Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
June 6, 2019

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) 212862, pretomanid tablets for oral administration, submitted by The Global Alliance for TB Drug Development, Inc., proposed as part of a combination regimen with bedaquiline and linezolid in adults for the treatment of pulmonary extensively drug resistant and treatment-intolerant or non-responsive multidrug-resistant tuberculosis (TB).

These summary minutes for the June 6, 2019 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration were approved on ___July 30, 2019_____.

I certify that I attended the June 6, 2019 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
LaToya Bonner, PharmD	Lindsey R. Baden, MD
Acting Designated Federal Officer, AMDAC	*Chairperson, AMDAC*

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
June 6, 2019

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on June 6, 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 The Global Alliance for TB Drug Development, Inc. The meeting was called to order by Lindsey R. Baden, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Acting Designated Federal Officer). There were approximately 150 people in attendance. There were nine Open Public Hearing speaker presentations.

A verbatim transcription will be available, in most cases, approximately ten to twelve weeks, following the meeting date.

Agenda: The committee discussed new drug application (NDA) 212862, pretomanid tablets for oral administration, submitted by The Global Alliance for TB Drug Development, Inc., proposed as part of a combination regimen with bedaquiline and linezolid in adults for the treatment of pulmonary extensively drug resistant and treatment-intolerant or non-responsive multidrug-resistant tuberculosis (TB).

Attendance:
AMDAC Members Present (Voting): Lindsey R. Baden, MD (Chairperson); Dean A. Follmann, PhD; Michael D. Green, MD, MPH; Barbara M. Gripshover, MD; Jennifer Lee, PharmD, MAS; Ighovwerha Ofotokun, MD, MSc; Sankar Swaminathan, MD; Roblena E. Walker, PhD (Consumer Representative); Peter J. Weina, PhD, MD, FACP, FIDSA

AMDAC Members Not Present (Voting): Timothy H. Burgess, MD, MPH, FACP; Nina M. Clark, MD; Joanna M. Schaenman, MD, PhD; George K. Siberry, MD, MPH

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

Temporary Members (Voting): Demetre C. Daskalakis, MD, MPH; Susan S. Ellenberg, PhD; Marc Ghany, MD, MHSc; Matthew Bidwell Goetz, MD; Joan F. Hilton, ScD, MPH; Keith D. Lindor, MD; Philip LoBue, MD; Thomas A. Moore, MD, FACP, FIDSA; Patricia Lupole (Patient Representative)

FDA Participants (Non-Voting): John Farley, MD, MPH; Sumathi Nambiar, MD, MPH; Yuliya Yasinskaya, MD; Elizabeth O'Shaughnessy, MD; Daniel Rubin, PhD

Acting Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD

Open Public Hearing Speakers: Lee Reichman, MD; Rana Nauman; Eric Goosby, MD (on behalf of RADM (ret.) Kenneth G. Castro); Eric Goosby, MD; Joanne Carter (RESULTS); Jessica Salzwedel; Jennifer Furin, MD; Stephanie Fox-Rawling (National Center for Health Research); Mark Harrington (Treatment Action Group)

The agenda was as follows:

Call to Order and Introduction of Committee	**Lindsey R. Baden, MD** Chairperson, AMDAC
Conflict of Interest Statement	**LaToya Bonner, PharmD** Acting Designated Federal Officer, AMDAC
FDA Introductory Comments	**Yuliya Yasinskaya, MD** Medical Team Leader Division of Anti-Infective Products (DAIP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**The Global Alliance for TB Drug Development, Inc.**
Introduction and Overview of Pretomanid New Drug Application	**Mel Spigelman, MD** President and Chief Executive Officer TB Alliance
Unmet Need for Treatment of Highly-Resistant Tuberculosis	**Neil Schluger, MD** Chief of the Division of Pulmonary, Allergy and Critical Care Medicine Columbia University Department of Medicine
Nix-TB Results - Efficacy and Safety	**Daniel Everitt, MD** Vice President and Senior Medical Officer TB Alliance
Clinical Perspective on Treatment for Highly-Resistant Tuberculosis	**Francesca Conradie, MD** Deputy Director, Clinical HIV Research Unit University of the Witwatersrand Department of Medicine
Clarifying Questions	

FDA PRESENTATIONS

Presentation of Clinical Efficacy	**Daniel Rubin, PhD** Statistical Reviewer Division of Biometrics IV, Office of Biostatistics Office of Translational Sciences, CDER, FDA
Presentation of Clinical Safety	**Elizabeth O' Shaughnessy, MD** Clinical Reviewer DAIP, OAP, OND, CDER, FDA

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Question to the Committee:

1. **VOTE**: Has the Applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of pretomanid as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis?

   Vote Result: **Yes: 14** **No: 4** **Abstain: 0**

   a. If yes, please provide any recommendations concerning labeling.

   b. If no, what additional studies/analyses are needed?

Committee Discussion: *The majority of the Committee voted "Yes", agreeing that the Applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of pretomanid as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis. The Committee members who voted "Yes" stressed that their vote is in support of the drug regimen of the combination of pretomanid with bedaquiline and linezolid and not necessarily pretomanid alone. These committee members also emphasized that patients should be well informed of the risks, and that strict monitoring*

should be implemented to support safe use prior to prescribing the drug regimen of pretomanid, bedaquiline, and linezolid.

The Committee members who voted "No" mentioned that the Applicant had not provided any clinical data supporting the contribution of pretomanid to the regimen for the proposed indication. These same Committee members agreed that the Nix-TB trial was lacking in number of participants, diversity and statistical rigor. One Committee member emphasized that the Applicant showed the contribution of pretomanid in mice but failed to provide any clinical evidence to support the contribution of pretomanid to the regimen. Another Committee member noted that the data were difficult to interpret because single-arm studies are vulnerable to bias, comparisons to historical literature or matched historical controls did not include control patients treated with bedaquiline or pretomanid regimens, and the sample size was too small to gather sufficient efficacy and safety data.

Collectively, the Committee members agreed that post marketing surveillance is needed to collect additional safety data for pretomanid as part of the bedaquiline and linezolid regimen. One Committee member commented that Southeastern Asian nations have a high burden of XDR-TB and MDR-TB; therefore, broadening the patient population would better reflect a real-world setting. In addition, the Committee urged the Applicant to implement safety monitoring procedures in future studies of pretomanid as a component of this particular regimen, especially in pediatric patients, women, and individuals with underlying liver disease. Lastly, the Committee advised that the labeling for the proposed regimen (pretomanid, bedaquiline, and linezolid) should include complete blood counts and liver function tests at baseline and monitoring during therapy due to reports of hematopoietic cytopenias and hepatotoxicity. One Committee member stressed that the regimen should be prescribed only by TB experts, at least until further safety data are available. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 3:12 p.m.