Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
January 11, 2018

Location: College Park Marriott Hotel and Conference Center, General Vessey Ballroom 3501 University Blvd. East, Hyattsville, Maryland

Topic: The committee discussed new drug application (NDA) 210693, ciprofloxacin dispersion for inhalation, sponsored by Aradigm Corp., for the proposed indication of treatment of non-cystic fibrosis bronchiectasis patients with chronic lung infections with *Pseudomonas aeruginosa*.

These summary minutes for the January 11, 2018 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 January 11, 2018 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
January 11, 2018

The following is the final report of the Antimicrobial Drugs Advisory Committee meeting held on January 11, 2018. 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/ucm587657.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 January 11, 2018, at the College Park Marriott Hotel and Conference Center, General Vessey Ballroom 3501 University Blvd. East, Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Aradigm Corporation. 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 120 people in attendance. There were 11 Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed new drug application (NDA) 210693, ciprofloxacin dispersion for inhalation, sponsored by Aradigm Corp., for the proposed indication of treatment of non-cystic fibrosis bronchiectasis patients with chronic lung infections with *Pseudomonas aeruginosa*.

Attendance:
AMDAC Members Present (Voting): Lindsey R. Baden, MD (Chairperson); Nina M. Clark, MD; Demetre C. Daskalakis, MD, MPH; Dean A. Follmann, PhD; Michael D. Green, MD, MPH; Barbara M. Gripshover, MD; Jonathan R. Honegger, MD; Ighovwerha Ofotokun, MD, MSc; Joanna M. Schaenman, MD, PhD; Peter Weina, PhD, MD, FACP, FIDSA

AMDAC Members Not Present (Voting): Amanda H. Corbett, PharmD, BCPS, FCCP; Vincent Lo Re, MD, MSCE

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

Temporary Members (Voting): Paula Carvalho, MD; Jonathan Green, MD; Michelle Harkins, MD; Randy W. Hawkins, MD (Acting Consumer Representative); Joan F. Hilton, DSc, MPH; Jasan L. Zimmerman (Patient Representative)

FDA Participants (Non-Voting): Edward Cox, MD, MPH; Sumathi Nambiar, MD, MPH; Thomas Smith, MD; María C. Allende, MD; CDR LaRee Tracy, MA, PhD

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

Open Public Hearing Speakers: Paula Kerr; Amy Leitman (NTM Info & Research); Dr. Keira A. Cohen; Mary Kitlowski; Heidi Snellenburg; Craig Kephart on behalf of George P. Reynolds; Timothy R. Aksamit, MD (COPD Foundation); Lannie Hulnick on behalf of David Bickman; Stephanie Fox-Rawlings (National Center for Health Research); Patrick A. Flume, MD; Kyle Walker

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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	**Aradigm Corporation**
Introduction	**Juergen Froehlich, MD, MBA, FCP** Chief Medical Officer, Aradigm Corporation
Unmet Medical Need / Disease Background	**Gregory Tino, MD** University of Pennsylvania – Perelman School of Medicine
Efficacy	**Igor Gonda, PhD** CEO and President, Aradigm Corporation **Janet Wittes, PhD** President, Statistics Collaborative, Inc.
Safety	**Juergen Froehlich, MD, MBA, FCP**
Benefit / Risk	**Sanjay Sethi, MD, FACP** University at Buffalo, State University of New York **James Chalmers, MD** Ninewells Hospital and Medical School – Department of Respiratory Medicine Dundee
Clarifying Questions	
BREAK	

FDA PRESENTATIONS

Presentation of Efficacy Evaluation	**CDR LaRee Tracy, MA, PhD** Statistical Reviewer Division of Biometrics IV Office of Biostatistics Office of Translational Sciences (OTS), CDER, FDA
Presentation of Clinical Safety	**Maria Allende, MD** Medical Officer DAIP, OAP, OND, CDER, FDA
Summary Presentation	**Thomas Smith, MD** Clinical Team Leader DAIP, OAP, OND, CDER, FDA

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 of ciprofloxacin dispersion for inhalation in delaying the time to first exacerbation after starting treatment in non-cystic fibrosis bronchiectasis patients with chronic lung infections with *Pseudomonas aeruginosa*?

    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: 3 No: 12 Abstain: 1

    Committee Discussion: *Three committee members voted "Yes" that the applicant provided substantial evidence of the safety and efficacy of ciprofloxacin dispersion for inhalation in delaying the time to first exacerbation after starting treatment in non-cystic fibrosis bronchiectasis (NCFB) patients with chronic lung infections with Pseudomonas aeruginosa. One member stated that there appeared to be positive findings in patients with more severe*

disease and there was a positive trend in secondary endpoints. A compelling and unmet need for this patient population was also discussed. It was noted that labeling should reflect frequency of exacerbations, which was proposed as the clinically significant endpoint of interest. It was suggested that additional pharmacokinetic and safety trials be done in children. There were also comments about the heterogeneity of the disease, and the issue of NTM (Nontuberculous mycobacteria) should be addressed. One member expressed a desire to be able to offer something to patients that would be covered by insurance and suggested using biomarkers to determine which patients would benefit from inhaled ciprofloxacin. The majority of the committee members voted "No." There were concerns with the inconsistency of the data between the two clinical trials, ORBIT-3 and ORBIT-4. Some members noted that the data did not meet the burden of proof for safety and efficacy in delaying the time to first exacerbation. Members wanted to have objective measures of adherence in future studies along with data regarding any reduction in use of antibacterial drugs and steroids spared patients are on ciprofloxacin dispersion for inhalation. It was noted that it would be important to assess whether preventive use of inhaled ciprofloxacin would result in a decrease of antimicrobial drugs used for treatment purposes. It was further noted that cough, bronchospasm, and hemoptysis may be due to drug inhalation or the disease process and should be monitored more closely to assess their significance. Other potential secondary endpoints that were recommended were: duration of exacerbation, number of hospitalizations, quality of life and treatment location (inpatient versus outpatient). Inducible resistance was also an issue of concern given that this product is inhaled and will provide very low plasma concentrations but may have subtherapeutic levels, especially in the GI tract. Also, monitoring for induced antimicrobial resistance and emergent pathogens in other body sites besides the lung (such as the GI tract) would be important. There was also discussion about reassessing the study design for NCFB and finding better endpoints. In this disease long term use of this agent, for an unknown duration, may present unknown problems which need to be monitored for and defined. The primary end-point of time to first exacerbation may not be the best end point and others should be considered such as overall number or exacerbations, severtiy of the exacerbations, impact on systemic antimicrobial use to name a few of the suggestions made. Studies with patients acting as their own control in a cross over fashion were suggested to overcome the heterogeneity of the patient population and, possible Phase 4 effectiveness studies were proposed. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:15 p.m.