Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
June 9, 2016

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

Topic: The committee discussed biologics license application (BLA) 761046, bezlotoxumab (MK-6072) injection, submitted by Merck Sharpe & Dohme Corp., for the proposed indication of prevention of Clostridium difficile infection recurrence. These summary minutes for the June 9, 2016 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration were approved on July 6, 2016.

I certify that I attended the June 9, 2016 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
June 9, 2016

The following is a final report of the meeting of the Antimicrobial Drugs Advisory held on June 9, 2016. 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: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm496389.htm

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

The Antimicrobial Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on June 9, 2016, at the FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Merck Sharpe & Dohme Corp. The meeting was called to order by Lindsey R. Baden, MD (Chairperson). The conflict of interest statement was read into the record by Lauren Tesh, PharmD, BCPS (Designated Federal Officer). There were approximately 120 people in attendance for the meeting. There was one Open Public Hearing speaker.

Issue: The committee discussed biologics license application (BLA) 761046, bezlotoxumab (MK-6072) injection, submitted by Merck Sharpe & Dohme Corp., for the proposed indication of prevention of *Clostridium difficile* infection recurrence.

Attendance:

Antimicrobial Drugs Advisory Committee Members Present (Voting): Ellen M. Andrews, PhD (Consumer Representative); Lindsey R. Baden, MD (Chairperson); Amanda H. Corbett, PharmD, BCPS, FCCP; Demetre C. Daskalakis, MD, MPH; Dean A. Follmann, PhD; Michael Green, MD, MPH; Barbara M. Gripshover, MD; Jonathan Honegger, MD; Joanna Schaenman, MD, PhD; Peter Weina, MD, PhD, FACP, FIDSA

Antimicrobial Drugs Advisory Committee Members Not Present (Voting): Vincent Lo Re, MD, MSCE; Luis Z. Ostrosky, MD; Marc H. Scheetz, PharmD, MSc

Temporary Members (Voting): Juan C. Gea-Banacloche, MD; Matthew B. Goetz, MD; Joan Hilton, ScD, MPH; Thomas A. Moore, MD, FACP, FIDSA; Christina Surawicz, MD; Jeanine Thomas (Patient Representative)

Antimicrobial Drugs Advisory Committee Member Present (Non-Voting): Barry M. Bernstein, MD (Industry Representative)

FDA Participants (Non-Voting): Edward M. Cox, MD, MPH; Cheryl Dixon, PhD; Hiwot Hiruy, MD, PhD; Dmitri Iarikov, MD, PhD; Shrimant Mishra, MD, MPH; Sumati Nambiar, MD, MPH

Open Public Hearing Speaker: Nancy C. Caralla (C Diff Foundation) (statement read by Scott Battles)

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 Introductory Remarks	**Sumati Nambiar, MD, MPH** Division Director Division of Anti-Infective Products (DAIP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	
Bezlotoxumab Introduction	**Donnette Staas, PhD** Director, Regulatory Affairs Merck
Clinical Program Overview and Efficacy	**Dayla Guris, MD, MPH** Executive Director, Clinical Research Merck
Clinical Program: Safety	**LCDR James Phillip Trinidad, MPH, MS** Epidemiologist DEPI-II, OPE, OSE, CDER, FDA
Conclusions and Benefit-Risk	**Mark Wilcox, MD** Clinical Consultant to Merck Consultant and Head of Microbiology Professor of Medical Microbiology Leeds Teaching Hospitals & University of Leeds, UK Lead on CDI, Public Health England, UK
Clarifying Questions to the Presenters	
BREAK	
FDA PRESENTATIONS	
Presentation of Clinical Efficacy	**Cheryl Dixon, PhD** Statistical Reviewer Division of Biometrics IV (DB IV) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA

Presentation of Clinical Safety	**Hiwot Hiruy, MD, PhD** Medical Officer DAIP, OAP, OND, CDER, FDA

Clarifying Questions to the Presenters

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 effectiveness of bezlotoxumab for the prevention of *C. difficile* infection recurrence in patients aged 18 years and older?

   a. If yes, please discuss your rationale and provide any recommendations concerning labeling.

   b. If no, please discuss your rationale and what additional studies/analyses are needed.

   Vote Result: Yes: 10 No: 5 Abstain: 1

   Committee Discussion: *The majority of the committee voted "Yes," indicating that the applicant demonstrated substantial evidence of the safety and effectiveness of bezlotoxumab for the proposed indication of prevention of C. difficile infection recurrence in patients aged 18 years and older. However, the committee was concerned that the mechanism of action of bezlotoxumab was unclear. Some committee members felt that the endpoint of C. difficile recurrence as defined in the trials was not optimal for the primary efficacy analysis. . The committee recognized that the drug met an unmet medical need and served as a novel option for the prevention of C. difficile recurrence. If approved, the committee members recommended the drug should be used with caution in patients who have underlying heart disease and that should be noted in the drug label. A few experts recommended studies to be conducted in pediatric patients.*

   Those members who voted "No" stated that they did not see substantial evidence of the efficacy of bezlotoxumab in the prevention of C. difficile recurrence had been consistently demonstrated. One committee member indicated that C. difficile infection is a common disease and additional trials of bezlotoxumab may be feasible and warranted. Some committee members were concerned about potential interference of bezlotoxumab with cure of the initial episode of C. difficile infection. They noted that a drug indicated for recurrence should have been given at day 14, after treatment of the initial infection and should not have

been administered early on in treatment. The one member who abstained from voting was not convinced of the therapeutic benefit of the drug over standard of care therapies. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:15 pm.