Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
November 30, 2021

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

Topic: The committee discussed Emergency Use Authorization (EUA) 000108, submitted by Merck & Co. Inc., for emergency use of molnupiravir oral capsules for treatment of mild to moderate COVID-19 in adults who are at risk for progressing to severe COVID-19 and/or hospitalization.

These summary minutes for the November 30, 2021 meeting of the Antimicrobial Drugs Advisory Committee were approved on December 15, 2021.

I certify that I attended the November 30, 2021 meeting of the Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
November 30, 2021

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 30, 2021. 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 Merck & Co., Inc. The meeting was called to order by Lindsey R. Baden, MD (Chairperson). The conflict-of-interest statement was read into the record by Joyce Yu, PharmD (Acting Designated Federal Officer). There were approximately 2500 people online. There were 4 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 Emergency Use Authorization (EUA) 000108, submitted by Merck & Co. Inc., for emergency use of molnupiravir oral capsules for treatment of mild to moderate COVID-19 in adults who are at risk for progressing to severe COVID-19 and/or hospitalization.

Attendance:

Antimicrobial Drugs Advisory Committee Members Present (Voting): Lindsey R. Baden, MD *(Chairperson)*; Timothy H. Burgess, MD, MPH, FACP; Michael D. Green, MD, MPH; W. David Hardy, MD; Sally A. Hunsberger, PhD; Jennifer Le, PharmD, MAS, FIDSA, FCCP, FCSHP, BCPS-ID; Richard A. Murphy, MD, MPH; Federico Perez, MD, MS; George K. Siberry, MD, MPH; Sankar Swaminathan, MD; Roblena E. Walker, PhD; Peter J. Weina, PhD, MD, FACP, FIDSA

Antimicrobial Drugs Advisory Committee Member 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): John M. Coffin, PhD; Janet D. Cragan, MD, MPH; Sascha Dublin, MD, PhD; David A. Eastmond, PhD; A. Oveta Fuller, PhD; Terry Gillespie *(Patient Representative)*; James E.K. Hildreth Sr., MD, PhD; Daniel B. Horton, MD, MSCE; Miriam C. Poirier, PhD; Uma M. Reddy, MD, MPH; Rita S. Schoeny, PhD

FDA Participants (Non-Voting): Peter Stein, MD; John Farley, MD, MPH; Debra Birnkrant, MD; Robert H. Heflich, PhD; Patrick R. Harrington, PhD; Aimee Hodowanec, MD; Mark Seaton, PhD, DABT

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

Open Public Hearing Speakers Present: Michael A. Carome, MD (Public Citizen); Rustem F. Ismagilov; Meg Seymour (National Center for Health Research); Clay Frederick, PhD

The agenda was as follows:

Call to Order	**Lindsey R. Baden, MD** Chairperson, AMDAC
Conflict of Interest Statement and Introduction of Committee	**Joyce Yu, PharmD** Acting Designated Federal Officer, AMDAC
FDA Introductory Remarks	**John Farley, MD, MPH** Director Office of Infectious Diseases (OID) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**Merck & Co., Inc.**
Introduction	**Sean Curtis, MD, MPH** Senior Vice President Global Regulatory Affairs & Clinical Safety Merck & Co., Inc
Mechanism of Action	**Daria J. Hazuda, PhD** Vice President, Infectious Disease and Vaccines Merck & Co., Inc
Nonclinical Safety	**Kerry Blanchard, PhD** Senior Vice President, Preclinical Development Merck & Co., Inc
Clinical Efficacy and Safety	**Nicholas Kartsonis, MD** Senior Vice President Clinical Research, Infectious Diseases/Vaccines Merck & Co., Inc
Benefit-Risk Conclusion	**Nicholas Kartsonis, MD**
BREAK	
FDA PRESENTATIONS	
Emergency Use Authorization (EUA) Request 108 Molnupiravir (MOV) Capsules	**Aimee Hodowanec, MD** Senior Medical Officer Division of Antivirals (DAV) OID, OND, CDER, FDA

FDA PRESENTATIONS (CONT.)

Molnupiravir: Nonclinical Toxicology Findings	**Mark Seaton, PhD, DABT** Research Review Officer Division of Pharmacology/Toxicology-Infectious Diseases OID, OND, CDER, FDA
Genotoxicity Safety Assessment of Molnupiravir	**Robert H. Heflich, PhD** Director Division of Genetic and Molecular Toxicology National Center for Toxicological Research Office of the Chief Scientist Office of the Commissioner, FDA
Clinical Overview	**Aimee Hodowanec, MD**
FDA Clinical Virology Review of Molnupiravir	**Patrick R. Harrington, PhD** Senior Clinical Virology Reviewer DAV, OID, OND, CDER, FDA
Review Issues and Proposed Risk Mitigation Strategies	**Aimee Hodowanec, MD**
Clarifying Questions for Presenters	

LUNCH

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. **DISCUSSION:** Please discuss the potential use of molnupiravir during pregnancy – both in terms of risk and benefit.

    a. Comment if you think molnupiravir should be accessible for use in pregnancy in certain scenarios, and if so, please describe what those scenarios might be.

    b. Do the concerns regarding the use of molnupiravir during pregnancy extend to the use of molnupiravir in individuals of childbearing potential? If so, are there mitigation strategies that should be considered?

    Committee Discussion: *The Committee members described the following as possible scenarios in which molnupiravir could be considered and made accessible to pregnant individuals: those with multiple comorbidities and deemed at very high risk for severe COVID-19 associated illness and who are early in their disease course and are not being effectively treated with available alternative therapy such as monoclonal antibodies (mAbs), or for whom alternative treatments are not available or accessible. The Committee members also considered the pregnancy trimester a possible factor in deciding to use molnupiravir. There appeared to be consensus that molnupiravir should not be used in the first trimester. In general, the Committee members agreed that the decision to use molnupiravir should be made using a shared decision making approach to ensure that pregnant individuals are informed of molnupiravir's potential fetal risks. One Committee member stated that there would not be a scenario in which they would recommend molnupiravir to a pregnant individual. With regards to use of molnupiravir in individuals of childbearing potential, the Committee members agreed with the Agency's proposed mitigation strategies to confirm that a woman is not pregnant and is using effective contraception before taking molnupiravir. Several Committee members noted that a shared decision making approach should still be used in these individuals. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Please discuss the concern regarding the observed increased rate of viral mutations involving the spike protein among participants receiving molnupiravir. In your discussion, please comment on what, if any, additional risk mitigation strategies or limitations on the authorized population could be considered. What monitoring strategies should be considered to better understand and mitigate these concerns?

    Committee Discussion: *Overall, most Committee members expressed concerns over the mutagenicity of molnupiravir on the viral genome, particularly in the spike gene. The Committee members agreed that there should be risk mitigation strategies for individuals receiving molnupiravir to prevent escape of potentially novel viral variants. One Committee member recommended the continued use of precautions such as avoiding sharing rooms with individuals on treatment, wearing masks, and completing two negative SARS-CoV-2 tests prior to ending isolation. Another Committee member suggested using pharmacies to facilitate viral sampling of individuals receiving molnupiravir as a monitoring strategy to better understand the risk of generating and spreading viral variants. However, one Committee member noted that the overall impact of molnupiravir on viral evolution may be*

minimal given that selective pressures on the spike protein, which are not directly affected by the drug, are the primary driver of SARS-CoV-2 evolution. Although some other Committee members similarly noted their concerns over the increased rate of viral mutations are lessened given the drug's ability to quickly reduce virus production, there were specific concerns over prolonged viral replication in immunocompromised individuals. These Committee members expressed a need for additional studies in immunocompromised individuals. Please see the transcript for details of the Committee's discussion.

3. **VOTE:** Do the known and potential benefits of molnupiravir outweigh the known and potential risks of molnupiravir when used for the treatment of mild-moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death?

    a. If yes, please describe the appropriate authorized population such as risk factors for disease progression and pregnant individuals. Please comment on the proposed risk mitigation strategies and if additional risk mitigation strategies are needed.

    b. If no, please describe your reasons for concluding that the overall benefit-risk for molnupiravir is not favorable for any population based on the data available at this time.

    Vote Result: Yes: 13 No: 10 Abstain: 0

    Committee Discussion*: A slight majority of Committee members voted that the known and potential benefits of molnupiravir outweighed its known and potential risks when used for the treatment of mild-moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death. The Committee members who voted "Yes" described the authorized population as high-risk, unvaccinated individuals. Some Committee members stated they would not recommend molnupiravir in pregnant individuals unless alternative treatments were not available. These Committee members also recommended against its use during the first trimester of pregnancy. Several Committee members who voted "Yes" expressed concern about potential mutagenicity. In general, Committee members were supportive of the Agency's proposed risk mitigation strategies, and mentioned additional strategies such as shared decision making prior to treatment and minimizing household contacts while on treatment. Committee members who voted "No" cited the following as reasons for concluding that the overall benefit-risk ratio was unfavorable: 1) a high number-needed-to-treat compared with placebo, 2) unclear efficacy against the Delta variant, 3) potential to drive viral mutations, and 4) mutagenicity risks. Several Committee members also expressed concerns over monitoring treatment adherence. Overall, Committee members agreed there is a need for additional safety data, as well as further studies in the vaccinated and immunocompromised. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 5:32 p.m. ET.