Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
March 16, 2023

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 new drug application (NDA) 217188, for PAXLOVID (nirmatrelvir and ritonavir co-packaged tablets) for oral use, submitted by Pfizer, Inc. The proposed indication is treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death

These summary minutes for the March 16, 2023 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration were approved on April 28, 2023.

I certify that I attended the March 16, 2023 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
March 16, 2023

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on March 16, 2023. 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 Pfizer, Inc. The meeting was called to order by Lindsey Baden, MD (Chairperson). The conflict of interest statement was read into the record by Joyce Frimpong (Acting Designated Federal Officer). There were approximately 639 people in attendance. There were no 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 new drug application (NDA) 217188, for PAXLOVID (nirmatrelvir and ritonavir co-packaged tablets) for oral use, submitted by Pfizer, Inc. The proposed indication is treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Attendance:
Antimicrobial Drugs Advisory Committee Members Present (Voting): Lindsey R. Baden, MD (Chairperson); Michael D. Green, MD, MPH; W. David Hardy, MD; Sally A. Hunsberger, PhD; Richard A. Murphy, MD, MPH; Nimish Patel, PharmD, PhD; Federico Perez, MD, MS; George K. Siberry, MD, MPH; Sankar Swaminathan, MD; Roblena E. Walker, PhD (Consumer Representative)

Antimicrobial Drugs Advisory Committee Members Not Present (Voting): Ighovwerha Ofotokun, MD, MSc

Antimicrobial Drugs Advisory Committee Member Present (Non-Voting): Richa S. Chandra, MD, MBA (Industry Representative)

Temporary Members (Voting): Adaora A. Adimora, MD, MPH; Paula Carvalho, MD; Nina Clark, MD; Terry Gillespie (Patient Representative); Kim Scarsi, PharmD, MS; Shivanjali Shankaran, MD; Paige Waterman, MD

FDA Participants (Non-Voting): John Farley, MD, MPH; Debra Birnkrant, MD; Glen Huang, DO; Stephanie Troy, MD; Jonathan Rawson, PhD; Patrick Harrington, PhD

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

Open Public Hearing Speakers: None

The agenda was as follows:

Call to Order	**Lindsey R. Baden, MD** Chairperson, AMDAC
Introduction of Committee and Conflict of Interest Statement	**Joyce Frimpong, PharmD** Acting Designated Federal Officer, AMDAC
FDA Opening Remarks	**John Farley, MD, MPH** Director Office of Infectious Diseases (OID) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Pfizer, Inc.**
Introduction	**James Rusnak, MD, PhD** Senior Vice President Chief Development Officer Internal Medicine, Anti-infectives, and Hospital Global Product Development Pfizer, Inc.
Efficacy from EPIC Randomized Clinical Trials	**Jennifer Hammond, PhD** Vice President Development Head Antivirals Global Product Development Pfizer, Inc.
Effectiveness from Real-world Studies	**John McLaughlin, PhD** Vice President, Global Medical Lead Covid & Influenza Pfizer, Inc.
Efficacy Conclusions and Safety from EPIC Randomized Clinical Trials	**Jennifer Hammond, PhD**
Safety from Post-Marketing Surveillance	**Lubna Merchant, MS, PharmD** Director, Risk Management Center of Excellence, Worldwide Safety Pfizer Inc.
COVID-19 Rebound, Continued Development, and Conclusions	**James Rusnak, MD, PhD**
BREAK	
FDA PRESENTATIONS	

Overview	**Glen Huang, DO** Clinical Reviewer Division of Antivirals (DAV) OID, OND, CDER, FDA
Efficacy Issues	
Efficacy of PAXLOVID in High-Risk Adults Who Were Previously Vaccinated Against COVID-19 or Had a Prior SARS-CoV-2 Infection	**Stephanie Troy, MD** Clinical Reviewer DAV, OID, OND, CDER, FDA
Efficacy of PAXLOVID in the Setting of the SARS-CoV-2 Omicron Variant	**Jonathan Rawson, PhD** Clinical Virology Reviewer DAV, OID, OND, CDER, FDA
Impact of PAXLOVID on COVID-19 Rebound	**Patrick Harrington, PhD** Clinical Virology Reviewer DAV, OID, OND, CDER, FDA
Optimal Duration of PAXLOVID Treatment in Immunocompromised Patients	**Stephanie Troy, MD**
Safety Issue	
Serious Adverse Reactions Due to DDIs	**Stephanie Troy, MD**
LUNCH	
Clarifying Questions	
OPEN PUBLIC HEARING	
Charge to the Committee	**Debra Birnkrant, MD** Director DAV, OID, OND, CDER, FDA
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion (cont.)	

ADJOURNMENT

Questions to the Committee:

1. **VOTE:** Is the overall benefit-risk assessment favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death?
    a. If yes, please provide your rationale.
    b. If no, please provide your rationale and list what additional studies/trials are needed

    Vote Result: Yes: 16 No: 1 Abstain: 0

    Committee Discussion*: A majority (94%) of the committee members agreed that the overall benefit-risk assessment is favorable for PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults who are non-immune and at high risk for progression to severe COVID-19, including hospitalization or death. The committee members acknowledged that it will be important to identify who is still at high risk for progression to severe disease in the current setting when most people have some baseline SARS-CoV-2 immunity to understand who is most likely to benefit from PAXLOVID. Several committee members commented that since the absolute magnitude of benefit from PAXLOVID has decreased since the trials were conducted due to increasing levels of baseline SARS-CoV-2 immunity from vaccination or prior infection, the risks of treatment (mainly the drug-drug interactions) will have greater weight when making a benefit-risk assessment for use of PAXLOVID in an individual patient. There was also discussion about the continued emergence of new SARS-CoV-2 variants, and the committee indicated the importance of having an antiviral product like PAXLOVID available, considering that it has retained activity against variants to date and, given the conserved nature of the M^{pro} drug target, is predicted to retain activity against future variants. Committee members also stated that the absence of other oral, easy-to-administer, effective alternative therapies are also favorable factors when considering the benefit-risk assessment for PAXLOVID. Several committee members commented that it will be important to communicate that PAXLOVID will have the greatest benefit if taken early after symptom onset, specifically within 5 days as was studied in the trials. When it came to safety, drug-drug interactions were an area of significant concern, and many agreed that this is an issue that needs to be addressed further. There was discussion that risk mitigation is needed in terms of better communicating the risk of drug-drug interactions as primary care providers are primarily prescribing PAXLOVID and may not be familiar with ritonavir drug-drug interactions. Completion of studies pertaining to pregnancy, pediatrics, and in the immunocompromised population was emphasized. The committee member who voted "No" was concerned that the community does not understand where PAXLOVID fits in, who will benefit, and therefore who will be able to access and use it in a timely and appropriate way. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION**: Please comment on the strength of evidence for use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, in the following populations:

a. Individuals who are vaccinated against COVID-19 or had prior SARS-CoV-2 infection
b. Individuals infected with Omicron subvariants
c. Individuals who are immunocompromised

Please comment if additional data are needed in these populations.

Committee Discussion: *Committee members agreed that a patient-level benefit-risk assessment, i.e., clinical judgement or personalized medicine, will be needed for the use of PAXLOVID, but more data are needed to guide physicians in understanding who meets the risk criteria and who will benefit in the right population. Members of the committee also stated that having systematic data on which populations are still at high risk for progression to severe disease in the current era of high population immunity will allow physicians to be more informed, as the issue is not whether there is benefit, but rather in which patients the magnitude of benefit of PAXLOVID will outweigh the risks. The committee agreed that ongoing surveillance and research should be conducted to ensure that emerging Omicron subvariants and other future variants continue to be susceptible to PAXLOVID and to detect the possible emergence of resistant variants. The committee recommended that pharmacovigilance plans and nonclinical studies should be implemented to study PAXLOVID activity against new emerging variants. Concerning the immunocompromised population, committee members stated that the clinical development plan for investigating use of PAXLOVID in immunocompromised patients, including the clinical trial EPIC-IC, seems to be comprehensive. However, there was concern that with the wide spectrum of immunocompromising conditions, one study may be insufficient to fully inform decision making with this population. Several committee members commented that collection of samples to look for prolonged viral shedding and emergence of resistant virus would be important in EPIC-IC. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION**: Please comment on the strength of evidence for an association between use of PAXLOVID in the treatment of mild-to-moderate COVID-19 and 'COVID-19 rebound'. Please comment if additional data are needed.

Committee Discussion: *Regarding COVID-19 rebound, many of the committee members highlighted that the clinical trial data show that COVID-19 rebound occurred in both the placebo and PAXLOVID groups and that PAXLOVID use did not appear to be the driving factor for COVID-19 rebound. Committee members also commented that they are seeing reassuring data in the published literature, and that as health care professionals it is essential to effectively convey the information. Multiple committee members noted that the main issue is that the perception that PAXLOVID causes COVID-19 rebound persists, even among the medical community, although this is not supported by data but rather by anecdotal reports and confirmation bias. Members emphasized the importance of communicating information based on the science and data and putting it into context so that those who would benefit from treatment are not turned away due to a concern that is not fully understood. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 3:55 p.m.