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.


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/ Joyce Yu, PharmD Acting Designated Federal Officer, AMDAC

/s/ Lindsey R. Baden, MD 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:

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