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Testimony Before the Food and Drug Administration's Antimicrobial Drugs Advisory Committee Meeting Regarding the Emergency Use Authorization Request for Molnupiravir for Treatment of COVID-19

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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group. I have no financial conflicts of interest.

With respect to the requirements that must be satisfied in order for the Food and Drug Administration (FDA) to issue an Emergency Use Authorization (EUA) for molnupiravir for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19), the key question facing the FDA and this committee is whether the known and potential benefits of molnupiravir, when used to treat COVID-19, outweigh the known and potential risks of the drug, and if so, for which patients.

With respect to the known and potential benefits of molnupiravir, the updated full-population analysis of data from Trial MK-4482-002 (hereafter referred to as Trial 2) for all 1,433 randomized subjects revealed a modest, at best, reduction in the risk of all-cause hospitalization or death through Day 29 (6.8% [48/709] in the molnupiravir group versus 9.7% [68/699] in the placebo group), which represented an absolute risk reduction of molnupiravir compared with placebo of -3% (95% confidence interval [CI]: -5.9%, -0.1%) and a relative risk reduction of 30% (95% CI: 1%, 51%).[1] In addition, there was only one death in the molnupiravir group and nine deaths in the placebo group.[2] Notably, data from the post-interim analysis population for Trial 2, which included 646 subjects enrolled during a period when the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) delta variant became the predominant variant causing COVID-19 cases, found that the incidence of all-cause hospitalization or death through Day 29 was 6.2% in the molnupiravir group versus 4.7% in the placebo group, with only one death (<1%) in each group (see table below excerpted from FDA presentation slides).[3]

[1] Food and Drug Administration. Center for Drug Evaluation and Research. Addendum to FDA briefing, Antimicrobial Drugs Advisory Committee meeting. November 30, 2021. https://www.fda.gov/media/154419/download. Accessed November 29, 2021.
[2] Merck & Co., Inc. Addendum to briefing materials for the Antimicrobial Drugs Advisory Committee meeting. November 30, 2021. https://www.fda.gov/media/154422/download. Accessed November 29, 2021.
[3] Food and Drug Administration. FDA presentation slides for the Antimicrobial Drugs Advisory Committee meeting. November 30, 2021. https://www.fda.gov/media/154473/download. Accessed November 30, 2021

P002 Efficacy Analysis

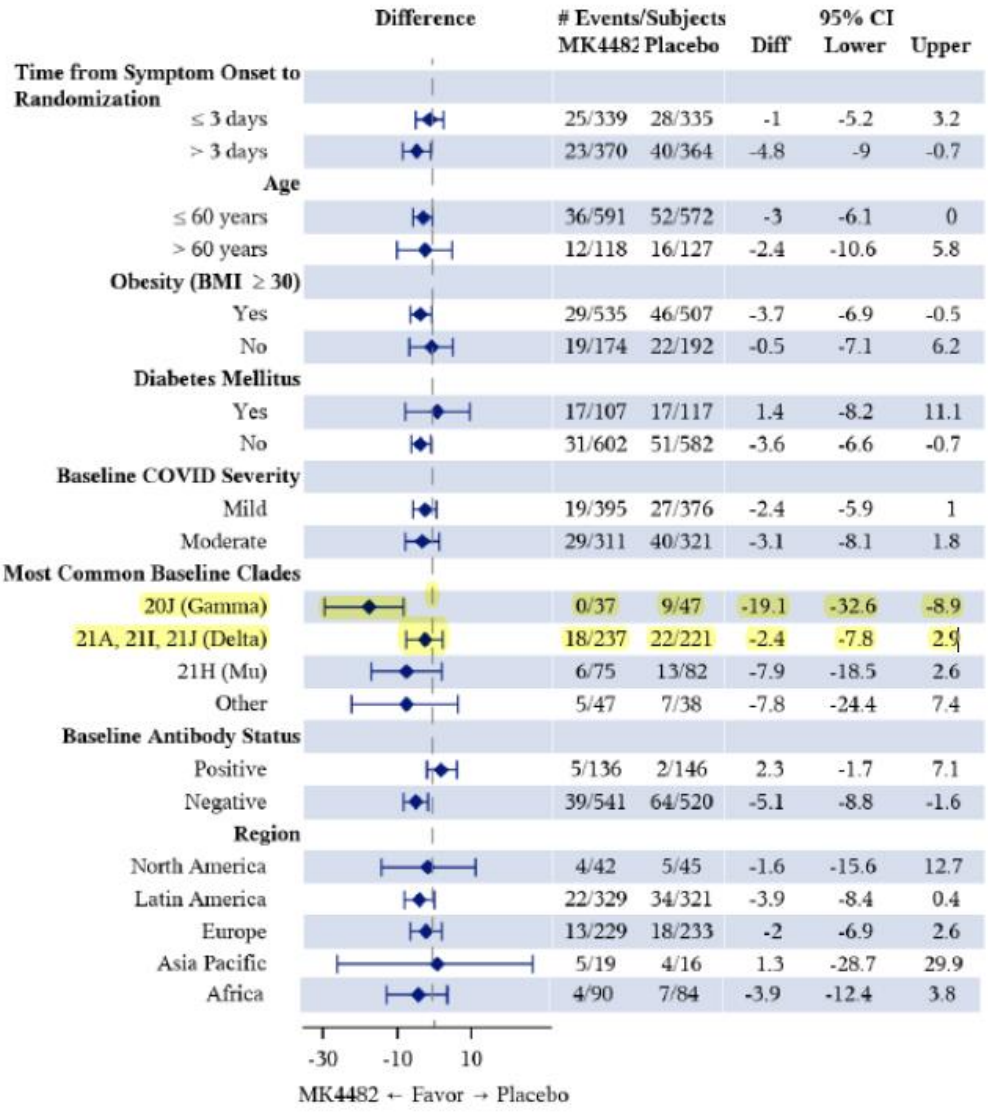
	Interim Analysis Population Enrollment Dates: 5/7/2021 – 08/5/2021		Post-Interim Analysis Population[a] Enrollment Dates: 8/6/2021 – 10/2/2021		Full Population Enrollment Dates: 5/7/2021 – 10/2/2021	
	MOV	PBO	MOV	PBO	MOV	PBO
Hospitalization or death by Day 29	28/385 (7.3%)	53/377 (14.1%)	20/324 (6.2%)	15/322 (4.7%)	48/709 (6.8%)	68/699 (9.7%)
Death by Day 29	0 (0%)	8/377 (2.1%)	1/324 (<1%)	1/322 (<1%)	1/709 (<1%)	9/699 (1.3%)

[a]The Post-Interim Analysis Population includes those participants who had not reached Day 29 by the interim analysis data cutoff date of 9/18/2021.
Abbreviations: MOV, molnupiravir; PBO placebo

Importantly, subgroup analyses for Trial 2 and in vitro assessments of antiviral activity of the ribonucleoside analog N^4-hydroxycytidine (the major initial metabolite of the prodrug molnupiravir) suggest that the known and potential benefits of molnupiravir, at least at the proposed dosage of 800 milligrams (mg) every 12 hours, may be substantially lower in patients infected with the SARS-CoV-2 delta variant, which is currently responsible for more than 99% of COVID-19 cases in the U.S, compared with the known and potential benefits in patients infected with SARS-CoV-2 gamma or other variants. In particular, as shown in Figure 1 of FDA's addendum to its briefing document (see below), the absolute risk reduction of molnupiravir compared with placebo for all-cause hospitalization or death through Day 29 was -19.1 (95% CI: -32.6, -8.9) for patients infected with the gamma variant but only -2.4 (95% CI: -7.8, 2.9) for patients infected with the delta variant.

Figure 1

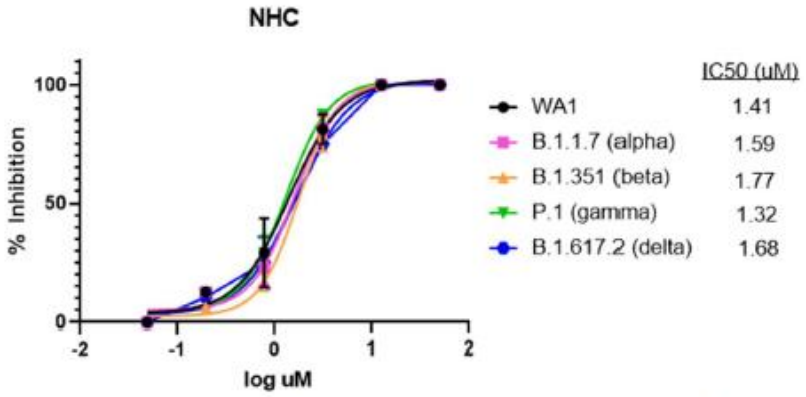
Incidence of Hospitalization or Death Through Day 29 by Subgroup (Protocol 002 – Full Population)



These clinical findings are consistent with data from in vitro studies of the antiviral activity of N^4-hydroxycytidine, shown in Figure 2 of the sponsor's briefing document (see below), which revealed a half-maximal effective concentration (IC_{50}) of 1.32 micromolar (µM) against the gamma variant and 1.68 µM against the delta variant.[4]

[4] Merck & Co., Inc. Briefing document for the Antimicrobial Drugs Advisory Committee meeting. November 30, 2021. https://www.fda.gov/media/154421/download. Accessed November 29, 2021.

Figure 2 Antiviral Activity of NHC Against SARS-CoV-2 Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) Variants of Concern



IC_{50} = half-maximal effective concentration; NHC = N-hydroxycytidine or EIDD-1931; SARS-CoV-2= SARS-associated coronavirus-2

Subgroup analyses also found no reduction in the risk of all-cause hospitalization or death through Day 29 in subjects who tested positive for anti-SARS-CoV-2 antibodies at baseline (the absolute risk reduction of molnupiravir compared with placebo for all-cause hospitalization or death through Day 29 was 2.3 [95% CI: -1.7, 7.1] in subjects with positive baseline antibodies).[5]

With respect to the known and potential risks of molnupiravir, although no major safety signals were identified in Trial 2 or other clinical trials, several potential safety concerns pertaining to the drug were identified in preclinical studies, including embryofetal toxicity, bone and cartilage toxicity, and mutagenicity, including mutagenicity in vitro in mammalian cells and possibly in vivo in the Pig-a assay.[6]

There is also evidence that molnupiravir may increase the rate of mutations in the viral spike protein, which, in theory, could enhance SARS-CoV-2 spike protein evolution and accelerate the development of new variants that escape the immune protection provided by COVID-19 vaccines or natural immunity following SARS-CoV-2 infection or that are resistant to the currently authorized anti-SARS-CoV-2 monoclonal antibodies.[7] The risk of evolutionary viral mutations may be enhanced by tissue exposure to low N^4-hydroxycytidine concentrations, which is likely to occur given the proposed 12-hour dosing interval of molnupiravir and pharmacokinetic data that demonstrated a mean N^4-hydroxycytidine maximum plasma concentration (Cmax) of 10.8 µM and an effective N^4-hydroxycytidine half-life of only 3.3 hours in subjects receiving 800 mg of molnupiravir every 12 hours.[8]

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[5] Food and Drug Administration. Center for Drug Evaluation and Research. Addendum to FDA briefing, Antimicrobial Drugs Advisory Committee meeting. November 30, 2021. https://www.fda.gov/media/154419/download. Accessed November 29, 2021.

[6] Food and Drug Administration. Center for Drug Evaluation and Research. Briefing document for the Antimicrobial Drugs Advisory Committee meeting. November 30, 2021. https://www.fda.gov/media/154418/download. Accessed November 29, 2021.

[7] *Ibid.*

[8] Merck & Co., Inc. Briefing document for the Antimicrobial Drugs Advisory Committee meeting. November 30, 2021. https://www.fda.gov/media/154421/download. Accessed November 29, 2021.

Based on the available clinical and preclinical data for molnupiravir, there is significant uncertainty regarding whether the known and potential benefits of molnupiravir for treating COVID-19 at the proposed dosage outweigh the known and potential risks of the drug.

If the FDA decides to issue an EUA for molnupiravir for certain adult patients who are at high risk for progression to severe COVID-19, we recommend the following:

(1) The FDA should further assess whether the dosage of 800 mg every 12 hours is adequate to provide sustained effective antiviral activity against the SARS-CoV-2 delta variant in vivo.

(2) Given (a) the robust protection provided by COVID-19 vaccines against severe disease that results in hospitalization or death, (b) the overall modest, at best, benefit of molnupiravir as a treatment for mild-to-moderate COVID-19 in the unvaccinated patient population enrolled in Trial 2, and (c) the subgroup analyses showing no reduction in the risk of all-cause hospitalization or death through Day 29 in subjects who tested positive for SARS-CoV-2 antibodies at baseline, the FDA should exclude fully vaccinated individuals from the population of patients eligible to receive the drug, except perhaps vaccinated people who are immunocompromised.

(3) Given (a) the substantial evidence of embryofetal toxicity found in preclinical animal studies, (b) the modest benefit of molnupiravir as a treatment for mild-to-moderate COVID-19, and (c) the availability of authorized anti-SARS-CoV-2 monoclonal antibody products for the treatment of mild-to-moderate COVID-19 in individuals who are at high risk for progression to severe COVID-19, the FDA should exclude pregnant women from the population of patients eligible to receive the drug.

(4) Given the potential risk of embryofetal toxicity, the agency should require that prescribing health care professionals verify that an individual of childbearing potential is not pregnant if clinically indicated. For all patients of childbearing potential verified to be not pregnant, the agency should recommend the use of an effective method of contraception — which would include abstinence from sexual intercourse — for the duration of molnupiravir treatment and for four days after the final dose of the drug.

(5) Given (a) the absence of data on the presence of molnupiravir or its metabolites in human milk, (b) the detection of N^4-hydroxycytidine in plasma of nursing pups from lactating rats administered molnupiravir, and (c) the substantial evidence of bone and cartilage toxicity in preclinical animal studies, the FDA should recommend that lactating individuals not breastfeed for the duration of molnupiravir treatment and for four days after the final dose of the drug.

(6) If the FDA subsequently issues an EUA for another oral antiviral drug product for which the known and potential benefits appear to be greater than those for molnupiravir and for which there are not safety concerns regarding embryofetal toxicity, bone and cartilage toxicity, mutagenicity, and acceleration of the development of new SARS-CoV-2

variants, the agency should promptly consider whether the EUA for molnupiravir should be revoked.