Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
August 8, 2018

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

Topic: The committee discussed new drug applications 209816, for omadacycline tablets and 209817 for omadacycline injection, sponsored by Paratek Pharmaceuticals, Inc., for the proposed indications of community acquired bacterial pneumonia and acute bacterial skin and skin structure infections.

These summary minutes for the August 8, 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 8, 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 8, 2018

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on August 8, 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 Paratek 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 75 people in attendance. There were eight (8) 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 discussed new drug applications 209816, for omadacycline tablets and 209817 for omadacycline injection, sponsored by Paratek Pharmaceuticals, Inc., for the proposed indications of community acquired bacterial pneumonia and acute bacterial skin and skin structure infections.

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; Ighovwerha Ofotokun, MD, MSc; 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

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

Temporary Members (Voting): Erica Brittain, PhD; William J. Calhoun, MD, FACP; Emma D'Agostino, BS (Acting Consumer Representative); Scott E. Evans, MD, FCCP; James Floyd, MD, MS; Sean Hennessy, PharmD, PhD; Tina L. Nelkin (Patient Representative); Michael Proschan, PhD; Erik R. Swenson, MD

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

FDA Participants (**Non-Voting):** John Farley, MD, MPH; Sumathi Nambiar, MD, MPH; Joseph Toerner, MD, MPH

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

Open Public Hearing Speakers: Teena Chopra, MD, MPH (Detroit Medical Center, Wayne State University, and Vibra Hospital); Scott R. Battles; Nick Van Hise, PharmD, BCPS (C Diff Foundation); Philip Giordano, MD, FAECP; Nicolette Theriault; Seema Mehta, MD, MS; Stephen Brunton, MD; Stephanie Fox-Rawlings, PhD (National Center for Health Research)

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	Paratek Pharmaceuticals, Inc.
Introduction	**Evan Loh, MD** President, Chief Operating Officer & Chief Medical Officer Paratek Pharmaceuticals
Unmet Need	**Keith S. Kaye, MD, MPH** Professor of Internal Medicine Director of Clinical Research, Division of Infectious Diseases University of Michigan Medical School
Efficacy	**Anita Das, PhD** Statistical Consultant
Safety	**Evan Loh, MD**
Benefit Risk	**Eric Mortensen, MD, MSc** Division Chief, General Internal Medicine, UConn Health Center Professor of Medicine, University of Connecticut School of Medicine
Clarifying Questions	

BREAK

FDA PRESENTATION

Safety and Efficacy Analyses — **Joseph Toerner, MD, MPH**
Cross Disciplinary Team Leader
Deputy Director for Safety
DAIP, OAP, OND, CDER, FDA

Clarifying Questions

OPEN PUBLIC HEARING

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 omadacycline for the treatment of acute bacterial skin and skin structure infections?

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

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

    Vote Result: Yes: 17 No: 1 Abstain: 0

    Committee Discussion: *The majority of the committee members agreed that the applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of acute bacterial skin and skin structure infections (ABSSSI). These committee members noted that omadacycline was non-inferior to linezolid in two randomized controlled trials in ABSSSI. Committee members noted that it is beneficial to have a new intravenous to oral option for this indication and that the potential gastrointestinal side effects are manageable. One member recommended additional studies regarding safety and tolerability in children. Regarding labeling, because only a few patients in the trials had bacteremia, committee members suggested that the indication should not include patients with concurrent bacteremia. Some committee members expressed concern about few elderly patients in the ABSSSI trials and recommended that it should be noted in the labeling. It was also mentioned that the label should include detailed information about the mortality signal from the community acquired bacterial pneumonia (CABP) trial. The one member that voted "NO", noted concerns with the ABSSSI trial population being younger than what might be encountered in clinical practice, and that given that the CABP trial showed a potential safety*

signal in the elderly, that this might be seen in clinical practice when treating ABSSSI. Please see the transcript for details of the committee discussion.

2. **VOTE:** Has the applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of community acquired bacterial pneumonia?

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

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

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

Committee Discussion: *The majority of the committee members agreed that the applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of community acquired bacterial pneumonia (CABP). It was noted that omadacycline met the requirement for noninferiority to moxifloxacin for the treatment of CABP. It was questioned whether the 8 vs. 3 deaths (omadacycline vs.moxifloxacin) could be a chance finding. Most committee members shared the concern about the potential for increased risk of mortality associated with omadacycline use in the treatment of CABP, but some also suggested that deaths were to be expected among CABP patients and were reassured that there was no common mechanism among the deaths reported. Committee members noted that mortality rates observed in the omadacycline group were in line with mortality rates observed in other randomized trials conducted in CABP. It was noted that the risk factors for mortality appeared to be in older patients with greater disease severity. Nearly all members suggested postmarketing evaluation(s) to answer the mortality question as well as to gather more information on specific subgroups including those with bacteremia and in individuals with higher Pneumonia Patient Outcomes Research Team (PORT) scores. The committee members recommended a postmarketing randomized controlled trial as well as a non-randomized observational study. One committee member recommended to include details about sex and gender response in those postmarketing studies. Those that voted "NO", agreed with the efficacy of omadacycline in CABP, but were concerned with the safety signal. One committee member was concerned about the non-adrenergic and vagolytic effect of omadacycline and increased heart rate that was observed in nonclinical and healthy volunteer studies. One member was concerned that three deaths occurred very early in the study. There was also concern about patients who were critically ill, elderly and those with comorbidities. Since omadacycline is proposed in both oral and IV formulation, one member was concerned that it would be difficult to restrict the use of omadacycline for CABP in the postmarket setting due to the convenience of its use. Regarding labeling, one member noted concerns regarding omadacycline efficacy in patients with polymicrobial infection, and thus recommended to include in the label that omadacycline should not be used for empiric therapy. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 1:20 p.m.