Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Antimicrobial Drugs
Advisory Committee Meeting
November 16, 2017

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

Topic: The committee discussed new drug application (NDA) 209367, ciprofloxacin inhalation powder, sponsored by Bayer HealthCare Pharmaceuticals, Inc., for the proposed indication of reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (≥18 years of age) with respiratory bacterial pathogens.

These summary minutes for the November 16, 2017 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration were approved on March 15, 2018.

I certify that I attended the November 16, 2017 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/
Lauren D. Tesh, PharmD, BCPS
Designated Federal Officer, AMDAC

/S/
Lindsey R. Baden, MD
Chairperson, AMDAC

Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
November 16, 2017

The following is the final report of the Antimicrobial Drugs Advisory Committee meeting held on November 16, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anti-Infective Products and posted on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm551361.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 16, 2017, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland 20903. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Bayer HealthCare Pharmaceuticals, Inc. The meeting was called to order by Lindsey R. Baden, MD (Chairperson). The conflict of interest statement was read into the record by Lauren D. Tesh, PharmD, BCPS (Designated Federal Officer). There were approximately 145 people in attendance. There were 7 Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed new drug application (NDA) 209367, ciprofloxacin inhalation powder, sponsored by Bayer HealthCare Pharmaceuticals, Inc., for the proposed indication of reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (≥18 years of age) with respiratory bacterial pathogens.

Attendance:
AMDAC Members Present (Voting): Lindsey R. Baden, MD; Nina M. Clark, MD; Amanda H. Corbett, PharmD, BCPS, FCCP; Michael D. Green, MD, MPH; Barbara M. Gripshover, MD; Ighovwerha Ofotokun, MD, MSc; Peter Weina, PhD, MD, FACP, FIDSA

AMDAC Members Not Present (Voting): Ellen M. Andrews, PhD (Consumer Representative); Demetre C. Daskalakis, MD, MPH; Dean A. Follmann, PhD; Jonathan R. Honegger, MD; Vincent Lo Re, MD, MSCE; Joanna M. Schaenman, MD, PhD

AMDAC Member Present (Non-Voting): Nicholas A. Kartsonis, MD (Industry Representative)

Temporary Members (Voting): Erica Brittain, PhD; Paula Carvalho, MD; Susan S. Ellenberg, PhD; Jonathan Green, MD, MBA; Michelle Harkins, MD; Randy W. Hawkins, MD (Acting Consumer Representative); Erik R. Swenson, MD; Jasan L. Zimmerman (Patient Representative)

FDA Participants (Non-Voting): Edward Cox, MD, MPH; Sumathi Nambiar, MD, MPH; Thomas Smith, MD; Peter Kim, MD, MS; Christopher Kadoorie, PhD

Designated Federal Officer (Non-Voting): Lauren D. Tesh, PharmD, BCPS

Open Public Hearing Speakers: Christa Warden; Robert A. Wise, MD (COPD Foundation); Michael P. Mayer; Megan Polanin (National Center for Health Research); Marcy Weiner; Mary Kitlowski; Jamie Lamson Sullivan on behalf of Barbara J. McGuirk

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The agenda was as follows:

Call to Order and Introduction of Committee	**Lindsey R. Baden, MD** Chairperson, AMDAC
Conflict of Interest Statement	**Lauren D. Tesh, PharmD, BCPS** Designated Federal Officer, AMDAC
FDA Opening Remarks	**Thomas Smith, MD** Clinical Team Leader Division of Anti-Infective Products (DAIP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Bayer HealthCare Pharmaceuticals, Inc.**
Introduction	**Jana Napolitano, MSc** Vice President, Regulatory Affairs Strategy – Pulmonology, Anti-Infectives and Ophthalmology Bayer
Medical Landscape in Non-Cystic Fibrosis Bronchiectasis	**Pamela McShane, MD** Assistant Professor of Medicine Section of Pulmonary and Critical Care Medicine University of Chicago
Efficacy and Microbiology	**Jeff Alder, PhD** Senior Director, Global Clinical Development, Bayer
Safety	**Gesa Schomakers, MD** Head of Therapeutic Area Anti-Infectives, Pharmacovigilance Benefit-Risk Management, Bayer
Clinical Perspective on Ciprofloxacin DPI Safety & Effectiveness	**Timothy Aksamit, MD** Associate Professor of Medicine Pulmonary Disease and Critical Care Medicine Mayo Clinic, Rochester
Conclusion Clarifying Questions	**Jeff Alder, PhD**
BREAK	

FDA PRESENTATIONS

Presentation of Clinical Efficacy	**Christopher Kadoorie, PhD** Statistical Reviewer Division of Biometrics IV Office of Biostatistics Office of Translational Sciences (OTS), CDER, FDA
Presentation of Clinical Safety	**Peter Kim, MD, MS** Medical Officer DAIP, OAP, OND, CDER, FDA
Summary Presentation	**Thomas Smith, MD**

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **VOTE:** Has the applicant provided substantial evidence of the safety and efficacy for the ciprofloxacin dry powder (DPI) 14-day regimen in delaying the time to first exacerbation after starting treatment?

    a. If yes, please provide any recommendations concerning labeling.
    b. If no, what additional studies/analyses are needed? Please discuss appropriate endpoints, drug regimens and trial duration.

    Vote Result: Yes: 6 No: 9 Abstain: 0

    Committee Discussion: *Six committee members voted "Yes" that the applicant provided substantial evidence of the safety and efficacy for the ciprofloxacin dry powder (DPI) 14-day regimen in delaying the time to first exacerbation after starting treatment. These committee members noted the following: there was consistency among the combined data, there was confidence in the safe use of this product, though more frequent assessment of patient reported outcomes is needed in future trials. It was also noted that if the ciprofloxacin DPI 14-day regimen was approved now, phase 4 studies should be conducted to obtain more data to improve and refine the use criteria for ciprofloxacin DPI. Nine committee members voted "No." These committee members noted that there were concerns with the inconsistency in the data between the two Phase III clinical trials RESPIRE-1 and RESPIRE-2 regarding efficacy. It was further noted that the durability of the treatment effect over time remained*

unclear since the durations of the two trials were only one year each. The committee suggested that future trials be of longer duration given that non-cystic fibrosis bronchiectasis (NCFB) is a lifelong disease. The committee also commented that the use of "time to first exacerbation" was a complicated endpoint whose meaning was unclear and suggested that markers of efficacy such as frequency of exacerbations and severity of exacerbations as indicated by need for hospitalization, number of hospitalizations, need for intravenous antibacterial drugs, and/or assessing total days of antibacterial therapy for exacerbations. The committee also noted additional endpoints of interest to include changes in pulmonary function (FEV_1) and emergence of antimicrobial resistance (over time and in the GI tract). It was also suggested that the use of macrolide therapy could be standardized at baseline across trial arms to potentially lessen heterogeneity in the clinical trial patient population. Additionally, some committee members suggested that subjects could serve as their own controls in a cross-over study design. It was also recommended that drug concentrations at other body sites beyond the respiratory tract should be monitored. Regarding safety, the committee did not have specific concerns about adverse reactions attributed to the use of inhaled ciprofloxacin dry powder for inhalation in comparison to the control group that received a placebo dry powder; however, including a control arm in future trials that did not receive any powder could aid in assessing adverse reactions due solely to inhaling a dry powder. There were notable concerns from the committee regarding possible development of antibacterial resistance that could lead to an attenuated benefit over time, especially given chronic sub-therapeutic exposure to ciprofloxacin at other body sites beyond the respiratory tract and the relatively small benefit in those who improved on inhaled ciprofloxacin DPI. Please see the transcript for details of the committee discussion.

2. **VOTE:** Has the applicant provided substantial evidence of the safety and efficacy for the ciprofloxacin DPI 28-day regimen in delaying the time to first exacerbation after starting treatment?

   a. If yes, please provide any recommendations concerning labeling.
   b. If no, what additional studies/analyses are needed? Please discuss appropriate endpoints, drug regimens and trial duration.

   Vote Result: Yes: 1 No: 14 Abstain: 0

   ***Committee Discussion**: One committee member voted "Yes" that the applicant provided substantial evidence of the safety and efficacy for the ciprofloxacin dry powder (DPI) 28-day regimen in delaying the time to first exacerbation after starting treatment. This member noted that the combined data indicated a potential signal for efficacy. Fourteen of the committee members voted "No", that the applicant did not provide substantial evidence of the safety and efficacy for the ciprofloxacin DPI 28-day regimen in delaying the time to first exacerbation after starting treatment. The committee members raised similar issues related to the inconsistent trial results for the ciprofloxacin DPI 28-day regimen as with the 14-day regimen and made comparable recommendations regarding future study designs as in question #1. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:03 p.m.