Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting
June 17, 2022

Location: Please note that due to the impact of the COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconference platform.

Topic: The committee discussed supplemental new drug applications (sNDAs) 210793-s008 and 207318-s011, efficacy supplement resubmission for NUPLAZID (pimavanserin) tablets, submitted by Acadia Pharmaceuticals Inc., for the proposed treatment of hallucinations and delusions associated with Alzheimer's disease psychosis.

These summary minutes for the June 17, 2022 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration were approved on July 8, 2022.

I certify that I attended the June 17, 2022 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Joyce Frimpong, PharmD	Rajesh Narendran, MD
Designated Federal Officer, PDAC	Chairperson, PDAC

Final Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting June 17, 2022

The Psychopharmacologic Drugs Advisory Committee (PDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 17, 2022. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Acadia Pharmaceuticals, Inc. The meeting was called to order by Rajesh Narendran, MD (Chairperson). The conflict of interest statement was read into the record by Joyce Frimpong, PharmD. There were approximately 1,069 people online. There were 21 Open Public Hearing (OPH) speaker presentations.

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

Agenda: The committee discussed supplemental new drug applications (sNDAs) 210793-s008 and 207318-s011, efficacy supplement resubmission for NUPLAZID (pimavanserin) tablets, submitted by Acadia Pharmaceuticals Inc., for the proposed treatment of hallucinations and delusions associated with Alzheimer's disease psychosis.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members Present (Voting): Walter S. Dunn, MD, PhD; Jess G. Fiedorowicz, MD, PhD; Satish Iyengar, PhD; Sonia L. Krishna, MD, FAPA, DFAACAP; Rajesh Narendran, MD (Chairperson); Kim O. Witczak (Consumer Representative)

Psychopharmacologic Drugs Advisory Members Not Present (Voting): Jessica J. Jeffrey, MD, MPH, MBA; William R. Keller, MD, MBA; Patrick S. Thomas, Jr., MD, PhD

Psychopharmacologic Drugs Advisory Committee Member Present (Non-Voting): Robert W. Baker, MD (Industry Representative)

Temporary Members (Voting): Liana G. Apostolova, MD, MSc, FAAN; Merit E. Cudkowicz, MD, MSC; Dean Follmann, PhD; Colette Johnston (Patient Representative); Paul Stander, MD, MBA; Madhav R. Thambisetty, MD, PhD

FDA Participants (Non-Voting): Billy Dunn, MD; Tiffany R. Farchione, MD; Bernard Fischer, MD; Paul Bossie, MD; Xiang Ling, PhD

Designated Federal Officer (Non-Voting): Joyce Frimpong, PharmD

Open Public Hearing Speakers: Gus Alva, MD, DFAPA; Gary Smalls, MD; Chad Worz, PharmD (American Society of Consultant Pharmacists); Susan Peschin (Alliance for Aging Research); John Schall (Caregiver Action Network); Sidney M. Wolfe, MD (Public Citizen's Health Research Group); Karl Steinberg, MD; Aaron Ritter, MD; Nina Zeldes, PhD (National

Center for Health Research); Leigh F. Callahan, PhD; Agustin Artiles; George T. Grossberg, MD; Meryl Comer (Us Against Alzheimer's); Jed A. Levine (CaringKind); Howard Kirshner, MD (Clinical Neurological Society of America); Nadine Arce; Anita Royal; Jany Moreira; Daniel Claassen, MD; Stephen Chambers; Adriane Fugh-Berman, MD (Georgetown University Medical Center, PharmedOut)

The agenda was as follows:

Call to Order	**Rajesh Narendran, MD** Chairperson, PDAC
Introduction of Committee and Conflict of Interest Statement	**Joyce Frimpong, PharmD** Designated Federal Officer, PDAC
FDA Opening Remarks	**Tiffany R. Farchione, MD** Director Division of Psychiatry (DP) Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Acadia Pharmaceuticals Inc.**
Introduction	**Daryl DeKarske, MPH** Sr. Vice President, Global Head of Regulatory Affairs and Translational Sciences Acadia Pharmaceuticals Inc.
Unmet Need	**Pierre Tariot, MD** Director, Banner Alzheimer's Institute Research Professor of Psychiatry University of Arizona College of Medicine
Efficacy	**Clive Ballard, MD** Pro-Vice Chancellor and Executive Dean Professor of Age-related Diseases College of Medicine and Health University of Exeter United Kingdom **Suzanne Hendrix, PhD** President and CEO, Pentara Corporation
Overview of Safety	**Mary Ellen Turner, MD, MPH** Sr. Vice President, Pharmacovigilance and Corporate Safety Officer Acadia Pharmaceuticals Inc.

Benefit-Risk	**Serge Stankovic, MD** President Acadia Pharmaceuticals Inc.
Clarifying Questions to Applicant	
BREAK	
FDA PRESENTATIONS	
Pimavanserin (NUPLAZID) for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis	**Paul Bossie, MD** Clinical Reviewer DP, ON, OND, CDER, FDA **Xiang Ling, PhD** Statistical Reviewer Division of Biometrics I (DBI) Office of Biostatistics (OB) Office of Translational Sciences (OTS) CDER, FDA
Clarifying Questions to FDA	
LUNCH	
OPEN PUBLIC HEARING	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the evidence supports the effectiveness of pimavanserin for the treatment of hallucinations and delusions in the Alzheimer's disease psychosis (ADP) population. In your discussion, comment on the strengths, limitations, and the extent to which each of the following potential sources of evidence contribute to your overall assessment of effectiveness:
    - Study 019
    - Study 045
    - The prior approval of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis

Committee Discussion: *Regarding Study 019, some committee members felt that the study was not adequate, with members noting the issues with study protocol deviations, although some felt those issues appeared to have been somewhat addressed by the Agency's review. The committee members also noted concerns about the separation (on the primary endpoint) only at Week 6, with a very small effect, and some concerns that the effect was not maintained. There were also questions raised about the construct validity of the outcome measures used in the study, lack of signal on the secondary measures, and lack of functional outcome improvement. Some members raised concerns about the racial and ethnic composition of the study. Some committee members thought that because this study was designed as a phase 2 trial, it did not provide sufficient evidence (as a larger phase 3 trial would have provided). On the other hand, some members felt that Study 019 was positive and that the data were supportive, if not perfect. These members concluded that the study was persuasive despite the audit for the protocol deviations and noted that the study was technically a win.*

Regarding Study 045, some committee members believed that the randomized trial design was not the best to study efficacy because of the selection bias of only including responders and withdrawing the drug. Some committee members also acknowledged that because Study 045 was terminated early and the Alzheimer's disease subgroup was underpowered, it did not allow for the study to truly gauge the efficacy in Alzheimer's disease psychosis. Some members did not find the dopaminergic drug issue convincing, and that the post hoc analysis in the separate groups was not a randomized comparison that could provide clear-cut efficacy data.

Regarding the prior approval of pimavanserin for Parkinson's disease psychosis (i.e., Study 020), some of the committee members noted that it was irrelevant or that the relevance was unclear because it is a different illness, although others agreed there may be some overlap between the two conditions and some biological plausibility and that psychosis could be effectively treated with pimavanserin. Some committee members expressed the opinion that, because pimavanserin had been administered safely to large population of patients with Parkinson's disease psychosis, it could be reasonable to go forward in the Alzheimer's disease population.

Please see the transcript for details of the Committee's discussion.

2. **VOTE:** Does the available evidence support a conclusion that pimavanserin is effective for the treatment of hallucinations and delusions in the ADP population?
    - If yes, provide the rationale.
    - If no, provide your rationale and a recommendation for what further evidence should be generated.

Vote Result: **Yes: 3** **No: 9** **Abstain: 0**

Committee Discussion: *The majority of the committee members voted "No," i.e., that the available evidence does not support a conclusion that pimavanserin is effective for the treatment of hallucinations and delusions in the ADP population. Those who voted "No" stated the need for an additional randomized controlled trial, with adequate ethnic and*

racial representation, and a longer duration to assess efficacy. The committee members who voted "Yes" noted that there was a strong unmet need and that the studies demonstrated modest efficacy, particularly Study 019. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 4:21 p.m.