committee members commented on the potential for concern for exacerbations, particularly in the US population. It was noted that one of the primary benefits was the convenience and potentially improved adherence over hypertonic saline. However, because DPM did not reduce exacerbations, an unintended effect might be to increase overall exacerbation rates. The committee members also noted that since patients with CF routinely experience exacerbation, it may be difficult to determine if an exacerbation was associated with DPM versus the normal disease course. One committee member noted an absence of concern for hemoptysis in the adult population. The committee suggested that monitoring discontinuation of hypertonic saline and risk of exacerbation should be performed in post-marketing studies. Please see the transcript for details of the Committee discussion.*

3. **VOTE:** Do the data provide substantial evidence of efficacy for DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies?
    a. If no, what further data are needed?

Vote Result: Yes: 10 No: 6 Abstain: 0

***Committee Discussion:** The majority of the committee agreed that the data provided substantial evidence of efficacy for DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. The committee members who voted "Yes" commented that while the effect size was minimal as reflected by improvement in FEV_1, this small increase could be clinically meaningful in some patients. The committee also commented on the ease of use of DPM having an impact on patient adherence and lowering administration time when compared to hypertonic saline. The members who voted "No" commented on the small effect on FEV_1 and the lack of clarity on whether this is a clinically meaningful difference. They also commented regarding whether the small effect was sustained effect over the 26-week period as well as lack of support from secondary endpoints. The committee discussed additional studies in those patients who are non-adherent to or unable to take hypertonic saline, those with more advanced disease, and patients at higher risk for exacerbations. Please see the transcript for details of the Committee discussion.*

4. **VOTE**: Are the safety data adequate to support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies?
    a. If no, what further data are needed?

    Vote Result: Yes: 10 No: 6 Abstain: 0

    Committee Discussion: *The majority of the committee agreed that the safety data are adequate to support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. The committee members who voted "Yes" commented that exacerbations appear to be a natural process of the disease and may represent a lack of effectiveness rather than an adverse effect. Thus, committee members voting "Yes" did not feel that DPM would cause harm in most patients. They also mentioned the need for formal post marketing surveillance. The committee members who voted "No" commented on the lack of information about which patients will be at risk for exacerbations and the presence of a consistent safety signal. These committee members also expressed concerns relating to different treatment patterns in the United States (US) population and those of European countries. Please see the transcript for details of the Committee discussion.*

5. **VOTE**: Does the benefit-risk profile support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies?
    a. If no, what further data are needed?

    Vote Result: Yes: 9 No: 7 Abstain: 0

    Committee Discussion: *A slight majority of the committee agreed that the benefit-risk profile support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. These committee members commented on the ease of use of DPM, that the primary endpoint was met, and that a subset of patients will benefit from DPM. One committee member noted that it is difficult to think that treatment approaches in Europe differ much from those in the US. It was also noted that longer studies and a clarification of exacerbation risk are needed. The committee members who voted "No" commented on the insufficient efficacy data and the need for substantial evidence of efficacy to vote in favor of DPM's approval. They also commented on concerns with durability and overall effect, and the presence of practice variation across different countries. One committee member expressed the desire to see additional 6-month randomized withdrawal trial data. Please see the transcript for details of the Committee discussion.*

The meeting was adjourned at approximately 4:25 p.m.