U.S. Food and Drug Administration

Center for Drug Evaluation and Research

FDA Briefing Document

Antimicrobial Drugs Advisory Committee Meeting

November 30, 2021

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this Emergency Use Authorization for molnupiravir (MOV) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
EFD	embryo-fetal development
EOT	end of treatment
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
GD	gestation day
IV	intravenous
mAb	monoclonal antibody
MOV	molnupiravir
NGS	next-generation sequencing
NHC	N^4-hydroxycytidine
NHC-TP	NHC-triphosphate
NOAEL	no-observed-adverse-effect level
NP	nasopharyngeal
NTD	N-terminal domain
OP	oropharyngeal
PPND	pre- and postnatal development
Q12H	every 12 hours
RNA	ribonucleic acid
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SC	subcutaneous

1. INTRODUCTION AND CHARGE TO THE ADVISORY COMMITTEE

This Advisory Committee briefing document summarizes the data submitted to support the Emergency Use Authorization (EUA) of molnupiravir (MOV) for the 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.

Currently three antivirals monoclonal antibodies (mAbs) are authorized for the treatment of mild-to-moderate COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death. These products all require intravenous (IV) or subcutaneous (SC) injection for administration.

MOV is an oral prodrug with antiviral activity against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). MOV is metabolized to the cytidine nucleoside analogue, N^4-hydroxycytidine (NHC), which distributes into cells where NHC is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP acts by a mechanism known as viral error catastrophe, also referred to as viral lethal mutagenesis. NHC-TP incorporation (as NHC-monophosphate [NHC-MP]) into viral SARS-CoV-2 ribonucleic acid (RNA) by the viral RNA-dependent RNA polymerase (RdRp, nsp12), results in an accumulation of errors in the viral genome leading to inhibition of replication.

The recommended dosage in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. Treatment should be started within 5 days of symptom onset.

The Food and Drug Administration (FDA, Agency) asks the Advisory Committee (the Committee) to discuss the available data regarding the known and potential benefits and the known and potential risks of MOV to support the proposed authorized use, taking into consideration the mechanism of action of MOV, the proposed risk mitigation strategies, the existing authorizations for IV and SC mAbs, and the oral route of administration of MOV.

This briefing document summarizes the overall and subgroup efficacy results from the phase 2/3 clinical trial, Trial MK-4482-002 and summarizes the known and potential risks of MOV, specifically the nonclinical findings of mutagenicity, embryo-fetal toxicity, and impaired bone and cartilage growth, as well as the potential for MOV to enhance SARS-CoV-2 evolution or immune escape.

The Agency is seeking advice from the Committee regarding the population for authorized use. This briefing document outlines the various benefit and risk issues to solicit the Committee's advice regarding the use of MOV in specific populations.

If MOV is authorized, the Agency and the Sponsor are in agreement that MOV will not be authorized for use in patients less than 18 years of age.

The Agency's current assessment is that MOV should not be authorized for initiation of treatment in hospitalized patients because benefit of treatment with MOV was not observed in participants already hospitalized due to COVID-19 (see Section 3.1). However, should a patient require hospitalization after starting treatment with MOV, the patient may complete the full 5-day treatment course at the healthcare provider's discretion.

Regarding use in pregnancy, one approach is not to authorize MOV for use during pregnancy because there are no clinical scenarios where the benefit outweighs the risk. Alternatively, a less restrictive approach for use of MOV during pregnancy could be considered. Under this alternative approach, MOV would not be recommended for use during pregnancy and information would be provided to prescribers regarding the potential risks of use in pregnancy through a Warning and Precaution, however, prescribers could use MOV during pregnancy at their discretion in certain clinical scenarios where the benefits were thought to outweigh the risks. The Agency seeks advice from the Committee regarding the option to limit the use of MOV to nonpregnant adults only or the option to consider certain clinical scenarios for which use of MOV during pregnancy may be appropriate.

Additional considerations regarding the patient population for authorized use include, but are not limited to, how "high risk" is defined for progression to severe COVID-19 and whether SARS-CoV-2 vaccination status should be taken into consideration when making a decision about the use of MOV. Other issues for which we are seeking the Committee's input are described later in this document.

2. BACKGROUND

There are several types of human coronaviruses including some that commonly cause mild upper-respiratory-tract illness. The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named coronavirus disease 2019 (COVID-19). COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. According to the World Health Organization, approximately 246 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of October 31, 2021, including nearly 5 million deaths. In the US, according to the Centers for Disease Control and Prevention (CDC), as of November 5, 2021, approximately 46 million cases of COVID-19 had been reported with approximately 750,000 deaths.

SARS-CoV-2 variants have emerged over time and continue to emerge. According to the CDC's national surveillance report for the period of October 10, 2021, to October 16, 2021, the most common variant of concern in the United States is the Delta (B.1.617.2) variant, representing 99.6% of circulating SARS-CoV-2 in the U.S. SARS-CoV-2 variants of concern have primarily been characterized as having certain changes in the

viral spike protein that could impact virus transmissibility or susceptibility to antibody-based therapeutics or vaccine-induced immune responses.

Patients with symptomatic SARS-CoV-2 infection, or COVID-19, can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath or abnormal chest imaging. Moderate illness is defined as the presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥94% on room air. Severe and critical illness are defined as worsening pulmonary status requiring hospitalization, supplemental oxygen, noninvasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or extracorporeal membrane oxygenation[1,2]

The progression of SARS-CoV-2 infection to severe COVID-19 can occur in adults of any age, but the risk increases with age. Per the CDC, over 80% of COVID-19 deaths occur in adults aged 65 years and older, and more than 95% of COVID-19 deaths occur in adults aged 45 years and older. Irrespective of age, certain underlying comorbidities or conditions, including but not limited to cancer, chronic kidney disease, chronic lung disease, obesity, diabetes, pregnancy, and immunocompromised states, increase the risk for progression to severe COVID-19. People who have experienced long-standing systemic health and social inequities, such as racial and ethnic minorities and those with disabilities, are also at increased risk of worse outcomes.[3]

To date, there are no FDA-approved therapies for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progression to severe COVID-19 and/or hospitalization. There are three monoclonal antibodies that are authorized, but not approved, for this same emergency use, discussed below.

One approved antiviral drug is FDA-approved for more severe COVID-19. Remdesivir (Veklury®) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor approved for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization.

Several anti-SARS-CoV-2 mAb regimens are currently authorized for emergency use for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19. including hospitalization or death. Casirivimab 1200 mg and imdevimab 1200 mg were authorized to be administered together on November 21, 2020 (the authorized dose was subsequently changed to casirivimab 600 mg and imdevimab 600 mg). Bamlanivimab

[1] COVID-19 NIH Treatment Guidelines: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/

[2] Guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (February 2021)*

[3] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (accessed October 6, 2021))

700 mg and etesevimab 1400 mg were authorized to be administered together on February 9, 2021. Of note, bamlanivimab 700 mg as monotherapy was authorized for emergency use on November 9, 2020, and the authorization was subsequently revoked on April 16, 2021, due to a sustained increase in variants resistant to bamlanivimab alone resulting in increased risk for treatment failure. Sotrovimab was authorized on May 26, 2021. Each of the authorized mAbs have similar Authorized Use Statements and identical high risk descriptions included in the Health Care Provider Fact Sheets.[4]

There are currently no FDA-approved therapies for treatment of COVID-19 in outpatients. Further, there are no oral drugs authorized for emergency use for the treatment of mild-to-moderate COVID-19.

2.1. Eligibility of the Product for an Emergency Use Authorization

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug & Cosmetic Act (FD&C Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus, SARS-CoV-2, that causes COVID-19.[5] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the FD&C Act (21 U.S.C. 360bbb-3), participant to terms of any authorization issued under that section.[6]

Based on this declaration, FDA may issue an EUA after determining the following statutory requirements are met:

- The chemical, biological, radiological, or nuclear agent referred to in the March 27, 2020, EUA declaration by the Secretary of the U.S. Department of Health and Human Services (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.

[4] Casirivimab and imdevimab: https://www.fda.gov/media/145611/download; bamlanivimab and etesevimab: https://www.fda.gov/media/145802/download; sotrovimab: https://www.fda.gov/media/149534/download

[5] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. February 4, 2020.

[6] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

As part of its authorization, the FDA will establish, to the extent practicable given the circumstances, conditions in the EUA that it finds necessary or appropriate to protect the public health. This includes, for example, appropriate conditions designed to ensure that health care professionals administering the product, or individuals to whom the product is administered, are informed (e.g., through dissemination of authorized Fact Sheets) of the significant known and potential benefits and risks of the emergency use of the authorized product. Additional examples include, but are not limited to, conditions for the monitoring and reporting of adverse events associated with the emergency use of the product and conditions on the manufacturing of the authorized product.

FDA's authorization of a medical product under an EUA is not the same as the Agency's approval or licensure of a product under its relevant statutory authorities. If authorized, FDA will periodically review the circumstances and appropriateness of the EUA. FDA will also regularly review the EUA Sponsor's progress toward the approval or licensure of the authorized product. The EUA will be effective until the circumstances described in the March 27, 2020, EUA declaration justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic no longer exist, the criteria for issuance are no longer met, or other circumstances make revocation appropriate to protect the public health or safety.

2.2. Briefing Document Orientation

The available clinical and nonclinical data in support of this EUA application are presented in Section 3 (Assessment of Benefit) and Section 4 (Assessment of Risk). Within these sections, the Agency has identified six review issues for considerations (one review issue pertaining to benefit and five review issues pertaining to risk). For each identified review issue, background details are provided along with the Agency's assessment and key discussion considerations. The benefit and risk review issues are synthesized together in Section 5 to provide the Agency's overall benefit-risk consideration. Points for the Advisory Committee consideration are presented in Section 6.

3. ASSESSMENT OF BENEFIT

Issuance of an EUA requires, among other things, the Agency's determination that the known and potential benefits of the drug outweigh the known and potential risks. FDA has issued guidance for industry *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (February 2021), which provides the Agency's current recommendations on phase 2 and phase 3 trials for drugs under development to treat or

prevent COVID-19. The recommendations within this guidance document focus on the population, trial design, efficacy endpoints, safety considerations, and statistical considerations for such clinical trials. The Sponsor's MOV development program is consistent with the Agency's recommendations outlined in this guidance.

Efficacy data in support of this EUA application come from an ongoing randomized, placebo-controlled, double-blinded trial (MK-4482-002) in outpatient participants who are at high risk for progression to severe COVID-19 with an endpoint of hospitalization or death by at least Day 28. In addition, a brief summary of data from Part 1 of Trial MK-4482-001 in hospitalized participants is provided to support the Agency's current assessment that MOV should not be authorized for initiation of treatment in hospitalized patients.

3.1. Trial MK-4482-002, Part 2: A Trial in Outpatients With Mild-to-Moderate COVID-19

3.1.1. Trial Design

Clinical data supporting this EUA are based on an interim analysis of data from 775 randomized participants in the phase 3/part 2 portion of trial, MK-4482-002 (also referred to as P002 or MOVe-OUT) (NCT #04575597). MK-4482-002 was a randomized, placebo-controlled, double-blind clinical trial studying MOV for the treatment of outpatients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19 and/or hospitalization. Participants were randomized 1:1 to receive 800 mg of MOV or placebo orally Q12H for 5 days. The primary endpoint was the percentage of participants who were hospitalized for ≥24 hours for acute care or died from any cause through Day 29.

3.1.2. Key Eligibility Criteria

Eligible participants were 18 years of age and older and had one or more of the following predefined risk factors for disease progression: over 60 years of age, diabetes, obesity (body mass index ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The trial included symptomatic participants not vaccinated against SARS CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of randomization. Pregnant women were excluded from the trial and use of contraception was required for all participants of childbearing potential. Receipt of mAbs was prohibited prior to randomization and through Day 29.

3.1.3. Baseline Demographics and Characteristics

At baseline, for all 775 randomized participants, the median age was 41 years (range:18 to 88); 14% of participants were over 60 years of age and 3% were 75 years of age or older; 52% of participants were male; 52% were white, 6% black or African American, 2% Asian, 58% Hispanic or Latino. Only 5% of participants were enrolled from sites in

North America; the majority (609/775) of participants were enrolled from sites in Latin America (56%) and Europe (23%). Among 179 participants enrolled from sites in Europe, 72% were enrolled from sites in Russia, 17% from Ukraine, and 11% from countries in Western Europe. Forty-nine percent of participants received MOV or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (77%), age over 60 years (14%), and diabetes (14%). The most common SARS-CoV-2 genotype clades at baseline were 21A/I/J (Delta; 42.1%), 21H (Mu; 28.5%), and 20J (Gamma; 15.7%), based on the SARS-CoV-2 viral sequence data that were available for 68% (527/775) of trial participants. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

3.1.4. Primary Efficacy Analysis

Table 1 provides the results of the primary endpoint (the percentage of participants who were hospitalized or died through Day 29 due to any cause).

Table 1. Interim Efficacy Results in Outpatient Adults With COVID-19, MK-4482-002, Part 2

Parameter	MOV 800 mg (N=385) n (%)	Placebo (N=377) n (%)	Risk Difference* (95% CI)	p-Value
All-cause hospitalization or death through Day 29[†]	28 (7.3%)	53 (14.1%)	-6.8 (-11.3, -2.4)	0.0024
Hospitalization	28 (7.3%)	52 (13.8%)		
Death	0 (0%)	8 (2.1%)		
Unknown[‡]	0 (0%)	1 (0.3%)		

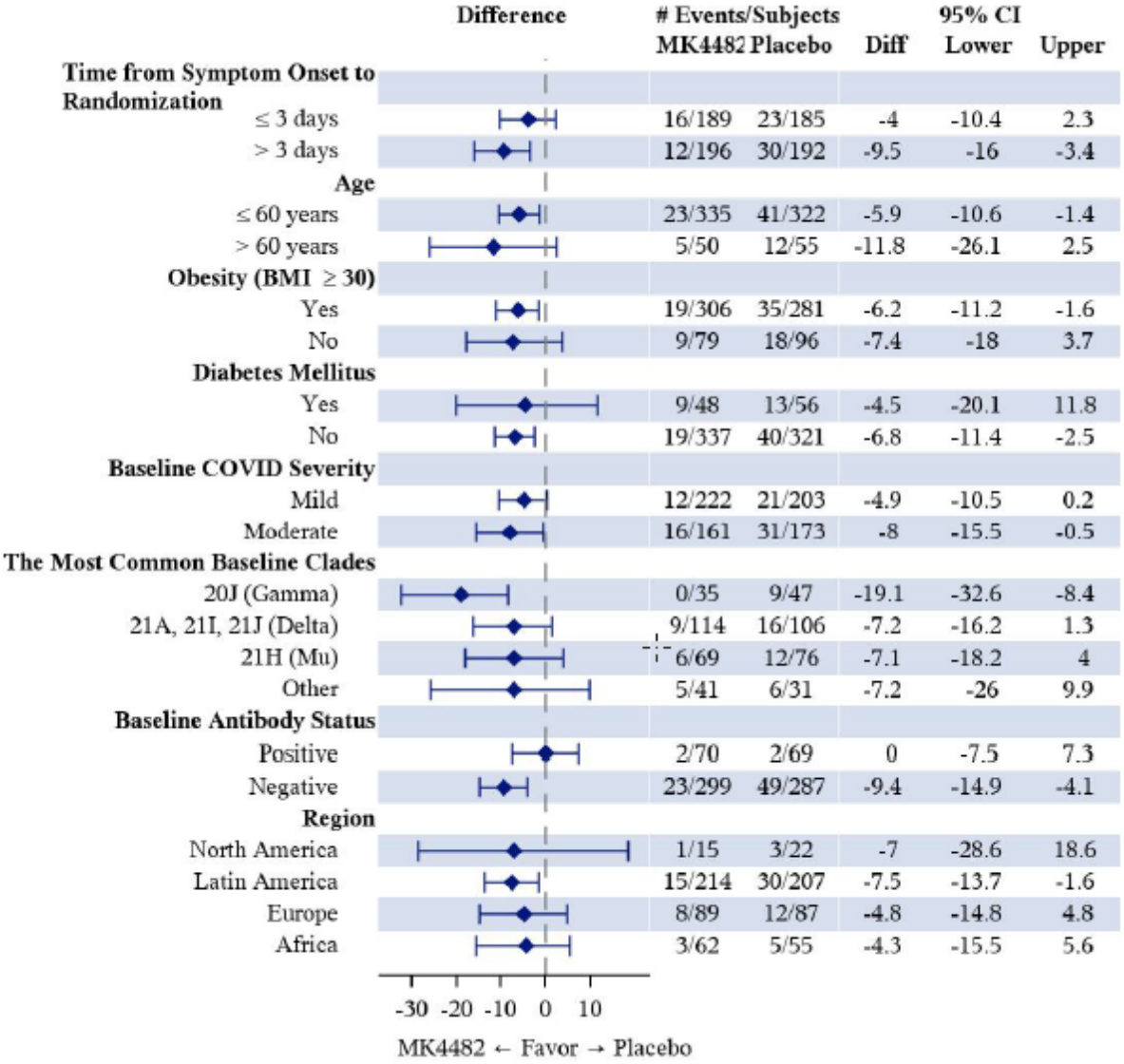
* Risk difference of MOV-placebo based on the Miettinen and Nurminen method stratified by time of COVID-19 symptom onset (≤3 days versus >3 [4-5] days).
[†] Defined as ≥24 hours of acute care in a hospital or an acute care facility (e.g., emergency room).
[‡] Participants with unknown status at Day 29 are counted as having an outcome of all-cause hospitalization or death in the efficacy analysis.
All participants who died through Day 29 were hospitalized prior to death.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; MOV, molnupiravir

Relative risk reduction of MOV compared to placebo was 52% (95% CI: 33%, 80%) based on the Cochran-Mantel-Haenszel method stratified by time of COVID-19 symptom onset (≤3 days versus >3 [4 to 5] days).

Efficacy results were generally consistent across subgroups including age (>60 years), at risk medical conditions (e.g., obesity, diabetes), baseline COVID-19 severity (mild, moderate) and SARS CoV-2 variants, including Delta (based on available variant identification data from 68% of participants).

Based on review of line listings, tables, and figures provided by the Sponsor, the Agency agrees with the overall efficacy findings. However, we note the following results from subgroup analyses, in particular the results by baseline antibody status (Figure 1), which will be discussed further in Section 3.3.

Figure 1. Incidence of Hospitalization of Death Through Day 29 by Subgroup, MK-4482-002 Part 2



Source: Response to FDA 11/5/2021 information request.
Abbreviations: BMI, body mass index; CI, confidence interval; COVID, coronavirus disease 2019

3.2. Trial MK-4482-001: A Trial in Hospitalized Patients

Trial MK-4482-001 was a phase 2/3 clinical trial conducted in adults hospitalized with COVID-19. In Part 1 (phase 2) of the trial, 293 participants were randomized 1:1:1:1 to receive MOV 200 mg, 400 mg, 800 mg, or placebo Q12H for 5 days. In Part 1 of the trial, there was no difference in the time to sustained recovery (the primary endpoint) across the MOV arms and the placebo arm in P001. All-cause mortality through Day 29 was evaluated as a secondary endpoint and revealed that a numerically higher proportion of participants died in each of the MOV groups (MOV 200 mg [four participants, 5.5%], MOV 400 mg [eight participants, 11.0%], and MOV 800 mg [three participants, 4.2%])

compared with placebo [two participants, 2.7%]). The deaths in this trial were largely related to COVID-19 and were not assessed to be drug-related (see Section 4.2).

The Sponsor ultimately concluded that treatment with MOV is likely to have a greater benefit if initiated earlier in the disease course during peak viral replication (≤5 days of symptom onset) compared with initiation during the later stages of disease when the host inflammatory response predominates. As patients who are hospitalized due to COVID-19 are likely to be later in the course of disease and early initiation of MOV treatment may be difficult in this population, the Sponsor decided not to initiate enrollment in Phase 3 (Part 2) of P001. Based on the absence of demonstrated benefit and the observed mortality imbalance in the MOV groups compared to placebo, the Agency's current assessment is that MOV should not be authorized for initiation of treatment in hospitalized patients, and this briefing document will focus on key review issues related to the evaluation of potential benefit in the outpatient population.

3.3. Key Review Issues Relevant to Evaluation of Potential Benefit In Outpatients

3.3.1. Issue #1: Patient Selection for Authorized Use

In the primary analysis, a statistically significant treatment effect was demonstrated in the overall mITT population. However, there are potential safety concerns pertaining to MOV, including embryofetal toxicity, bone and cartilage toxicity, and mutagenicity, as well as evidence that MOV may increase the rate of changes in the viral spike protein, which, in theory, could enhance SARS-CoV-2 spike protein evolution (please see Sections 4.3.2 for an in-depth discussion of these safety considerations).

It is important to identify patients likely to receive the greatest benefit from MOV treatment, therefore, the Agency seeks the Committee's recommendations regarding patient selection for authorized use. Patient selection considerations of particular interest include identification of patients at "high risk for progression to severe COVID-19, including hospitalization or death" and the potential for high-risk adults who are fully vaccinated against SARS-CoV-2 to derive benefit from MOV treatment.

Background

Part 2 of MK-4482-002, SARS-CoV-2 enrolled adults with laboratory-confirmed SARS-CoV-2 infection with associated signs and symptoms of mild-to-moderate COVID-19. All participants were required to have one or more of the following risk factors for severe illness from COVID-19: age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity (body mass index ≥30 kg/m^2), a serious heart condition, or diabetes mellitus. In addition, receipt of a COVID-19 vaccine was prohibited any time prior to randomization and through Day 29.

There are three anti-SARS-CoV-2 mAb therapies currently authorized for similar use to the proposed authorization for MOV (i.e., treatment of mild-to-moderate COVID-19 in

individuals at increased risk for progression to severe COVID-19, including hospitalization or death).[7] The factsheets for these three mAb therapies provide examples of risk factors for progression to severe COVID-19 and refer prescribers to the CDC website[8] for a complete listing of high-risk criteria to assess eligibility for treatment under the EUA. Please see Appendix 8.1 for an example of an Authorized Use Statement and a listing of risk factors from an authorized mAb factsheet. The criteria outlined by the CDC are broader than the criteria used to determine eligibility for participation in Part 2 of MK-4482-002 and are also broader than the eligibility criteria for the pivotal mAb clinical trials in participants with mild-to-moderate COVID-19 which supported the mAb EUA authorizations.

The initial authorizations of these mAb therapies were based on data from unvaccinated individuals. Data are available from an outpatient clinical trial of REGEN-COV, an authorized monoclonal antibody therapy, showing clinical benefit in both participants with a positive and negative baseline SARS-CoV-2 antibody status (Table 2). These data supported the decision to authorize mAbs for use in both vaccinated and unvaccinated individuals.

Table 2. COVID-19-Related Hospitalization or All-Cause Death Through Day 29 by Baseline Serostatus in the Phase 3 Trial COV-2067

Subpopulation	REGEN-COV 1200 mg Events/N (%)	Placebo Events/N (%)	Relative Risk Reduction (95% CI)
Baseline seronegative	3/500 (0.6)	18/519 (3.5)	83% (42%, 95%)
Baseline seropositive	1/177 (0.6)	6/164 (3.7)	85% (NA, 98%)

Source:(Weinreich et al. 2021)
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019

In MK-4482-002, MOV efficacy data in subgroups of participants, including participants who were anti-SARS-CoV-2 seropositive and seronegative at baseline, were reviewed to assess if there were potential differences in efficacy by baseline characteristics and if this information might inform patient selection for the MOV authorization.

Assessment

As shown in Figure 1, efficacy was generally consistent across the following subgroups: age (>60 years), high-risk medical conditions (e.g., obesity, diabetes), baseline COVID-19 severity (mild, moderate) and common SARS-CoV-2 clades. However, an analysis of the primary endpoint among the small subgroup of participants who were positive for anti-SARS-CoV-2 antibodies[9] at baseline revealed no difference between treatment and

[7] The mAbs are authorized for use pediatric patients (12 years of age and older weighing at least 40 kg), however, MOV will be not be authorized for patients less than 18 years of age.
[8] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
[9] Based on the Roche Elecsys® Anti-SARS-CoV-2 assay, which is a qualitative assay that detects serum antibody (regardless of isotype) reactive to the SARS-CoV-2 nucleocapsid (N) protein Chan, CW, K Parker, V Tesic, A Baldwin, NY Tang, XMR van Wijk, and KJ Yeo, 2020, Analytical and clinical evaluation of the automated Elecsys Anti-SARS-CoV-2 Antibody Assay on the Roche Cobas e602 Analyzer, Am J Clin Pathol, 154(5):620-626..

placebo groups for the incidence of hospitalization or death through Day 29 (2.9% in both groups) (Table 3). In contrast, for the subgroup of participants negative for anti-SARS-CoV-2 antibodies at baseline, more placebo-treated participants (17.1%) were hospitalized or died by Day 29 compared to MOV-treated participants (7.7%). The treatment difference (MOV – placebo) was -9.4% with a 95% CI of (-14.9%, -4.1%).

Given the small size of the seropositive at baseline subgroup and the small number of events in this subgroup, robust conclusions regarding MOV efficacy in seropositive participants cannot be made. Further, in routine clinical practice, ascertainment of serostatus prior to the initiation of treatment for COVID-19 is not feasible given the currently available assays and the turnaround time for results.

Table 3. Incidence of Hospitalization or Death Through Day 29 by Baseline Antibody Status (mITT)

SARS-CoV-2 Baseline Antibody Serostatus	MOV 800 mg N=385 n/m (%)	Placebo N=377 n/m (%)	Difference (MOV – Placebo) % (95% CI)[a]
Positive	2/70 (2.9)	2/69 (2.9)	0 (-7.5, 7.3)
Negative	23/299 (7.7)	49/287 (17.1)	-9.4 (-14.9, -4.1)
Unknown	16	21	

Source: Emergency Use Authorization request, Table 1.1-16.
[a] The corresponding confidence interval is based on the Miettinen and Nurminen method.
M, number of participants in the modified intent-to-treat population with the corresponding group.
N, number of participants died or hospitalized through Day 29.
Unknown survival status at Day 29 was counted as having an outcome of hospitalization or death.
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; MOV, molnupiravir; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

Given the limitations of the above analysis of efficacy by serostatus, we conducted a review of the literature to further explore the prospect of benefit among fully vaccinated patients (who are expected to be seropositive). Our review attempted to characterize the frequency of and risk factors for breakthrough COVID-19 infections leading to hospitalization or death among fully vaccinated individuals. Reports with sufficient detail to allow for adequate assessment of individual patient characteristics were limited and most reported on breakthrough infections occurring before the SARS-CoV-2 Delta variant became the dominant circulating strain.

According to the CDC, as of August 28, 2021, the rate of COVID-19 associated hospitalization among fully vaccinated adults aged ≥18 years was 4.5 per 100,000 population (compared to 83.6 per 100,000 among unvaccinated adults). The rate of COVID-19 death was 0.95 per 100,000 fully vaccinated population compared to 10.76 per 100,000 in the unvaccinated population.[10] The available literature suggests that most breakthrough infections occur in patients with advanced age and/or with medical comorbidities. The reported comorbidities largely overlap with the CDC risk factors for severe COVID-19 (e.g., cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, obesity) (Bosch et al. 2021; Brosh-Nissimov et al. 2021; Green et al. 2021; Kim et al. 2021).

[10] https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html

Discussion

With respect to the MK-4482-002 participants who were seropositive due to prior or current infection, the subgroup analysis presented above suggests that there is no MOV treatment benefit. However, the number of participants included in these analyses was small and may have precluded the detection of a treatment benefit. Further, it is not known whether the presence of anti-SARS-CoV-2 antibodies at baseline is attributable to the current SARS-CoV-2 infection or a prior SARS-CoV-2 infection. Likely both scenarios are represented among the seropositive participants in MK-4482-002. It is also unclear how applicable the findings in patients with positive baseline nucleocapsid antibodies from natural immunity (from current or prior infection) are to patients with COVID-19 vaccination. It is likely that there are numerous variables that impact the protection conferred by antibodies from both natural infection and vaccination. Factors to consider include the recency of the prior COVID-19 illness or vaccination, whether a booster vaccine has been administered, the SARS-CoV-2 strain/variant causing the current and prior infections, and host factors that impact the immune response to a vaccine or natural infection.

Data suggest that among fully vaccinated adults with breakthrough COVID-19, hospitalization and death are uncommon but do occur. Data regarding the frequency of and risk factors for these outcomes in fully vaccinated individuals are still emerging. Available data suggest that the risk of breakthrough infection is higher with the Delta variant, though it is not clear if the increased rate of breakthrough infections is attributable directly to the Delta variant or to the fact that by the time the Delta variant became prominent, many individuals were farther out from vaccination and in some cases may have had waning immunity (Fowlkes A, et al. MMWR Aug 2021; Bernal JL, NEJM 2021).

Identifying specific subsets of vaccinated participants most likely to derive benefit from MOV is therefore challenging. Some immunocompromised patients may not have a robust immune response following vaccination and therefore may be represent a subgroup of vaccinated individuals more likely to derive benefit from MOV. However, immunocompromised patients may experience prolonged viral shedding following COVID-19 and this could be a concern given the increased rate of mutations to the spike protein observed in Part 1 of Trials MK-4482-001 and MK-4482-002 (see Section 4.3.2.5). Ultimately, assessing the benefit of MOV use in any given population requires a thorough understanding of the associated risks which are presented in Section 3.3.1. Please see Section 5 for a detailed discussion of the benefit and risk considerations for this EUA request.

4. ASSESSMENT OF RISK

4.1. Summary of the Clinical Safety Database

MOV 800 mg PO every 12 hours (Q12H) for 5 days is currently being evaluated in clinical trials in adults with confirmed COVID-19 in outpatient and hospitalized settings.

The safety database for this EUA request consists of 593 adults who have received MOV 800 mg PO Q12H for 5 days. This includes 515 outpatient adults with mild-to-moderate confirmed COVID-19 (i.e., the population for whom the EUA is being requested). In addition, there are supportive safety data from 72 adults hospitalized with COVID-19 and six healthy volunteers who all received MOV 800 mg PO Q12H for 5 days. The minimum duration of follow-up available for participants in each of the trials is displayed in Table 4. Given the short half-life of NHC (approximately 3.3 hours) and MOV metabolites (NHC-TP, approximately 15.5 hours), this duration of follow-up is considered adequate to assess safety.

Table 4. Summary of MOV 800 mg by Mouth Q12H for 5 Days Safety Database

Study	Population	Duration of Follow-up	No. of Participants Who Received MOV 800 mg Q12H × 5 Days
Primary Safety Data			
MK-4482-002 (MOVe-OUT, P002) Part 2, IA3/4	Outpatient adults with COVID-19 and with an increased risk of severe illness from COVID-19	Through at least Day 29[1]	386
Supportive Safety Data			
MK-4482-002 (MOVe-OUT, P002) Part 1, IA2	Outpatient adults with COVID-19	Through at least Day 29[1]	74
MK-4482-006 (EIDD-2801-2003, P006)	Outpatient adults with COVID-19	Through Day 28	55
MK-4482-001 MOVe-IN, P001) Part 1, IA2	Hospitalized adults with COVID-19	Through at least Day 29[1]	72
MK-4482-004 (EIDD-2801-1001, P004)	Healthy volunteers	Through 14 days after last dose	6
Total			593

Source: EUA request, File EUA.pdf, Table 82.
[1] The data submitted for this EUA request was based on an interim analysis that was conducted when all participants in Part 1 reached Day 29. Participants are then followed through Month 7, but these data are not available.
Abbreviations: COVID-19, coronavirus disease 2019; MOV, molnupiravir; Q12H, every 12 hours; EUA, Emergency Use Authorization

The MOV clinical safety database is notably smaller than the clinical safety databases for other products that the Division of Antivirals (the Division) has authorized for the treatment of mild-to-moderate COVID-19. The safety databases for sotrovimab, bamlanivimab, and casirivimab/imdevimab at the time of their initial authorizations ranged from 700 to more than 2000 participants at the to-be-authorized dose or higher. Please see Section 4.3.1 for further discussion regarding the adequacy of the clinical safety database.

4.2. Clinical Safety Overview

Outpatient Trial (MK-4482-002, Part 2)

The rates of serious AEs (SAEs), fatal AEs, and AEs leading to treatment discontinuation were all higher in the placebo arm than the MOV arm (Table 5). The majority of SAEs in both arms were COVID-19 related events.

Table 5. Adverse Event Summary During Treatment and 14-Day Follow-Up Period All Participants as Treated Population, MK-4482-002, Part 2

Adverse Event	MOV 800 mg (N=386)	Placebo (N=379)
Any AE	135 (35.0)	150 (39.6)
AEs related[1] to study drug	48 (12.4)	42 (11.1)
AEs leading to discontinuation of study drug	5 (1.3)	13 (3.4)
Any SAE	28 (7.3)	53 (14.0)
SAEs related[1] to study drug	0	0
SAEs leading to discontinuation of study drug	1 (0.3)	9 (2.4)
Fatal SAEs	0	10 (2.6)

Source: Emergency Use Authorization request, Table 4-3 in file p002v02saf.pdf.
[1] Determined by the investigator to be related to the drug.
Abbreviations: AE, adverse event; SAE, serious adverse event; MOV, molnupiravir

To date, no deaths have been reported among MOV participants and 10 (2.6%) deaths have been reported among placebo participants. The cause of death among placebo participants was predominantly COVID-19 related (e.g., COVID-19 pneumonia, COVID-19 with respiratory failure, and COVID-19 with septic shock). Other fatal AEs reported among placebo participants were staphylococcal bacteremia and metastases to lung.

Significant bone marrow toxicity was reported in a 28-day toxicology study in dogs. This finding prompted a careful assessment of hematologic parameters in clinical trials. Laboratory abnormalities reported in Part 2 of MK-4482-002 were predominantly Grades 1 and 2 in severity.[11] Hemoglobin laboratory abnormalities that were a worsened grade from baseline were more common among MOV participants than placebo participants. Grade 1 and 2 hemoglobin decreased abnormalities (8.5 – 10.4 g/dL in females and 9.0 – 10.9 in males) were reported in 4% and 1% of the MOV and placebo arms, respectively. Similar imbalances in hemoglobin abnormalities were observed in other trials among both outpatients and hospitalized patients with COVID-19. Abnormalities in other hematology laboratory parameters were either comparable between arms or occurred at a higher rate in placebo participants.

Hospitalized Trial (MK-4482-001, Part 1)

As previously described, Trial MK-4482-001 was a phase 2/3 clinical trial conducted in adults hospitalized with COVID-19. In Part 1 (phase 2) of the trial, 293 participants were randomized 1:1:1:1 to receive MOV 200 mg, 400 mg, 800 mg, or placebo Q12H for 5 days. When combining all MOV dose cohorts, the rates of AEs and SAEs were higher

[11] Based on the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, v. 2.1.

among placebo participants than among MOV participants. However, the proportion of participants experiencing a fatal adverse event was higher among participants receiving MOV (14/218, 6.4% combining all MOV dose groups) than among placebo participants (2/75, 2.7%). No fatal AEs were assessed as drug-related by the investigator. All fatal AEs appear to have been either directly or indirectly related to COVID-19. As noted above, the Sponsor stopped this trial for lack of benefit and MOV is not proposed for authorization for the treatment of patients hospitalized for COVID-19.

Of note, the imbalance in hemoglobin abnormalities that was observed in MK-4482-002 was also observed in this trial. Hemoglobin abnormalities (any grade) were reported in 22.4% of participants receiving MOV 800 mg compared to 8.3% of participants receiving placebo. As described above, the abnormalities were predominantly Grade 1 and 2 in severity.

4.3. Key Review Issues Relevant to Evaluation of Risk

4.3.1. Issue #2: Adequacy of the Clinical Safety Database

Background

As described above in Section 4.1, the safety database for this EUA request consists of 593 adults who have received MOV 800 mg PO Q12H for 5 days. This includes 515 outpatient adults with mild-to-moderate confirmed COVID-19 (i.e., the population for which the EUA is being requested). In addition, there are supportive safety data from 72 adults hospitalized with COVID-19 and six healthy volunteers who all received MOV 800 mg PO Q12H for 5 days.

Assessment

The MOV clinical safety database is notably smaller than the clinical safety databases for other products that the Division has authorized for the treatment of mild-to-moderate COVID-19. The smallest safety databases for an authorized mAb at the time of initial authorizations was over 700 participants. Safety databases for other authorized mAbs have ranged from >1350 to >2100 participants at the to-be-authorized dose or higher.

However, based on 593 participants, the only imbalance in adverse events observed in Part 2 of Trial MK-4482-002 was a higher rate of Grade 1 and 2 hemoglobin abnormalities among MOV participants compared to placebo participants (see Section 4.2).

Discussion

While the clinical safety data base was small, there were no major safety concerns identified in Trial MK-4482-002. The Agency plans to work with the Sponsor to ensure that additional safety data will be collected to support a new drug application submission.

4.3.2. Nonclinical and Clinical Virology Findings and Review Issues

This section describes the identified pharmacology/toxicology risk review issues with respect to mutagenicity, embryo-fetal toxicity, and bone and cartilage development findings.

4.3.2.1. Issue #3: Mutagenicity

Background

MOV (molnupiravir; MK-4482; EIDD-2801) and its metabolite (N^4-hydroxycytidine (NHC); EIDD-1931) were positive for mutagenicity in in vitro Ames assays, but MOV was negative in a follow-up in vivo assay. Given the negative in vivo assay results, and considering the 5-day treatment duration with MOV, the Agency pharmacology/toxicology experts have concluded the risk of mutagenicity in the clinic is low.

Assessment

Summary of Genotoxicity Concerns

Mechanistically, the nucleoside triphosphate anabolite of MOV, NHC-TP, acts as a competitive, alternative substrate for the virally encoded RNA-dependent RNA polymerase. The apparent incorporation into nascent chain viral RNA results in increased mutational frequency in the viral genome, resulting in induction of viral error catastrophe and the production of nonviable virus. Given the mechanism of action, NHC-diphosphate could theoretically be transformed by ribonucleotide reductase in human cells to the 2′-deoxyribonucleotide form and the deoxynucleotide subsequently incorporated into cellular DNA, leading to DNA mutations. To assess the mutagenic potential of MOV, a battery of in vitro and in vivo mutagenicity assays was conducted by the Sponsor according to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines (ICH guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use). In addition, a 6-month carcinogenicity study in transgenic mice is ongoing.

Ames tests were conducted with the ester prodrug (MOV; EIDD-2801) and initial metabolite, NHC (EIDD-1931). EIDD-2801 was positive for mutagenicity in *Escherichia coli* strain WP2 uvrA and *Salmonella typhimurium* strain TA102, but negative in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537. EIDD-1931 was positive for mutagenicity in *E. coli* strain WP2 uvrA, but negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537. EIDD-1931 was not tested with strain TA102. The in vivo and in vitro micronucleus assays showed negative results.

Note that other nucleoside analogs have been tested for genotoxicity and were positive in in vitro and/or in vivo assessments (see Table 10).

MOV was further evaluated in two established in vivo assays for mutagenicity: the Pig-a assay and the transgenic Big Blue® rat assay. The results of the Pig-a assay were "equivocal" as the assay showed a positive trend but results did not exceed the range of negative historical control values. In the transgenic Big Blue® rat model, the drug was evaluated for increased mutant frequency at the lambda cII transgene in liver and bone marrow. The assay result was negative for in vivo mutagenicity.

Note that the Sponsor has submitted data on NHC-TP concentrations in rat tissues and human peripheral blood mononuclear cells (PBMCs), as well as in vitro assays assessing species differences in the conversion of NHC to NHC-TP in PBMCs. Based on assessment of that information, Agency reviewers have concluded that rats were likely exposed to clinically relevant concentrations of NHC-TP during the in vivo mutagenicity assay.

A consult with colleagues from the Agency's CDER Pharmacology/Toxicology Genotoxicity Subcommittee (GSc) was submitted regarding the overall weight of evidence of the genotoxicity data. The GSc confirmed the Division's conclusions that MOV and NHC were positive for mutagenicity in the in vitro bacterial reverse mutation (Ames) assay. The GSc also reaffirmed that the transgenic rodent (Big Blue® rat) study, and not the Pig-a study, was the primary assay for follow-up assessment of the Ames-positive findings. Lastly, the GSc confirmed that the negative response in the transgenic Big Blue® rat assay indicated that neither parent prodrug nor the metabolite NHC are in vivo mutagens. Therefore, the level of concern for mutagenicity in the clinical setting is low.

The GSc also confirmed that the positive results in the Ames assay were likely due to incorporation of the NHC-TP ribonucleotide into bacterial DNA. If incorporation occurs in humans, DNA replicase/repair in eukaryotic cells is highly efficient (as contrasted to bacterial replicase/repair). The negative results of the transgenic rodent mutation assay confirm that the ribonucleoside analog is not an in vivo mutagen under the conditions studied.

Based on the weight of evidence, including negative in vivo findings, as well as the short-term use (5 days), and the conclusion based upon expert input, the risk of genotoxicity following treatment with MOV is low.

4.3.2.2. Issue #4: Bone/Cartilage Formation-Related Findings

Background

MOV may affect bone and cartilage development. In a chronic (3-month) rat study, abnormal bone (growth plate) and cartilage formation were noted. Also, in embryo-fetal development (EFD) studies in rats and rabbits, delayed and incomplete ossification was noted in fetuses. Systemic exposures in pregnant rats and rabbits were approximately 8- and 7-fold, respectively, the mean clinical NHC exposure at 800 mg Q12H. As a result of the concerns related to bone and cartilage formation in development, the Sponsor is conducting a study to assess developmental effects of MOV in juvenile rats.

Assessment

Physis and Epiphysis Findings in Rats

In a 3-month repeat-dose study in rats, test article-related findings included abnormalities in long bone physis (growth plate) including increased physis thickness in all male rats administered 1000 mg/kg MOV, and increased epiphysis cartilage thickness in all female rats administered 1000 mg/kg MOV and all male rats administered 500 or 1000 mg/kg MOV. Changes to cartilage associated with the trachea were noted in male rats administered 500 (6/10) or 1000 (10/10) mg/kg MOV. Growth plate-related bone and/or cartilage findings were noted at systemic exposures approximately 5-fold higher (males) and 9-fold higher (females) than the mean clinical NHC exposure at 800 mg Q12H ($AUC_{0\text{-}24hr}$ =75.6 hr*µM). The no-observed-adverse-effect level (NOAEL) was not defined (i.e., <150 mg/kg) for males due to weight loss at the lowest dose and was defined as 200 mg/kg/day for females.

Mild to marked increased thickness of the physis of the long bones (femur and tibia) of male rats dosed at 1000 mg/kg/day was characterized by irregularly widened physis involving the zone of hypertrophic chondrocytes, and occasional disruption of the physis. According to the study pathologist, histomorphologic features of the changes observed in the bone were indicative of an alteration in the normal physiologic progression of hypertrophic chondrocytes towards osteogenesis, resulting in impaired transformation of cartilage into new bone (endochondral ossification).

Eosinophilic cytoplasmic alteration of the chondrocytes in the cartilage of the trachea was noted in male rats administered 500 and 1000 mg/kg/day. This change did not impact the overall structure or integrity of the cartilage and did not cause airway restriction.

There were no findings in a 28-day repeat-dose study in rats at similar systemic exposures (systemic exposures approximately 5-fold higher (males) and 9-fold higher (females) than the mean clinical NHC exposure at 800 mg Q12H.

Bone Effects in Rat and Rabbit Fetuses

Molnupiravir was administered orally to pregnant rats at 200, 500, and 1000 mg/kg/day from gestation days (GDs) 6 to 17 in a preliminary EFD study. There were MOV-related skeletal malformations, variations, and delays in ossification at 1000 mg/kg/day.

In an EFD study in rabbits, MOV was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Incomplete caudal vertebra and metacarpal ossification appeared to occur more at 400 mg/kg (9% of litters) and 750 mg/kg (6%) than in controls (2%). Although the incidence does not appear to increase with dose, this finding is noteworthy given the effects on bone and cartilage described previously in rats. Systemic exposures in pregnant rabbits at 400 and 750 mg/kg were approximately 7- and 18-fold the mean clinical NHC exposure.

4.3.2.3. Issue #5: Reproductive Toxicology Findings

Background

Nonclinical reproductive toxicology studies available for review include fertility studies in male and female rats, preliminary and pivotal EFD studies in rats and rabbits, and a pre- and postnatal development (PPND) study in rats.

In a preliminary EFD study in rats, the high dose was associated with reduced fetal body weight and an increase in post implantation loss, as well as external, visceral, and skeletal malformations. Systemic exposures (AUC) of NHC were approximately 8-fold the mean clinical NHC exposure. In the pivotal study, findings were limited to reduced fetal growth at systemic exposures approximately 3-fold the mean clinical NHC exposure.

There were no findings in a PPND study in rats (audited draft report). Notably, in the high dose group the mean maternal exposures to NHC were only 1.5-fold the mean clinical NHC exposure, significantly lower than 8-fold the clinical NHC exposures which resulted in embryo-fetal toxicity noted in the EFD study. In the PPND draft report, low concentrations of NHC, 0.09% of maternal exposures, were measured in 10-day old pups, suggesting that NHC is present in breast milk.

Due to the embryo-fetal toxicity and bone and cartilage development findings in vivo, the lower exposures tested in the PPND study, and the lack of a completed juvenile toxicology study, there are both known and possibly unknown risks for use of MOV in pregnant or lactating individuals and pediatric patients.

Assessment

Studies in Rats

Fertility Studies

No effects of treatment were noted on fertility parameters in male and female rats. Exposures at the NOEL were approximately 2- and 6-fold the mean clinical NHC exposure at 800 mg Q12H in males and females, respectively. To date, no analyses of sperm motility or morphology have been conducted in nonclinical studies. Due to a large sperm reserve in rodents, sperm assessment may detect effects on spermatogenesis that are not reflected in fertility (Blazak et al. 1985).

Embryo-Fetal Development Studies

In a preliminary EFD study, female rats were administered doses up to 1000 mg/kg from GDs 6 to 17 (a NOAEL was not defined for this study). Findings from that study are included below. In the pivotal study, rats were administered doses up to 500 mg/kg. In that study, findings were limited to reduced fetal growth at systemic exposures approximately 3-fold the mean clinical NHC exposure at 800 mg Q12H (NOAEL 250 mg/kg based on maternal and developmental findings; exposures were approximately equivalent to the mean clinical NHC exposure at 800 mg Q12H).

Key Study Findings (From Preliminary/Range-Finding EFD Study)

The 1000 mg/kg dose was associated with reduced fetal body weight and an increase in postimplantation loss, as well as external, visceral, and skeletal malformations in surviving fetuses at systemic exposures approximately 8-fold the mean clinical NHC exposure at 800 mg Q12H.

Maternal toxicity

At 8-fold the clinical NHC exposure (1000 mg/kg) in pregnant rats there was a transient decrease in food consumption between GDs 6 and 8 and an associated reduction in body weight between GDs 8 and 12.

External malformations

There were MOV-related fetal external malformations of the eyes (small or absent eye bulge) at 1000 mg/kg (8-fold the clinical NHC exposure in three fetuses from two litters, compared to none in controls).

Visceral malformations

At 1000 mg/kg/day, there were MOV-related fetal visceral malformations (absent kidney in two fetuses from two litters, compared to none in controls). There was one fetus in the 1000 mg/kg/day group with multiple cardiovascular and associated observations (ventricular septal defect, dilated pulmonary trunk, narrowed aortic arch, malpositioned aorta, large ventricle, and fluid-filled thoracic cavity). This fetus was also observed to have local edema at external examination. Because this was a singular occurrence and ventricular septal defect with similar associated abnormalities has been observed in vehicle controls in this laboratory, the abnormalities in this fetus were considered by the study director to be incidental and unrelated to MOV treatment.

Skeletal malformations

Consistent with the external malformation (small or absent eye bulge), there were MOV-related fetal coronal malformations at 1000 mg/kg/day (small or absent eye in four fetuses from three litters, compared to none in controls).

There were MOV-related skeletal malformations, variations, and delays in ossification at 1000 mg/kg/day. Specifically, there were increased incidences of rib malformations (primarily detached ribs), thoracic vertebra malformation, lumbar vertebra malformation, skull malformation, cervical ribs, trace supernumerary ribs, and incomplete ossification of thoracic vertebrae and/or sternebrae. The skull malformation observed in one fetus was a small eye socket (reduced spacing between the right frontal bone and zygomatic bone), presumably representing a small eye that was not observed at external examination. In addition, the mean number of ossified sacrocaudal vertebrae was reduced.

The incidence of cervical ribs in the 200 and 500 mg/kg/day dose groups were higher than in concurrent controls (five fetuses in two litters [litter mean 4.8%] and five fetuses

in three litters [litter mean 6.3%], respectively, versus two fetuses in two litters [litter mean 2.4%]).

There were no significant findings noted in the audited draft report from a PPND study in rats. However, the highest maternal exposures to NHC were 1.5-fold the mean clinical NHC exposure, significantly lower than the 8-fold NHC exposures at which embryo-fetal toxicity was seen in the EFD study in rats.

In the PPND study in rats, low concentrations of NHC, 0.09% of maternal exposures, were measured in 10-day old pups, suggesting that NHC is present in breast milk.

Studies in Rabbits

In an EFD study in rabbits, MOV was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Systemic exposures at 400 and 750 mg/kg were 7- and 18-fold the human NHC exposures at the recommended human dose. Developmental toxicity included reduced fetal body weights at the 750 mg/kg/day dose. Incomplete ossification at 400 and 750 mg/kg was possibly test article-related given the bone effects noted in the 3-month repeat-dose toxicology study in rats. Maternal toxicities included reduced food consumption and body weight gains, and abnormal fecal output at 750 mg/kg/day.

4.3.2.4. Review Issues #3 Through #5 Discussion and Proposed Risk Mitigation Strategies

The Agency proposes a multipronged risk mitigation strategy to address each of the potential safety signals identified in the nonclinical program. These risk mitigation strategies will be implemented though the "Fact Sheet for Healthcare Providers" and "Fact Sheet for Patients and Caregivers."[12] During your deliberations, please take these risk mitigation strategies into account as you consider the overall benefit-risk assessment.

The following risk mitigation strategies are proposed based on the embryo-fetal toxicity, bone and cartilage-related formation findings and mutagenicity. Risk mitigation strategies are proposed for pregnant and lactating individuals, individuals of childbearing potential, and pediatric patients.

Pregnancy

Given the nonclinical findings of embryo-fetal toxicity and bone and cartilage formation related events, the known and potential benefits of MOV may not outweigh the known and potential risks of MOV in pregnant individuals. One option is to not authorize MOV for use in pregnant individuals. There are alternative therapies available that are authorized for the treatment of mild-to-moderate COVID-19 that do not have an embryo-fetal toxicity safety signal (i.e., anti-SARS CoV-2 mAbs) that would be available to pregnant individuals should MOV not be available for use during pregnancy under the EUA. We seek the Committee's advice regarding use of MOV during pregnancy.

[12] Some components of the risk mitigation strategy may be specified as conditions to the authorization.

Individuals of Childbearing Potential

The Agency proposes to recommend that, prior to initiating treatment with MOV, prescribing health care provides should verify that an individual of childbearing potential is not pregnant if clinically indicated. Pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible. In all other patients, verify a patient is not pregnant based on the first day of last menstrual period in individuals who have regular menstrual cycles, using a reliable method of contraception correctly and consistently or have had a negative pregnancy test. A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly or consistently.

The Agency proposes to recommend that individuals of childbearing potential should use an effective method of contraception for the duration of treatment with MOV and for 4 days after the final dose.

Of note, based on in vitro study results, neither MOV nor NHC are substrates of CYP enzymes or P-gp and BCRP transporters. Neither MOV nor NHC are inhibitors or inducers of major drug-metabolizing enzymes or transporters. Therefore, the potential for MOV or NHC to interact with concomitant medications including hormonal contraceptives is considered unlikely.

Lastly, the Sponsor has created a pregnancy surveillance program to collect information on pregnancy outcomes in individuals who are exposed to MOV during pregnancy. A toll-free number will be provided in the fact sheets for healthcare providers and patients and caregivers to report exposures.

Lactation

There are currently no data on the presence of MOV or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. NHC was detected in the plasma of nursing pups from lactating rats administered MOV. Based on the previously discussed nonclinical concerns (i.e., bone and cartilage toxicity and mutagenicity) and the potential for an infant to be exposed to MOV through breastmilk, the Agency proposes to recommend that lactating individuals not breastfeed for the duration of treatment and for 4 days after the last dose of MOV. The Agency also proposes to recommend that prescribing healthcare providers should advise lactating individuals to interrupt breastfeeding and to instead pump and discard breastmilk during this period.

Pediatrics (Less Than 18 Years of Age)

As previously described, animal studies suggest that MOV may affect bone and cartilage growth. Further, COVID-19 is typically associated with a mild disease course in most pediatric patients. All of the mAbs authorized for the treatment of mild-to-moderate COVID-19 include adolescents (patients 12 years of age and older weighing at least 40 kg) in the authorization. A juvenile toxicity study in rats is planned to further inform

the safety of MOV in pediatric patients. If MOV is authorized, the Agency and Sponsor are in agreement that MOV not be authorized for use in patients less than 18 years old.

Other Risk Mitigation Strategies

The potential for MOV to cause mutagenicity in humans is thought to be low based on the available nonclinical data. The risk of mutagenicity is further reduced by the short 5-day treatment duration. A nonclinical carcinogenicity study is underway.

The Agency proposes that MOV not be authorized for use for longer than 5 consecutive days. Additionally, MOV will be dispensed in the original container and contains 40 capsules, which is one 5-day treatment course.

In addition to the above outlined risk mitigation strategies, the Fact Sheet for Patients and Caregivers has been organized to discuss the main risks first and several mandatory requirements for administration of MOV under EUA will be implemented. For example, the Sponsor has agreed that prescribing healthcare providers will be required to review the information in the Fact Sheet for Patients and Caregivers with the patient and to document that the patient has been given an electronic or hard copy of the Fact Sheet for Patients and Caregivers. Please see below for an excerpt from the Agency proposed Fact Sheet for Healthcare Providers describing these requirements.

> *In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of MOV, the following steps are required. Use of MOV under this EUA is limited to the following (all requirements must be met):*
>
> 1. *Treatment of mild-to-moderate COVID-19 in nonpregnant adults with a positive result of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.*
> 2. *As the prescribing healthcare provider, review the information contained within the "Fact Sheet for Patients and Caregivers" with your patient or caregiver prior to the patient receiving MOV. Healthcare providers must provide an electronic or hard copy of the "Fact Sheet for Patients and Caregivers" prior to the patient receiving MOV. The prescribing healthcare providers (to the extent practicable given the circumstances of the emergency) must document patient/caregiver has been:*
>
>   *Given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers."*
>
>   *Informed that:*
>
>   i. *Molnupiravir is an unapproved drug that is authorized for use under this EUA.*
>   ii. *There are no approved, available products for the treatment of COVID-19 in adults who have mild-to-moderate COVID-19 and are at risk for progressing to severe COVID-19 and/or hospitalization.*

iii. *Other therapeutics are currently authorized for the same use as molnupiravir, such as monoclonal antibody therapies.*
iv. *There are benefits and risks of taking MOV as outlined in the "Fact Sheet for Patients and Caregivers."*

For information on clinical studies of molnupiravir and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

3. *The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to MOV within 7 calendar days from the onset of the event.*

4.3.2.5. Issue #6 Effect of Molnupiravir on SARS-CoV-2 Spike Protein Sequences in Clinical Trials

Background

MOV inhibits SARS-CoV-2 replication by causing the accumulation of nucleotide changes in viral RNA, which ultimately render viral populations less fit or unviable. In theory, the random viral RNA mutagenic effects of MOV treatment could result in genetic changes anywhere in the viral genome, which under certain conditions could impact viral susceptibility to other antiviral agents or to the host immune response. Of particular importance, amino acid changes in the viral spike protein could contribute to reduced viral susceptibility to the host antibody response or to spike protein targeting mAb therapeutics.

This section summarizes analyses conducted by the Sponsor and FDA to characterize MOV treatment-emergent changes in the SARS-CoV-2 spike protein sequences in clinical trials (1) to confirm the mechanism of MOV action leading to accumulation of nucleotide changes in the SARS-CoV-2 genome, and (2) to determine if MOV treatment causes changes in the viral spike protein that could facilitate SARS-CoV-2 evolution or immune escape.

Assessment

SARS-CoV-2 Sequence Analysis Methods

The Sponsor conducted next-generation sequencing (NGS) analyses of SARS-CoV-2 RNA populations in nasopharyngeal (NP) and oropharyngeal (OP) samples collected from participants in MOV clinical trials. Briefly, samples with sufficient viral RNA levels were subjected to RT-PCR amplification and full genome sequencing using the Ion Torrent NGS platform. Variants were reported relative to the prototypic reference isolate, Wuhan-Hu-1. Nucleotide mutation rates were calculated as the number of nucleotide changes compared to reference or baseline sequences per 10,000 bases across the entire viral genome (~30,000 bases).

The NGS data from MK-4482-002, Part 1 (outpatient population/phase 2) and MK-4482-001 (hospitalized population/phase 2) were included in the EUA submission in both raw (.fastq) and analysis-ready formats, and independent FDA analyses of these data were conducted to characterize treatment-emergent amino acid changes in MOV- and placebo-treated participants. Treatment-emergent amino acid changes (i.e., detected in postbaseline samples but not baseline samples, regardless of NP/OP sample type) based on a variant sensitivity threshold of 5% were identified in the viral spike sequences and compared between MOV- and placebo-treated participants.

For MK-4482-002, Part 2, limited SARS-CoV-2 sequence analysis data were reported, so the treatment-emergent amino acid analyses focused primarily on MK-4482-002, Part 1, and MK-4482-001.

Analysis of SARS-CoV-2 RNA Mutation Rates

Based on available data from a small subset of participants (12%, 92/762) from MK-4482-002, Part 2, and consistent with the MOV mechanism of action, MOV treatment was associated with a modest but significantly higher nucleotide mutation rate in SARS-CoV-2 populations in NP swab samples collected on Day 5 (end of treatment (EOT)) (Table 6).

Table 6. MK-4482-002 (P002, Part 2): SARS-CoV-2 RNA Mutation Rate (Number of Nucleotide Changes/10,000 Nucleotides Sequenced Across Entire Genome)

		MOV 800 mg		Placebo		
Visit	Analysis Parameter	N	Median (Range)	N	Median (Range)	P-Value MOV vs. PBO[1]
Baseline	Number of SARS-CoV-2 mutations relative to reference (NP swab)	42	13.0 (9-20)	50	12.7 (10-16)	0.272
Day 5 (EOT)	Number of SARS-CoV-2 mutations relative to baseline (NP swab)	42	2.5 (0-46)	50	1.3 (0-30)	0.005

Source: FDA analysis of Sponsor-reported mutation rates.
[1] Wilcoxon test
Abbreviations: EOT, end of treatment; MOV, molnupiravir; NP, nasopharyngeal; PBO, placebo

Analyses conducted by the Sponsor indicate most of the nucleotide mutations observed were transition mutations, again consistent with the MOV mechanism of action, although MOV treatment was associated with increases in all types of analyzed nucleotide changes (Table 7; Sponsor's analysis).

Table 7. MK-4482-002 (P002, Part 2): Mean Number of SARS-CoV-2 RNA Transitions, Transversions, and Other Nucleotide Changes, Day 5 Relative to Baseline

		Transitions				Transversions								Other
Treatment	N	C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	(In/Del)
MOV	42	6.6	1.8	3.6	2.2	0.2	0.1	0.1	0.2	1.6	0.1	0.2	0.4	1.7
Placebo	50	4.1	1.1	0.4	0.5	0.1	0.0	0.0	0.0	1.0	0.0	0.1	0.2	1.2

Source: Report p002v02eff, pg. 153.
Abbreviations: Del, deletion; in, insertion; MOV, molnupiravir

MOV treatment in MK-4482-002, Part 1 and MK-4482-001 was also associated with a higher rate of detected nucleotide changes in postbaseline viral genomes, consistent with the results from MK-4482-002, Part 2.

Analysis of Spike Treatment-Emergent Amino Acid Changes: MK-4482-002, Part 1

Results for all three MOV arms in MK-4482-002, Part 1, were pooled for analyses of treatment-emergent amino acid changes in the spike protein. Specific amino acid changes or nucleotide structural mutations detected at the same amino acid position in ≥2 participants (pooled MOV and placebo) were identified and tabulated. Note that NGS analyses were generally restricted to samples collected up to Day 5 (EOT), so these analyses would not identify changes that emerged or persisted at later timepoints.

Results of these analyses are summarized in Table 8. Consistent with the MOV mechanism of action, a greater proportion of participants in the MOV arms relative to the placebo arm had at least one treatment-emergent amino acid substitution or other structural nucleotide change (deletion, insertion) detected in the spike gene, and amino acid changes were scattered throughout the coding sequence. A total of 81 emergent spike substitutions/changes was detected among 38 MOV-treated participants and nine placebo-treated participants. Each of the nine placebo-treated participants had one treatment-emergent spike amino acid substitution detected, while a total of 72 substitutions were detected in the 38 MOV-treated participants (median one substitution per participant, range 1 to 7). Amino acid changes, including substitutions, insertions, or deletions, were detected in multiple participants at several spike amino acid positions, mostly in MOV-treated participants.

Table 8. MK-4482-002 (P002, Part 1): Treatment-Emergent Amino Acid Changes (Through Day 5/EOT) Detected at ≥5% Frequency in Spike Sequences

Parameter	No. of Participants in MOV Arm (Pooled, n=113)	No. of Participants in Placebo Arm (n=39)
Any treatment-emergent spike AA change	38 (34%)	9 (23%)
AA Positions with ≥2 participants with change		
ΔP139-Y145	1*	0
P139S	1*	0
ΔL141-Y144	1*	0
ΔL141-Y144, Fins	1*	0
ΔY145	1*	0
G261I/V	2	0
S297L	1	1
T385I	2	0
E484K	2	0
P681H	2	0
S884F	1	1
A1022T	2	0

Source: FDA analysis.
* Each of these was detected in a separate participant at variant frequencies of ~6–20%.
Abbreviations: AA, amino acid; EOT, end of treatment; MOV, molnupiravir

Of particular interest, in some participants, MOV treatment was associated with amino acid changes at sites/regions of spike that are likely under immune or other evolutionary pressure. Amino acid changes at these sites are found in some SARS-CoV-2 variants of public health importance. Our analyses identified or confirmed the following:

- Five MOV-treated participants (0 placebo-treated participants) had treatment-emergent amino acid substitutions, insertions, or deletions in the region of amino acids P139-Y145 in the N-terminal domain (NTD). This is an exposed region of the spike protein that is believed to be under strong antibody selective pressure (Harvey et al. 2021), and deletions or substitutions in this region are found in several important SARS-CoV-2 variants.
- Two MOV-treated participants (0 placebo-treated participants) had treatment-emergent E484K, which is a key receptor-binding motif substitution associated with neutralizing antibody escape and is present in several important SARS-CoV-2 variants.
- Two MOV-treated participants (0 placebo-treated participants) had treatment-emergent P681H, which is adjacent to the spike furin cleavage site and is present in multiple SARS-CoV-2 variants, and is in the same position where a P681R substitution has been hypothesized to enhance infectivity of the Delta variant (Liu et al. 2021).

Importantly, analyses of raw NGS fastq data from the participants with the noted NTD changes confirmed the analyses of the analysis datasets. For example, while the ION Torrent NGS platform is prone to reporting single base insertion or deletion artifacts in homopolymeric sequence reads, the NGS reads in these NTD regions were generally of high quality and clearly indicated deletions of stretches of amino acid codons (i.e., multiples of three, up to 21 nucleotides).

Analysis of Spike Treatment-Emergent Amino Acid Changes: MK-4482-001

Similar analyses of SARS-CoV-2 spike sequence were conducted for clinical trial, Trial MK-4482-001 (hospitalized population) (Table 9). Consistent with the MOV mechanism of action and the results from MK-4482-002, Part 1, participants treated with MOV in MK-4482-001 were more likely to have at least one detected treatment-emergent spike amino acid change, compared with those treated with placebo. Again, some notable observations include the following:

- Five MOV-treated participants (one placebo-treated participant) had treatment-emergent amino acid substitutions or deletions in the region of amino acids P139-Y145 in the NTD.
- Two MOV-treated participants (0 placebo-treated participants) had treatment-emergent P681H, adjacent to the spike furin cleavage site.
- One MOV-treated participant (0 placebo-treated participants) had treatment-emergent N501Y, which is another important spike change that contributes to neutralizing antibody escape and virus attachment.

The specific treatment-emergent changes noted above were detected in six (7%) MOV-treated participants and one (4%) placebo-treated participant. Three of these changes were detected in one MOV-treated participant, and in a large fraction of sequences (32 to 77%): ΔY145, N501Y, and P681H. This same participant had several other treatment-emergent amino acid changes in the spike protein and elsewhere in the genome, and the Sponsor reported that the viral clade designation changed for this participant between baseline and Day 3, so it is unclear if this reflects extensive MOV-associated mutagenicity, coinfection with another SARS-CoV-2 variant, or a technical issue. All of the other changes were detected in separate participants at lower variant frequencies (5 to 12%).

Table 9. MK-4482-001 (P001, Part 1): Treatment-Emergent Amino Acid Changes Detected at ≥5% Frequency in Spike Sequences

Parameter	No. of Participants in MOV Arms (Pooled, n=89)	No. of Participants in Placebo Arm (n=27)
Any treatment-emergent spike AA change	31 (35%)	5 (19%)
AA Positions with ≥2 participants with change		
del_L141-Y144	2	0
G142V	1	0
ΔY145	2	1
A262S	1	1
N501Y	1*	0
P681H	2	0

Source: FDA analysis.
* Treatment-emergent only in one participant but noted because it is associated with reduced susceptibility to some monoclonal antibodies.
Abbreviations: AA, amino acid; MOV, molnupiravir

Analyses to Explore Potential Clinical Relevance of Detected Spike Protein Treatment-Emergent Amino Acid Changes

Additional analyses from MK-4482-002, Part 1, were conducted to explore the potential clinical impact of the MOV treatment-emergent changes in the spike protein, focusing particularly on the NTD changes and deletions of amino acids 139 to 145, and substitutions E484K and P681H. A total of seven (6%) MOV-treated participants had these treatment-emergent changes in spike. Two participants had two of these changes detected: P139S+P681H and ΔP139-Y145+P681H. In all seven participants, these spike protein changes of interest were detected as minority variants comprising 5–20% of the viral RNA population. Note that these seven participants represent only a subset of the spike amino acid changes detected in MOV- or placebo-treated participants, and several other emergent amino acid changes were detected in MOV- and/or placebo-treated participants at positions of unknown significance throughout the spike protein.

There was no evidence that the emergence of these spike protein amino acid changes affected the levels of viral RNA or cell culture infectious virus in NP or OP specimens, although it should be noted that culturable virus was rarely detected across the entire study population (~10 to 20% at baseline, 0 to 3% postbaseline, NP samples). Of the seven participants with the key spike protein changes of interest, only one participant had

cell culture infectious virus detected in an NP or OP specimen, and it was a baseline sample.

Furthermore, there was no evidence that the emergence of these spike amino acid changes contributed to enhanced disease, at least based on the clinical endpoint of hospitalization or death. None of the seven participants noted above reached this endpoint through Day 29. In addition, there was no clear evidence that participants with any treatment-emergent spike protein change were more or less likely to reach the clinical endpoint, although the hospitalization rate was low overall in MK-4482-002, Part 1.

Other observations and considerations from these analyses include the following:

- While treatment-emergent spike protein amino acid changes appeared to be detected at a higher rate in MOV-treated participants, it should be recognized that treatment-emergent spike amino acid changes were also observed in some participants treated with placebo, consistent with this being a protein under natural evolutionary pressure.
- A majority of the spike protein amino acid changes were detected as minority variants. Considering all of the 72 treatment-emergent spike amino acid changes detected in MOV-treated participants in MK-4482-002, Part 1, 56 (78%) of these changes were detected in <15% of the sequence population.
- Consistent with most changes occurring as minority variants, when sequence data were available for multiple postbaseline samples (NP or OP swabs, Day 3 or Day 5/EOT), the treatment-emergent spike amino acid changes were detected only in one sample, indicating compartmentalized or transient detection of these changes. Note that 38% (57/152) of participants in the MK-4482-002, Part 1, dataset had data from only a single postbaseline sample.
- Transition mutations are the types of mutations most often enriched by MOV and directly tied to its mechanism of action, but the types of nucleotide changes leading to the observed amino acid changes in spike were not all transition mutations. Other nucleotide changes leading to spike amino acid changes in these datasets included transversions, deletions and insertions. However, MOV (or more specifically, NHC-TP) apparently can increase the rate of other types of nucleotide changes detected in clinical viral specimens (Table 7). Also, in theory, some changes, such as deletions could arise from error repair mechanisms. In any case, any uncommon types of nucleotide changes could become enriched in the viral population if they confer a selective advantage.
- In a few individual participants, numerous treatment-emergent spike changes were detected in association with other changes elsewhere in the genome, as noted above for the MK-4482-001 participant with treatment-emergent ΔY145, N501Y, and P681H. It is unclear if this reflects extensive MOV-driven mutagenesis and selection, coinfection with multiple SARS-CoV-2 variants, or a technical issue.

Discussion

Collectively, these analyses indicate MOV treatment may increase the rate of emergence of SARS-CoV-2 populations with amino acid changes in the viral spike protein, consistent with its mutagenic mechanism of action. However, there remain many

uncertainties regarding these findings and their clinical and public health implications. At the individual patient level, there was no evidence that the emergence of spike amino acid changes affected virologic or clinical outcomes in outpatients with COVID-19 in MK-4482-002, Part 1.

It is challenging to predict the broader public health risk of MOV treatment-associated spike amino acid changes. On a per-patient basis the transmissibility of variants arising in patients is likely quite low. Most spike protein changes observed in MK-4482-002, Part 1, were detected as minority variants. Even in the absence of an antiviral effect, overall viral shedding levels will likely be declining rapidly by the time a MOV-associated spike amino acid variant emerges in treated outpatients with COVID-19. The antiviral activity of MOV, which is linked directly to its mutagenic activity, likely accelerates this viral clearance.

There was no clear evidence that emergence of spike protein amino acid changes in MK-4482-002, Part 1, was associated with a rebound in viral RNA shedding, and cell culture infectious virus was not detected in any MOV-treated participants by Day 5/EOT (and only in 4% of placebo-treated participants at Day 5).

Also note that the SARS-CoV-2 spike protein acquires genetic changes frequently, regardless of any MOV mutagenic activity. In the placebo arm in MK-4482-002, Part 1, 23% of participants with available data had a detected treatment-emergent amino acid change in the spike protein. Natural immune responses and other beneficial treatments and vaccines can also influence SARS-CoV-2 evolution.

In summary, concerns about the potential for MOV to enrich for low-level variants with spike protein amino acid changes within an individual treated patient may be low. However, it remains unclear if the potential for MOV-associated changes in the SARS-CoV-2 spike protein presents a public health risk, considering anticipated widespread use of MOV.

5. OVERALL BENEFIT-RISK CONSIDERATIONS

MOV is an oral antiviral drug that was associated with a relative risk reduction of 52% (95% CI 33%, 80%) in hospitalization or death through Day 29 compared to placebo in adults with mild-to-moderate COVID-19 and at high risk for progression to severe COVID-19. Currently no therapies are FDA-approved for the treatment of mild-to-moderate COVID-19, though three mAb regimens requiring IV or SC administration are authorized under EUA for this use.

Several potential risks to patients were identified based on findings from the available nonclinical data and include the risk of embryo-fetal toxicity, impaired bone and cartilage growth, and mutagenicity. Additional nonclinical data are being collected to better understand the risks these findings pose to patients, including a juvenile toxicology study and carcinogenicity study. These data will not be available to inform this authorization. Lastly, the currently available safety database for MOV is smaller than the safety

database for the three mAb therapies also authorized for the treatment of mild-to-moderate COVID-19 in patients[13] with positive results of direct SARS-COV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death at the time of their initial authorization. Given the limited safety database, rare adverse events that have not yet been reported with MOV use could occur.

Based on the currently known and potential risks, several risk mitigation strategies are proposed. Given the embryo-fetal toxicity and bone and cartilage findings, the Agency and the Sponsor are in agreement that MOV not be authorized for use in pediatric patients.

Regarding use in pregnancy, one approach is not to authorize MOV for use during pregnancy because there are no clinical scenarios where the benefit outweighs the risk Alternatively, a less restrictive approach for use of MOV during pregnancy could be considered. Under this alternative approach, MOV would not be recommended for use during pregnancy and information would be provided to prescribers regarding the potential risks of use in pregnancy through a Warning and Precaution, however, prescribers could use MOV during pregnancy in certain clinical scenarios where the benefits were thought to outweigh the risks. The Agency seeks advice from the Committee regarding the option to limit the use of MOV to nonpregnant adults only or the option to consider certain clinical scenarios for which use of MOV during pregnancy is warranted.

Further, the Agency has proposed recommendations for contraception use and assessing pregnancy status (see Section 4.3.2.4). Additional general risk mitigation strategies include a requirement for the prescribing healthcare provider to document that patients were informed about the benefits and risks of taking MOV.

Another means of optimizing benefit-risk is through patient selection. The known and potential risks of MOV may be more acceptable in patients with the greater prospect of benefit. As described in Section 3.3, various subgroup analyses of MK-4482-002 data were conducted and the literature was reviewed to help better inform patient selection.

First, there are multiple potential approaches to identifying patients at high risk for progression to severe COVID-19, including hospitalization and death. The authorized mAb Fact Sheets for Healthcare Providers includes a list of medical conditions or other factors that may place patients at higher risk for progression to severe COVID-19 and refers to the CDC website for a comprehensive listing of risk factors, which is updated as new information becomes available (see Section 8.1). This approach has the advantage of providing prescribers with a consistent approach to identifying patients eligible for receipt of an authorized product for the treatment of mild-to-moderate COVID-19. An alternative approach is to restrict the definition of high risk for progression to severe COVID-19 to a limited set of risk factors such as those utilized in the MK-4482-002

[13] The mAbs are authorized for use pediatric patients (12 years of age and older weighing at least 40 kg), however, MOV will be not be authorized for patients less than 18 years of age.

eligibility criteria (see Section 8.2), thus ensuring the authorized population reflects the population in which data from the trial are available to support effectiveness.

Next, vaccination status could be considered as a potential patient selection criterion. While vaccinated individuals were excluded from MK-4482-002, no treatment benefit was discernable among the small subgroup or participants who were seropositive (due to natural immunity) at baseline given the small number of events overall. However, there are numerous limitations to extrapolating findings from patients with natural immunity to those with vaccine-induced immunity. The risk of hospitalization and death among fully vaccinated individuals is known to be much lower than the risk among unvaccinated individuals. However, some risk remains. Data regarding those fully vaccinated patients at greatest risk for severe COVID-19 are limited, but it appears that risk factors for severe breakthrough COVID-19 are reasonably well-captured by the CDC's high-risk criteria (Bosch et al. 2021; Brosh-Nissimov et al. 2021; Green et al. 2021; Kim et al. 2021).

Lastly, in addition to the known and potential risks to individual patients, there is also a potential risk based on the finding of an increased rate of amino acid changes in the SARS-CoV-2 spike protein among participants treated with MOV. The clinical and public health implications of this finding remain uncertain. Fortunately, these changes did not appear to be associated with hospitalization or death among the small subset of participants from MOV clinical trials for whom these data are available. However, on a large scale, these changes could, in theory, enhance SARS-CoV-2 spike protein evolution. It is not clear that further restrictions on the authorized population would be sufficient to meaningfully impact this trajectory should these theoretical concerns be realized.

We look forward to the Committee opining on these complex benefit-risk considerations. Through these deliberations, we hope to gain a better understanding of the appropriate patient selection for authorized use and what risk mitigation strategies should be mandated in a potential authorization.

6. POINTS FOR ADVISORY COMMITTEE CONSIDERATION

1. Please discuss your level of concern regarding the use of molnupiravir during pregnancy. In your discussion, please comment if you think molnupiravir should be accessible for use in pregnancy in certain scenarios, and if so, please describe those scenarios. Lastly, please note whether your concerns regarding the use of molnupiravir during pregnancy extend to the use of molnupiravir in individuals of childbearing potential.
2. Please discuss your level of 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.
3. Please discuss whether the known and potential benefits of molnupiravir when used for the treatment of mild-moderate COVID-19 in adult patients who are at high risk

of severe COVID-19, including hospitalization or death (as per the example in Section 8.1 and consistent with the CDC website), outweigh the known and potential risks of molnupiravir?

Please consider the following when determining if the overall benefit-risk assessment is favorable or not:

- The efficacy results from Part 2 of Trial MK-4482-002, including the limitations of the data currently available regarding molnupiravir for use as proposed
- The weight of evidence of the nonclinical data
- The mechanism of action of the drug
- The proposed population for whom molnupiravir would be authorized
- The oral formulation of molnupiravir (dosage regimen: four 200 mg capsules Q12H for 5 days)
- The availability of authorized antivirals, namely monoclonal antibodies, administered IV or SC.

a. If yes, do you agree with the proposed risk mitigation strategies or are additional risk mitigation strategies needed?
b. If no, please indicate whether you think changes to the authorized population are needed or if you think that MOV should not be authorized in any population.

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8. APPENDIX

8.1. Example Authorized Use Statement Based on Neutralizing Monoclonal Antibodies

The following is an example of an Authorized Use Statement based on the Fact Sheets for Healthcare Providers for the authorized neutralizing monoclonal antibodies. This has been provided as an example of a possible authorized use and the criteria used to identify patients who are at high risk for severe COVID-19.

EMERGENCY USE AUTHORIZATION (EUA) OF DRUG X

AUTHORIZED USE

TREATMENT

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, DRUG X supplied as individual vials to be administered together, for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adult with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

DRUG X is not authorized for use in patients:

- who are hospitalized due to COVID-19

DRUG X has been authorized by FDA for the emergency uses described above.

DRUG X is not FDA-approved for these uses.

DRUG X is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of REGEN-COV under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

CRITERIA FOR IDENTIFYING HIGH-RISK INDIVIDUALS

The following medical conditions or other factors may place adults at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2)
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension

- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website.[14] Healthcare providers should consider the benefit-risk for an individual patient.

8.2. Trial MK-4482-002, Part 2, Individuals at Increased Risk for Severe Illness From COVID-19

According to the eligibility criteria for Trial MK-4482-002, Part 2, individuals with at least one of the following characteristics or underlying medical conditions were considered to be at increased risk for severe illness from COVID-19:

- Age >60 years
- Active cancer (excluding minor cancers not associated with immunosuppression or significant morbidity/mortality [e.g., basal cell carcinomas])
- Chronic kidney disease (excluding participants on dialysis or with reduced eGFR <30 mL/min/1.73m^2)
- Chronic obstructive pulmonary disease
- Obesity (body mass index of 30 kg/m^2 or higher)
- Serious heart conditions such as heart failure, coronary artery disease, or cardiomyopathies
- Diabetes mellitus

[14] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

8.3. Genotoxicity Profile of Selected Nucleoside Analogues

Table 10. Genotoxicity Profile of Selected Nucleoside Analogues

		In Vitro Mammalian Cell Assay		Carci
Drug	**Ames**	**MLA**	**HPRT**	
Molnupiravir	+ TA102/WP2uvrA	NA[2]	+[2]	Ongoing
Ribavirin	-	+	NA	-
Favipiravir	-	+	NA	NA
Didanosine	+WP2uvrA	+	NA	-
Zidovudine	+ TA102/WP2uvrA	+	+	+[3]
Adefovir	-	+	NA	-
Brincidofovir	-	NA	NA	+[4]
Cidofovir	-	NA	NA	+[5]
Emtricitabine	-	-	NA	-
Tenofovir	-	+	NA	+[6]
Telbivudine	-	NA	NA	-
Entecavir	-	NA	-	+[7]
Stavudine	-	NA	-	-/+[8]
Vidarabine	NA	+	NA	+[9]
Abacavir	-	+	NA	+[10]
Remdesivir	-	NA	NA	NA

1 Data from published research using optimized assay conditions (Zhou et al. 2021).
2 NA, not available (information not included in label).
[3] Mice – 7 vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) at the highest dose and one squamous cell papilloma in the vagina of a middle-dose animal. Systemic exposure was 3-fold the human exposure at the recommended dose of 100 mg every 4 hours. In one transplacental carcinogenicity study, vaginal tumors occurred in the offspring at 40 mg/kg/day or 3-fold the human exposure after 24 months of dosing. A second study identified tumors in the lung, liver, and female reproductive track of offspring dosed with 25 mg/kg/day.
Rats – nonmetastasizing vaginal squamous cell carcinomas at 24-fold the human exposure at the recommended dose. Zidovudine was mutagenic in an L5178Y mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose. Drug label.
[4] Mammary adenocarcinomas, carcinomas in squamous cells, Zymbal's gland, the uterus and small intestine, as well as hemangiosarcomas in the mesenteric and mediastinal lymph nodes, liver, and abdominal cavity in rats occurring after 26 oral doses and at less than the human exposure at the recommended dose. Positive for chromosomal aberrations w/o S9 in an in vitro assay Drug label.
[5] Mammary adenocarcinomas in rats after six 0.6 mg/kg/week subcutaneous doses; systemic exposure was 0.04-fold the human exposure. Mammary adenocarcinomas in female rats and Zymbal's gland carcinomas in both sexes at 1.1-fold the human systemic exposure after 26 weeks. Positive in mouse micronucleus test at >2000 mg/kg (65-fold the maximum human dose) and positive for chromosomal aberrations in human peripheral blood lymphocytes w/o S9 Drug label.
[6] Liver adenomas in female mice at 16-fold the human systemic exposure. Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice. Drug label.
[7] Mice – Lung adenomas and carcinomas in males and females at 3- and 40-fold the human systemic exposure; findings likely species specific. Hepatocellular adenomas and carcinomas in males at 42-fold the human exposure and hemangiomas of the ovaries and uterus and hemangiosarcomas of the spleen in females at 40-fold the human exposure.
[8] Noncarcinogenic in mice and rats at 39- and 168-fold the human exposure at the recommended dose, respectively. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at very high doses; 250 (mice)- and 732 (rats)-fold the human exposure. Positive in the in vitro human lymphocyte clastogenesis and mouse fibroblast assays and in vivo mouse micronucleus test Drug label.
[9] Mice – Liver tumors in females and kidney neoplasms in males. No exposure relationship provided.
Rats – Intestinal, testicular, and thyroid neoplasms and thyroid adenomas at low dose (30 mg/kg) in females and high dose (50 mg/kg) in females. No exposure relationship provided. Vidarabine induced mutations in mammalian cells (mouse L5178Y cell line) and was positive in a dominant lethal assay in mice. Vidarabine caused chromosome breaks and gaps when added to human leukocytes in vitro. Drug information.
[10] Malignant tumors in the preputial gland of male and clitoral gland of female mice and rats and liver of female rats at 6- to 32-fold the human exposure at the recommended dose of 600 mg. Drug label.
Abbreviations: HPRT, hypoxanthine phosphoribosyltransferase; MLA, mouse lymphoma assay; NA, not applicable