Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
August 7, 2018

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

Topic: The committee discussed new drug application (NDA) 207356, amikacin liposome inhalation suspension, submitted by sponsored by Insmed, Inc., for the proposed indication of treatment of nontuberculolous mycobacterial (NTM) lung disease caused by Mycobacterium avium complex in adults as part of a combination antibacterial drug regimen.

These summary minutes for the August 7, 2018 meeting of the Antimicrobial Drug Advisory Committee of the Food and Drug Administration were approved on October 14, 2018.

I certify that I attended the August 7, 2018 meeting of the Antimicrobial Drug 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
Antimicrobial Drugs Advisory Committee

/S/
Lindsey R. Baden, MD
Chairperson
Antimicrobial Drugs Advisory Committee

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
August 7, 2018

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on August 7, 2018, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided the briefing materials from the FDA and Insmed 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 100 people in attendance. There were thirteen (13) Open Public Hearing (OPH) presentations.

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

Agenda: The committee Committee discussed new drug application (NDA) 207356, amikacin liposome inhalation suspension, submitted by sponsored by Insmed, Inc., for the proposed indication of treatment of nontuberculolous mycobacterial (NTM) lung disease caused by Mycobacterium avium complex in adults as part of a combination antibacterial drug regimen.

Attendance:
Antimicrobial Drugs Advisory Committee Members Present (Voting): Lindsey R. Baden, MD (Chairperson); Demetre C. Daskalakis, MD, MPH; Michael Green, MD, MPH; Barbara M. Gripshover, MD; Jonathan R. Honegger, MD; Vincent Lo Re, MD, MSCE; Joanna M. Schaenman, MD, PhD; Peter Joseph Weina, PhD, MD

Antimicrobial Drugs Advisory Committee Members Not Present (Voting): Nina M. Clark, MD; Amanda H. Corbett, PharmD, BCPS, FCCP; Dean A. Follmann, PhD; Ighovwerha Ofotokun, MD, MSc

Antimicrobial Drugs Advisory Committee Member Not Present (Non-Voting): Nicholas A. Kartsonis, MD (Industry Representative)

Temporary Members (Voting): Ellen Andrews, PhD (Acting Consumer Representative); Erica Brittain, PhD; Scott E. Evans, MD, FCCP; Charles E. Hawkins, MS (Patient Representative); Henry Masur, MD; Michael Proschan, PhD

Acting Industry Representative to the Antimicrobial Drugs Advisory Committee (Non-Voting): Stuart Green, MD (Acting Industry Representative)

FDA Participants (Non-Voting): Edward Cox, MD, MPH; Sumathi Nambiar, MD, MPH; Peter Kim, MD, MS; Hiwot Hiruy, MD, PhD; Cheryl Dixon, PhD

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

Open Public Hearing Speakers: Amy Leitman (NTM Info & Research); Stephen J. Ruoss, MD; Julie V. Philley, MD; Philip Leitman (NTM Info & Research); Julie Kardachi; Melissa Hays; Elisha Malanga (COPD Foundation); Anne E. O'Donnell, MD; Linda Miglicco; Marcia O'Bryan; Laura Kelley (statement read by Tracey Sperry); Varuna Srinivesan, MD, MPH (National Center for Health Research); Michelle Fatibene

---

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	**Sumathi Nambiar MD, MPH** Director Division of Anti-Infective Products (DAIP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Insmed, Inc.**
Introduction	**Paul Streck, MD** Chief Medical Officer Insmed, Inc.
Unmet Need	**Shannon Kasperbauer, MD** Associate Professor Department of Medicine Division of Mycobacterial and Respiratory Infections National Jewish Health
Efficacy	**Eugene Sullivan, MD** Chief Product Strategy Officer Insmed, Inc.
Safety	**Peter Sallstig, MD** Vice President, Clinical Development Insmed, Inc.
Clinical Perspective	**David Griffith, MD** Professor of Medicine University of Texas Health Science Center at Tyler

Clarifying Questions

BREAK

FDA PRESENTATIONS

Presentation of Clinical Efficacy	**Peter Kim, MD, MS** Clinical Team Leader DAIP, OAP, OND, CDER, FDA
Presentation of Clinical Safety	**Hiwot Hiruy, MD, PhD** Medical Officer DAIP, OAP, OND, CDER, FDA

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

---

1. **VOTE:** Is the surrogate endpoint of sputum culture conversion based on three consecutive negative sputum cultures reasonably likely to predict clinical benefit?

   Vote Result: Yes: 8 No: 6 Abstain: 0

   Committee Discussion: *Eight committee members voted yes, that the surrogate endpoint of sputum culture conversion based on three consecutive negative sputum cultures is reasonably likely to predict clinical benefit. Some of these members agreed the surrogate endpoint aligns with what the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) 2007 guidelines recommend for the current standard of care treatment strategy of NTM based on sputum culture conversion to negative. Six committee members voted no, that the surrogate endpoint of sputum culture conversion based on three consecutive negative sputum cultures is not reasonably likely to predict clinical benefit. One member commented that amikacin liposome inhalation suspension (ALIS) seems safer than intravenous amikacin, even though sputum culture conversion might not confer a clinical benefit. One member noted that the study was not blinded and no clinical benefit was identified based on patient reported outcome measures. Another member noted that the six studies reviewed by the FDA showed that sputum culture conversion does not decrease*

symptoms in patients, increase functional benefit or decrease mortality. One member who voted "no" stated that the ATS/IDSA guidelines are written for individual patients and not populations and therefore should not be used as a rational for predicting clinical benefit from sputum culture conversion especially since the recommendations were based on low evidence, at the C, III rating. Please see the transcript for details of the committee discussion.

2. **VOTE:** Has the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of amikacin liposomal inhalation solution (ALIS) for the treatment of nontuberculous mycobacterial lung disease caused by *Mycobacterium avium* complex as part of a combination antibacterial drug regimen for adult patients?

    a. If yes, please provide any recommendations regarding labeling and please comment on the design of the trial that will need to be conducted to confirm clinical benefit.

    b. If no, please provide recommendations regarding additional studies/analyses that are needed.

Vote Result: Yes: 2 No: 12 Abstain: 0

Committee Discussion: *The majority of the committee members disagreed that the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of ALIS for the treatment of NTM lung disease caused by Mycobacterium avium complex as part of a combination antibacterial drug regimen for adult patients. The two committee members who voted "Yes" noted that if it works in a harder to treat population, then it should work overall. Those committee members who voted "NO" noted that the applicant was seeking a much broader indication than was studied. These members further noted that this product should only be approved in refractory patients with very limited or no other treatment options. Another consideration that was stated was that greater than 30% of the patients in the ALIS treatment arm discontinued study therapy prematurely in the Phase 3 clinical trial. It was suggested to have treatment naïve patients studied. Please see the transcript for details of the committee discussion.*

3. ***VOTE:*** *Has the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of ALIS for the treatment of nontuberculous mycobacterial lung disease caused by Mycobacterium avium complex as part of a combination antibacterial drug regimen for adult patients with limited or no treatment options?*

    a. If yes, please provide any recommendations regarding labeling and please comment on the design of the trial that will need to be conducted to confirm clinical benefit.

    b. If no, please provide recommendations regarding additional studies/analyses that are needed.

Vote Result: Yes: 12 No: 2 Abstain: 0

Committee Discussion: *The majority of the committee members agreed that the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of ALIS for the treatment of NTM lung disease caused by Mycobacterium avium complex as part of a combination antibacterial drug regimen for adult patients with limited or no treatment options. These members noted that there was sufficient safety with ALIS. One member stated that ALIS should only be used in patients who can't tolerate IV amikacin such as: the elderly, those with chronic kidney disease and patients who have received a lung transplant. Regarding labeling, the committee members recommended including: (1) there are limited data to support this claim and that efficacy was based on a surrogate endpoint, (2) only six months of data were available to support the microbiologic surrogate endpoint, and data supporting longer term durability of culture conversion is not currently available, (3) clinical benefit has not been established, and (4) there is an increased risk of hospitalizations with the use of this product. Some committee members who voted "YES", recommended that future studies be of longer duration to determine if the durable response of sputum culture conversion is sustained and if this confers clinical benefit to the patient. The committee members who voted "NO", stated that there was a lack of response in the 6-minute walk test, the patient outcomes were worse as evidenced by the dropout rate and increased hospitalizations in the treatment arm. One member also noted concern that if ALIS is approved there could be frequent off-label use in patients such as those infected with other NTM species, cystic fibrosis patients and those with Pseudomonas aeruginosa infections. Please see the transcript for details of the committee discussion.*

The meeting adjourned at approximately 5:15 p.m.