

FDA Introductory Remarks

Antimicrobial Drugs Advisory Committee Meeting
November 30, 2021

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Introduction



- Molnupiravir (MOV, MK-4482) is an oral prodrug of the antiviral ribonucleoside analog N-hydroxycytidine (NHC). MOV inhibits viral replication by causing an accumulation of errors in the viral genome leading to inhibition of replication.
- The sponsor, Merck & Co., Inc., has submitted a request for Emergency Use Authorization (EUA) of MOV. The emergency use under consideration is: treatment of mild-to-moderate COVID-19 in 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.
- The proposed oral dosage regimen is 800 mg (4 - 200 mg capsules) every 12 hours for 5 days.

Eligibility of MOV for EUA

- The FDA EUA authority to authorize an unapproved product or unapproved uses of an approved product for emergency use exists during a public health emergency after a declaration by the Secretary of the Department of Health and Human Services.
- The Secretary has determined¹ that a public health emergency exists that involves the virus, SARS-CoV-2, that causes COVID-19, and declared circumstances exists justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic².
- Based on this declaration, FDA may issue an EUA after determining statutory requirements are met.

¹pursuant to Section 564(b)(1)(C) of the Federal Food, Drug & Cosmetic Act (FD&C Act)

²pursuant to Section 564 of the FD&C Act (21 U.S.C. 360bbb-3)

EUA Statutory Requirements

- The chemical, biological, radiological, or nuclear agent referred to in the declaration by the Secretary (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 clinical 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.

EUA Statutory Requirements (continued)



- 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, FDA approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

EUA Considerations



- FDA's authorization of a medical product under EUA is not the same as the Agency's approval or licensure of a product.
- For an EUA, the Agency authorizes a Health Care Provider Fact Sheet and a Patient Fact Sheet. These are similar to Prescribing Information and Patient Labeling or a Medication Guide for approved products.
- As part of its authorization, FDA will establish, to the extent practicable, conditions in the EUA that it finds necessary to protect the public health.
- FDA will periodically review the circumstances and appropriateness of the EUA .



Available Therapies:

Treatment of Mild to Moderate COVID-19

- There are no FDA-approved therapies for the treatment of mild-to-moderate COVID-19.
- Three anti-SARS-CoV-2 monoclonal antibody regimens, administered intravenously (subcutaneous administration option for one product) 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 progressing to severe COVID-19, including hospitalization or death:
 - Casirivimab and imdevimab administered together (REGEN-COV)
 - Bamlanivimab and etesevimab administered together
 - Sotrovimab

Example Authorized Use Statement



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 adults 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 DRUG X under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Review Issues



- The Agency has identified several review issues which will be discussed today. These are issues which are important to consider as one seeks to ensure that the known and potential benefits outweigh the known and potential risks.
- Review issues:
 - Patient selection for authorized use
 - Bone/cartilage formation-related findings
 - Reproductive toxicology findings
 - Mutagenicity
 - Effect of MOV on SARS-CoV-2 spike protein sequences in clinical trials
- The Agency looks forward to your consideration of these issues, the appropriate authorized population, the adequacy of proposed risk mitigation strategies, and the overall benefit-risk assessment.



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ADMINISTRATION

Emergency Use Authorization (EUA) Request 108

Molnupiravir (MOV) capsules

Treatment of mild-to-moderate COVID-19 in 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

Antimicrobial Drugs Advisory Committee Meeting

November 30, 2021

Aimee Hodowanec, MD

Senior Medical Officer

Division of Antivirals, Office of Infectious Diseases

Center for Drug Evaluation and Research

Introduction

- The purpose of this meeting is to seek the Committee's assessment of the known and potential benefits of MOV and the known and potential risks of MOV for the proposed authorized use
 - The Agency is specifically seeking advice on the patient population and risk mitigation strategies for a potential authorization
- The Agency will present its assessment of the available nonclinical and clinical data in support of this EUA application, followed by a discussion of identified review issues and proposed risk mitigation strategies
- The Agency asks the Advisory Committee to consider the mechanism of action, proposed risk mitigation strategies, existing authorizations for intravenously and subcutaneously administered monoclonal antibodies (mAbs), and the oral route of administration of MOV in its deliberations



FDA Presentations

- Nonclinical Assessments
 - Summary of Nonclinical Findings
 - Mutagenicity
- Clinical Overview
- Virology Assessments
- Review Issues and Proposed Risk Mitigation Strategies

Emergency Use Authorization (EUA) Request 108 Molnupiravir (MOV) capsules

Clinical Overview

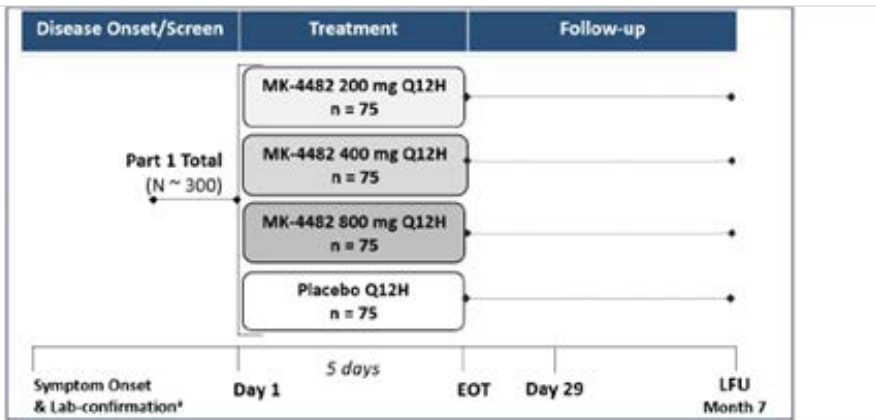
Aimee Hodowanec, MD
Senior Medical Officer
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Molnupiravir Clinical Development Program

- MK-4482-002 (P002) - Outpatient
 - A Phase 2/3 Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate MOV in Non-Hospitalized Adults with COVID-19
 - Part 1 (Phase 2) of trial is a dose ranging trial
 - Part 2 (Phase 3) of this trial is primary source of support for EUA
- MK-4482-001 (P001) – Hospitalized
 - A Phase 2/3 Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate MOV in Hospitalized Adults with COVID-19
 - Trial was stopped after Part 1 (Phase 2) as it was concluded that treatment with MOV is likely to have a greater benefit if initiated earlier in the disease course

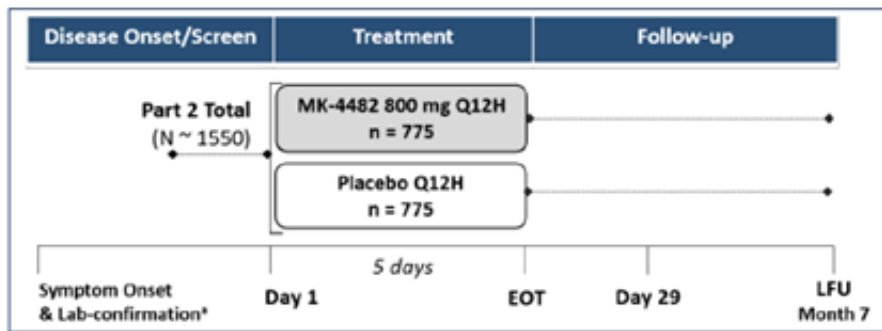
Trial P002: Study Schema

Part I Dose Ranging (Phase 2)



Primary Endpoint: The proportion of participants with hospitalization (all cause) or death by Day 29

Part 2 Evaluation of Selected Dose (Phase 3)



Trial conducted at sites in Latin America (46%), Europe (33%), Africa (12%), North America (6%) and Asia (3%)

Trial P002 Part 2: Eligibility Criteria

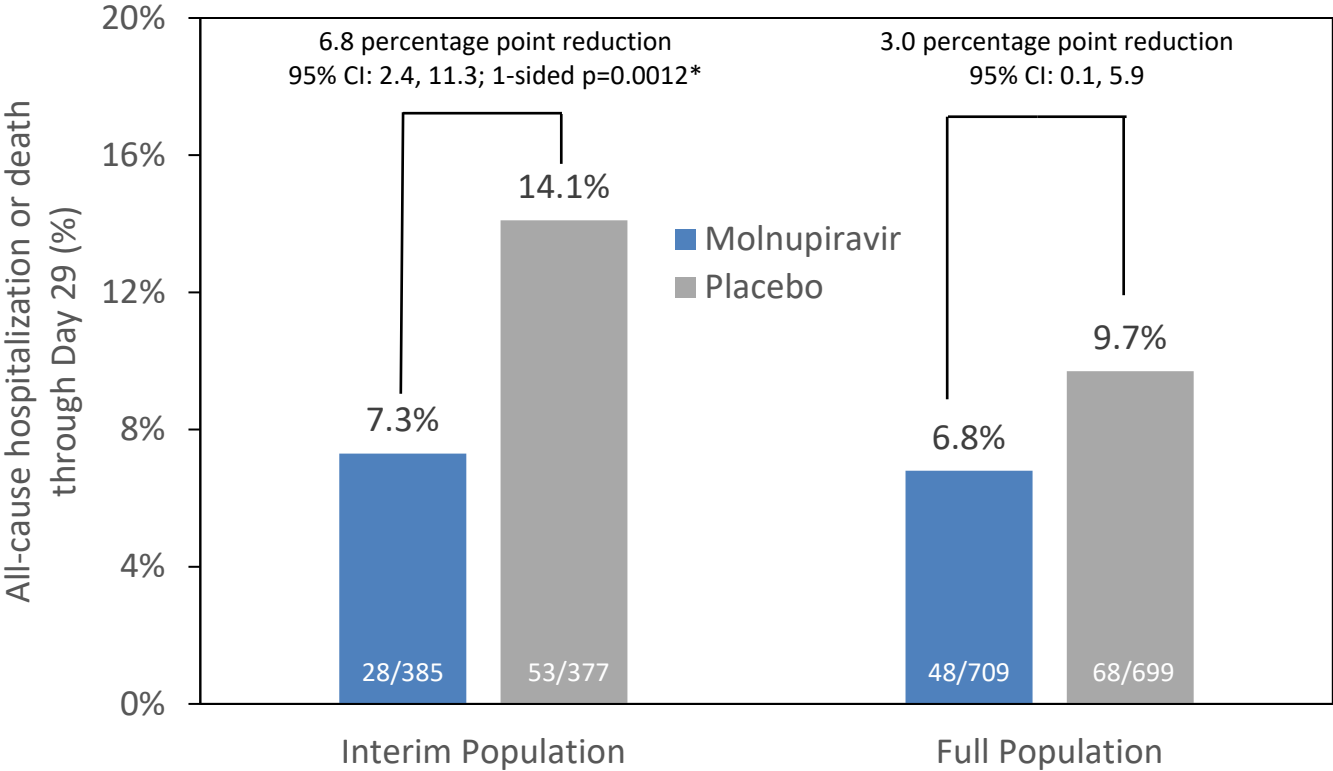
- Outpatient adults with mild or moderate COVID-19
 - Laboratory-confirmed SARS-CoV-2 infection with sample collection ≤ 5 days prior to randomization
 - Initial onset of COVID-19 signs/symptoms ≤ 5 days prior to randomization
- All participants at increased risk for severe illness from COVID-19
 - >60 years of age, active cancer, CKD, COPD, obesity (BMI ≥ 30), serious heart conditions (CAD, heart failure, cardiomyopathies), DM
- SARS-CoV-2 vaccines were prohibited any time prior to randomization and through Day 29
- Pregnant individuals excluded and contraception was required

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus

Trial P002: Efficacy and Safety Analyses

- The Agency has conducted an independent benefit-risk assessment based on the efficacy and safety data submitted by the Sponsor
 - Interim analysis: N = 775
 - Full analysis: N = 1433
- The Agency agrees with the Sponsor's top line safety and primary efficacy analyses
 - Secondary efficacy endpoints are still under review
- The Agency's presentations will highlight selected topics that are thought to warrant further discussion

P002 Primary Efficacy Analysis



* Met the pre-specified interim assessment stopping boundary (1-sided p-value <0.0092)
 Formal statistical testing was not performed for the full population assessment, because statistical significance was demonstrated at the interim population assessment. The nominal 1-sided p-value was 0.0218.

P002 Efficacy Analysis

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

^aThe Post-Interim Analysis Population includes those participants who had not reached Day 29 by the interim analysis data cutoff date of 9/18/2021.

Abbreviations: MOV, molnupiravir; PBO placebo

MOV Clinical Safety Database



Study	Population	No. of Participants Who Received MOV 800 mg Q12H × 5 Days
Primary Safety Data		
MK-4482-002 (P002) Part 2	High risk outpatients with COVID-19	710
Supportive Safety Data		
MK-4482-002 (P002) Part 1	Outpatients with COVID-19	74
MK-4482-006 (P006)	Outpatients with COVID-19	55
MK-4482-001 (P001) Part 1	Hospitalized adults with COVID-19	72
MK-4482-004 (P004)	Healthy volunteers	6
Total		917

Authorized mAb safety databases ranged from 700 to > 2100 participants

P002 Safety Conclusions

- Based on our review of the safety analyses provided by the Sponsor, no notable safety concerns were identified in Part 2 of Trial P002
- Given the finding of bone marrow toxicity in dogs, hematologic laboratory parameters were carefully assessed:
 - Clinically meaningful abnormalities in leukocyte, lymphocyte, platelet, and hemoglobin values were rare and occurred at a comparable rate between arms

Emergency Use Authorization (EUA) Request 108 Molnupiravir (MOV) capsules

Review Issues and Proposed Risk Mitigation Strategies

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Review Issues and Proposed Risk Mitigation Strategies

- Based on the available nonclinical and clinical data, the Agency has identified several review issues
- The main review issue is the proposed patient population for authorized use; it is important to identify patients likely to receive the greatest benefit from MOV treatment
- For the identified issues pertaining to risk, the Agency will propose risk mitigation strategies
- The Agency looks forward to the Committee's deliberations on the use of MOV in specific populations and the acceptability of the proposed risk mitigation strategies

Review Issues

- Patient population for authorized use
- Bone and cartilage toxicity
- Embryofetal toxicity
- Potential for mutagenicity
- Potential for enhanced viral evolution

Bone and Cartilage Toxicity

- MOV will not be authorized for use in patients less than 18 years of age due to:
 - Absence of clinical data from pediatric patients
 - The bone and cartilage findings in animals that may be relevant to pediatric patients and the unborn fetus
- Juvenile toxicity study results are forthcoming
- The Agency proposes a Warning and Precaution in the Fact Sheet describing the bone and cartilage toxicity

Embryofetal Toxicity

Use in Pregnancy

Given the embryofetal toxicity and the bone and cartilage toxicity, the following two approaches are under consideration:

1. MOV is not authorized for use in pregnancy
 - This approach is appropriate if there are no scenarios in which the benefit of MOV is thought to outweigh the risk during pregnancy
2. MOV is not recommended for use in pregnancy, but pregnancy will not be considered a limitation of authorized use
 - This approach would allow for use of MOV under the EUA during pregnancy in certain clinical scenarios in which the benefit of MOV is thought to outweigh the risk

Embryofetal Toxicity

Use in Pregnancy (continued)

- Both approach 1 and 2 would involve the inclusion of a Warning and Precaution regarding use during pregnancy in the fact sheet
- The Sponsor has established a pregnancy surveillance program to collect information on pregnancy outcomes in individuals who are exposed to MOV during pregnancy

Embryofetal Toxicity

Use in Individuals of Childbearing Potential

1. Assessment of pregnancy status:
 - Verify that patient is not pregnant based on the first day of last menstrual period in individuals who have regular menstrual cycles, are 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
 - Verification is not needed in individuals who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible
2. Recommendation for contraception use:
 - Individuals of childbearing potential should also use an effective method of contraception for the duration of treatment with MOV and for 4 days after the final dose

Mutagenicity

- The overall risk of mutagenicity in humans is considered low based on nonclinical data
- Short (5-day) treatment course further reduces risk
 - Molnupiravir will not be authorized for use for > 5 consecutive days
 - Molnupiravir will be dispensed in the original container containing a single treatment course (four 200 mg capsules Q12 x 5 days = 40 capsules)

Potential for Enhanced Viral Evolution

- Currently a theoretical concern
- Unclear that any restrictions on the authorized population could impact this potential
- Some concern that the potential for enhanced viral evolution may be greater in immunocompromised patients who may have more prolonged viral shedding

Patient Selection

- The Agency proposes that the use of MOV be limited to individuals who meet the following criteria:
 - Age \geq 18 years
 - Have a positive result of direct SARS-CoV-2 viral testing
 - Within 5 days of symptom onset at time of treatment
 - At high risk for progression to severe COVID-19, including hospitalization and death
 - Not hospitalized due to COVID-19

*As noted previously, limiting MOV authorization to nonpregnant individuals is also being considered

Time From Symptom Onset

- In Part 1 of P002, participants were required to be within 7 days of symptom onset at randomization
- Based on findings in Part 1, the eligibility criteria were modified for Part 2 of P002 such that participants had to be within 5 days of symptom onset
 - Randomization was stratified by ≤ 3 days or 4-5 days from symptom onset; treatment effect was relatively consistent in both subgroups
- The authorized monoclonal antibodies all require that patients be within 10 days of symptom onset
- No data to demonstrate benefit of MOV when initiated beyond 5 days from symptom onset

Defining High Risk

- Potential approaches to identifying patients at high risk for severe COVID-19:
 - Use criteria similar to those used for authorized mAbs (i.e., provide examples of conditions that place patients at high risk for severe COVID and refer to the CDC website for a complete listing of high-risk considerations)
 - Has the advantage of providing prescribers with a consistent approach to identifying high-risk patients eligible for receipt of an authorized therapy for treatment of mild-to-moderate COVID-19
 - Use a more restrictive list of criteria, such as those used in the Trial P002 eligibility criteria
 - Ensures the authorized population reflects the population in which data from the trial are available to support effectiveness

Proposed Language Modeling the Monoclonal Antibody Fact Sheets



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/m²)
- 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, see the CDC website:

<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

Defining High Risk for Part 2 of Trial P002

- The following criteria were used to identify patients at high risk for severe COVID-19 for participation in Part 2 of Trial P002:
 - > 60 years of age
 - Active cancer
 - CKD
 - COPD
 - Obesity (BMI \geq 30)
 - Serious heart conditions (CAD, heart failure, cardiomyopathies)
 - DM

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus

Trial P002: COVID-19 Vaccination Status and Baseline Serostatus

- Vaccinated patients were excluded from Trial P002
- Approximately 20% of participants were positive for anti-SARS-CoV-2 nucleocapsid antibody at baseline
 - Presence of antibodies at baseline may be attributable to the current SARS-CoV-2 infection or a prior SARS-CoV-2 infection

Incidence of Hospitalization or Death Through Day 29 by Baseline Antibody Status in P002, Part, 2 Full Analysis

SARS-CoV-2 Baseline Antibody Status^a	MOV 800 mg N=709 n/m (%)	Placebo N=699 n/m (%)	Difference (MOV – Placebo) % (95% CI)^b
Positive	5/136 (3.7)	2/146 (1.4)	2.3 (-1.7, 7.1)
Negative	39/541 (7.2)	64/520 (12.3)	-5.1 (-8.8, -1.6)

Source: Sponsor submission dated 11.22.2021.

^a Participants with unknown baseline SARS-CoV-2 antibody status are not included in this analysis.

^b 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; MOV, molnupiravir; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

Monoclonal Antibodies: COVID-19 Vaccination Status and Baseline Serostatus

- The monoclonal antibodies were authorized based on data from unvaccinated patients
- Monoclonal antibodies are authorized for use in patients with mild to moderate COVID-19 who are at high risk for progression to severe COVID-19, regardless of vaccination status

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

SARS-CoV-2 Baseline Antibody Status	Casirivimab/Imdevimab 1200 mg Events/N (%)	Placebo Events/N (%)	Relative Risk Reduction (95% CI)
Positive	1/177 (0.6)	6/164 (3.7)	85% (NA, 98%)
Negative	3/500 (0.6)	18/519 (3.5)	83% (42%, 95%)

Source: Weinreich 2021, NEJM: <https://doi.org/10.1056/nejmoa2108163> (Supplementary Appendix, Figure S3)

Limitations of Available Efficacy Data by Baseline Serostatus

- Ascertainment of serostatus prior to the initiation of treatment for COVID-19 is not feasible in clinical practice given the currently available assays and the turnaround time for results
- Unclear how applicable the findings in individuals with positive baseline nucleocapsid antibodies from natural immunity (from current or prior infection) are to individuals with COVID-19 vaccination

Breakthrough Infection

- Data regarding incidence of breakthrough infections (i.e., infections occurring in fully vaccinated individuals) and characteristics of patients experiencing breakthrough infections are emerging
 - Limited data reflective of Delta variant experience
- Available literature suggests that most breakthrough infections that result in hospitalization or death 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

Kim 2021, Am J Infect Control: <https://doi.org/10.1016/j.ajic.2021.10.003>; Bosch 2021, Clin Infect Dis: <https://doi.org/10.1093/cid/ciab932>; Brosch-Nissimov, Clin Microbiol Infect: <https://doi.org/10.1016/j.cmi.2021.06.036>; Green 2021, medRxiv: <https://doi.org/10.1101/2021.11.08.21265380>.

Conclusions

- MOV reduces the risk of hospitalization or death among adults with mild to moderate COVID-19 and who are at high-risk for progression to severe COVID-19
- MOV appeared generally safe in adults with mild to moderate COVID-19
- Several safety issues were identified based on nonclinical findings
- We look forward to the Committee's discussions on these complex benefit-risk considerations. Through your deliberations, we hope to gain a better understanding of the appropriate patient population for authorized use and what risk mitigation strategies should be mandated in a potential authorization

Molnupiravir: Nonclinical Toxicology Findings

Antimicrobial Drugs Advisory Committee Meeting

November 30, 2021

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Division of Pharmacology/Toxicology-Infectious Diseases

FDA/CDER/OND/OID



Introduction

Nonclinical Toxicology Findings

Bone marrow toxicity

- Significant findings in dogs administered molnupiravir (MOV) for 28 days included:
 - Severe/marked bone marrow cellularity decreases in femur and sternum at N⁴-hydroxycytidine (NHC) exposures less than the mean clinical exposure at the recommended human dose (RHD).
 - 10-fold decrease in platelet counts with subsequent hemorrhage in multiple tissues, especially in the gastrointestinal tract.
 - Platelet values in treated dogs tended to match control animals during the recovery period.
 - Hematology parameters are monitored in clinical trials.

Nonclinical Toxicology Findings

Mutagenicity

- MOV and NHC were positive for mutagenicity in *in vitro* Ames tests
- MOV was negative for mutagenicity in a follow up *in vivo* study in male transgenic rats
- Given the weight of evidence and the 5-day treatment duration with MOV, the risk of mutagenicity in the clinic is considered to be low
- Dr. Heflich will discuss the genotoxicity data in detail

Nonclinical Toxicology Findings

Bone and cartilage abnormalities

- Abnormal growth plate (bone and cartilage) formation was noted in rats following 3 months of daily dosing
- Findings were not present following 1 month of daily dosing, possibly due to the age of the animals at the start of dosing
- In studies of embryo-fetal development (EFD) toxicity:
 - incomplete ossification was noted in rabbit fetuses
 - delayed ossification was noted in rat fetuses
- Not thought to be relevant to adult humans

Nonclinical Toxicology Findings

Embryo-fetal developmental toxicity

- In an EFD study in rats, findings included:
 - reduced fetal body weight,
 - increased post-implantation loss, and
 - external, visceral, and skeletal malformations.
- In an EFD study in rabbits, findings included:
 - reduced fetal body weights, and
 - incomplete ossification



Bone and Cartilage Abnormalities

Bone/cartilage Findings in Rats

- MOV was administered to rats once daily by oral gavage at doses up to 1000 mg/kg for approximately 3 months. The high dose resulted in exposures 9- and 15-times the mean clinical NHC exposures in female and male rats, respectively.
- At ≥ 500 mg/kg, test article-related findings included:
 - increased growth plate thickness (in 10 of 10 high dose males) and/or cartilage changes (in 10 of 10 mid-dose and high dose males and 10 of 10 high dose females), and
 - altered cartilage of the trachea (in 6 of 10 mid-dose and 10 of 10 high dose males)
- Not thought to be relevant to adult humans

Bone/Cartilage Findings in Rats

- Mild to marked increased thickness of the growth plate of the femur and tibia of male rats dosed at 1000 mg/kg/day was characterized by irregularly widened growth plates involving the zone of hypertrophic chondrocytes, and occasional disruption of the growth plate.
- According to the study pathologist, 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.
- Growth plate-related bone and/or cartilage findings were noted at systemic exposures approximately 5-fold higher (in males) and 9-fold higher (in females) than the mean clinical NHC exposure at the RHD.
- Note that there were no significant findings in a 28-day study in rats at similar exposures, possibly due to the age of animals at start of dosing

Bone/cartilage Findings in Fetuses

- MOV was administered orally to pregnant rats from gestation days (GD) 6 to 17
- There were MOV-related skeletal malformations, variations, and delays in ossification at 1000 mg/kg/day (detached ribs, malformations of thoracic vertebrae, lumbar vertebrae, skull, cervical ribs, trace supernumerary ribs, and incomplete ossification of thoracic vertebrae and/or sternebrae).
- At 1000 mg/kg, systemic exposures of NHC in pregnant rats were approximately 8-times the mean clinical NHC exposure.

Bone/cartilage Findings in Fetuses

- MOV was administered orally to pregnant rabbits from GD 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-times the mean clinical NHC exposure.



Embryo-fetal Developmental Toxicity

Embryo-fetal Developmental Toxicity

- In a preliminary EFD study in rats, MOV was administered orally to pregnant rats at doses up to 1000 mg/kg/day from GD 6 to 17.
- In the pivotal study, MOV was administered orally to pregnant rats at doses up to 500 mg/kg/day from GD 6 to 17.

Embryo-fetal Developmental Toxicity

- Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1000 mg/kg/day (8 times the human NHC exposure at the RHD)
- Decreased fetal body weights and delayed ossification at ≥ 500 mg/kg/day (3 times the human NHC exposure at the RHD).
- There were no developmental toxicities at ≤ 250 mg/kg/day (0.8 times the human NHC exposure at the RHD).
- Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of two animals at 1000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

Embryo-fetal Developmental Toxicity

Maternal toxicity-rat

- Decreased body weight gain in females administered 1000 mg/kg does not appear to account for all malformations noted in fetuses from that group
 - For example, Animal number 20-0066 gained 22.7 grams of body weight between gestation days 6 and 10, within the range of body weight gain in control animals. Coronal malformations including small eye and missing eye were noted in the litter from that animal.
 - Also, Animal number 20-0077 lost 1.3 grams of body weight between gestation days 6 and 10, and no coronal malformations were noted in the litter from that animal.

Embryo-fetal Developmental Toxicity

- In an EFD study in rabbits, MOV was administered orally to pregnant rabbits at doses up to 750 mg/kg/day from GD 7 to 19
- Developmental toxicity included reduced fetal body weights at 750 mg/kg/day
- Incomplete ossification at 400 and 750 mg/kg was possibly test article-related given the bone effects noted previously
- Systemic exposures at 400 and 750 mg/kg were 7 and 18 times the human NHC exposures at the RHD
- Maternal toxicities included reduced food consumption and body weight gains, and abnormal fecal output at 750 mg/kg/day

Embryo-fetal Developmental Toxicity

Species	Dose, mg/kg/day	NHC Exposure Multiple	Developmental Effects
Rat	1000*	8	Embryo-fetal lethality and teratogenicity Reduced fetal body weights
	500	3	Reduced fetal body weights Delayed ossification
	250	1	None
Rabbit	750*	18	Reduced fetal body weights Incomplete ossification
	400	7	Incomplete ossification

*Maternal toxicity noted



Conclusions

Conclusions

- Abnormal growth plate formation was noted in rats following 3 months but not 1 month of daily dosing, possibly related to age differences at the start of dosing.
- A study of MOV toxicity in juvenile rats is ongoing.
- The Review Division has agreed that clinical trials of MOV in pediatric patients can be delayed until results from the juvenile rat study are finalized and reviewed.
- Embryo-fetal lethality and malformations of the eye, kidney, and axial skeleton in rat fetuses suggest that MOV may cause fetal harm when administered to pregnant individuals.



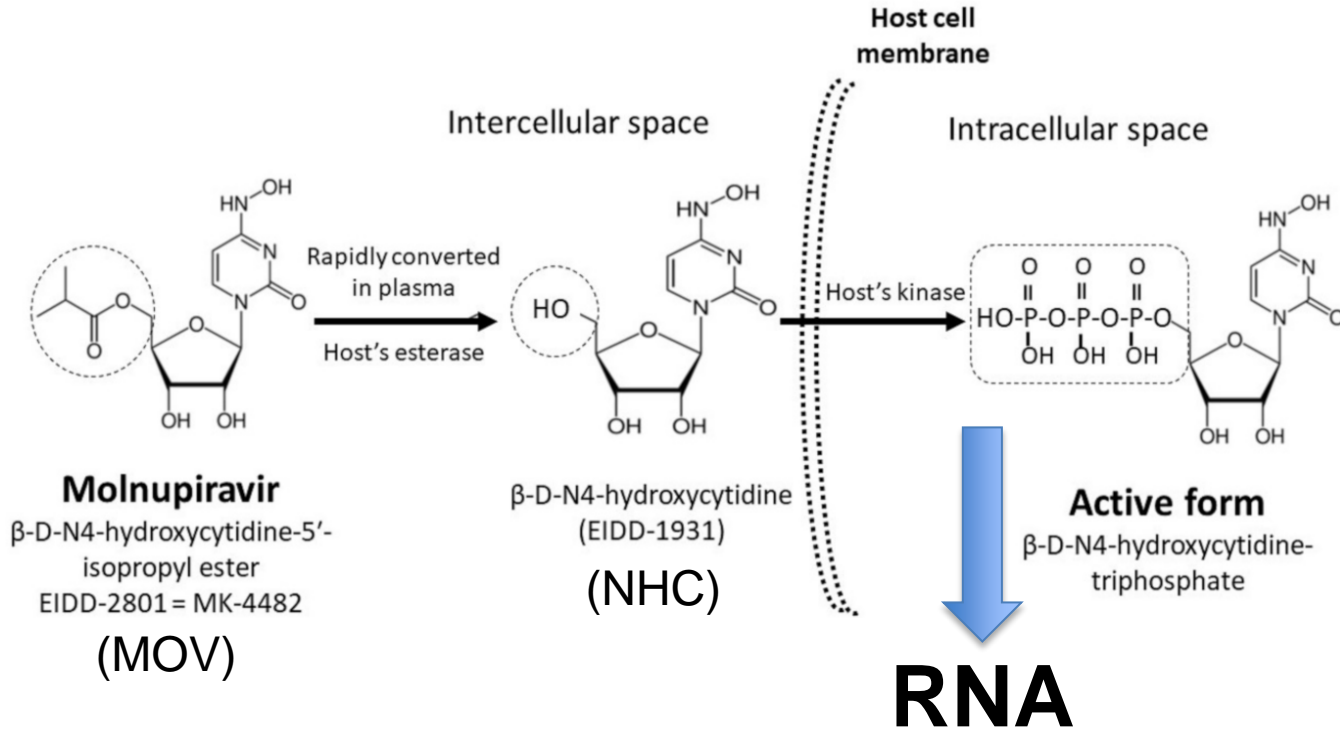
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ADMINISTRATION

Genotoxicity Safety Assessment of Molnupiravir

Antimicrobial Drugs Advisory Committee Meeting
November 30, 2021

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National Center for Toxicology Research

Metabolism and Mode of Action of Molnupiravir

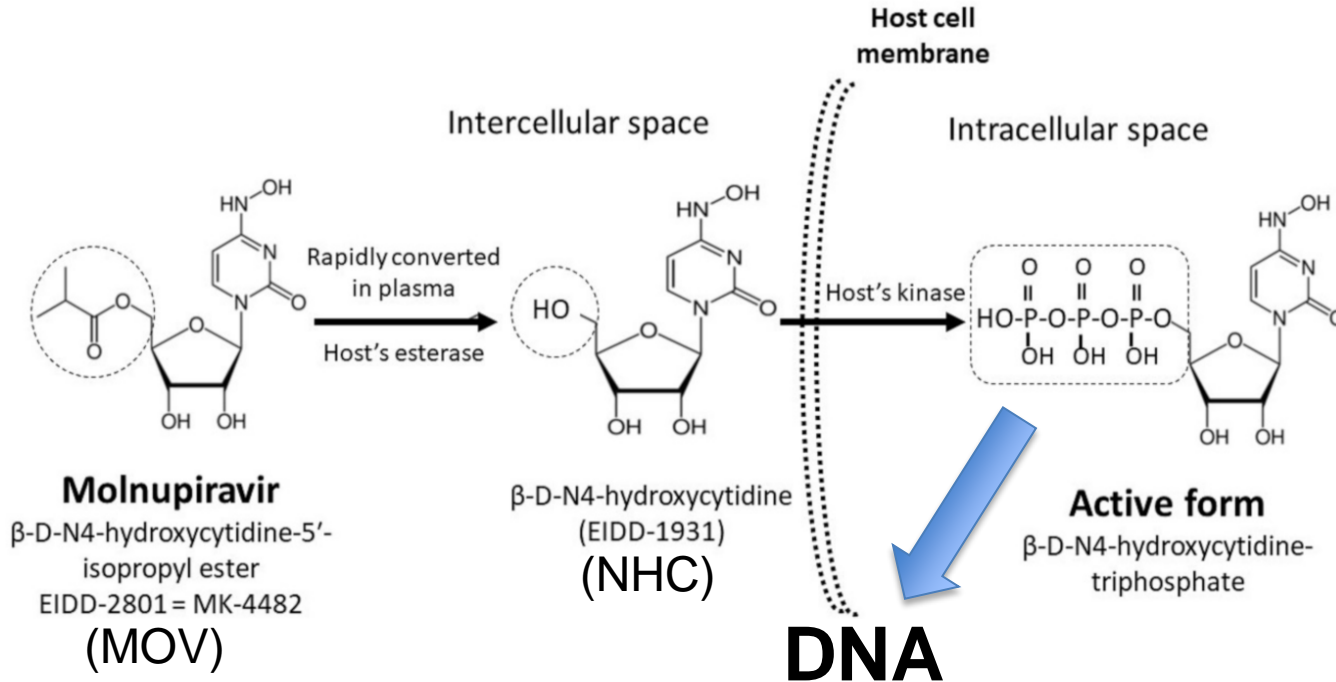


NHC can form base pairs with G (correct), and A (which could lead to mutation)

Figure adapted from Lee et al., *Antibiotics* (2021)

Incorporation into viral RNA results in 'mutation storm', lethal to the virus

Safety Concern for Molnupiravir?: Does this, or an alternate pathway, cause mutation in genomic DNA?



NHC can form base pairs with G (correct), and A (which could lead to mutation)

Figure adapted from Lee et al., *Antibiotics* (2021)

e.g.: reduction by ribonucleotide reductase, incorporation into nuclear DNA, mutation---with possible cancer, germ cell risk

Molnupiravir Genotoxicity Data from Guideline Studies

Test	Endpoint	Organism	Result	Notes
Ames	Gene mutation	Bacteria	Positive	MOV
Ames	Gene mutation	Bacteria	Positive	NHC
In vitro MN	Clastogenicity/ aneugenicity	Human lymphoblastoid TK6	Negative	
In vivo MN	Clastogenicity/ aneugenicity	Rat	Negative	Bone marrow target
<i>Pig-a</i>	Gene mutation	Rat	Equivocal	Bone marrow
Transgenic Rodent (TGR)	Gene mutation	Big Blue rat	Negative	Liver and bone marrow

Summarized from study reports

Ames Data: a bacterial gene mutation assay detecting specific mutations in specific mutation contexts



Strain	Target	Mutation detected	Test result	
			MOV	NHC
TA1535	G:C	BP substitution	Negative	Negative
TA100	G:C	BP substitution	Negative	Negative
TA1537	GCGC	Frameshift	Negative	Negative
TA98	GGGG	Frameshift	Negative	Negative
TA102	A:T	BP substitution	Positive	Not tested
WP2uvrA	A:T	BP substitution	Positive	Positive

Summarized from study reports

Rationale for Follow-Up in vivo Gene Mutation Assays on Molnupiravir



ICH S2(R1) states:

‘.....negative results in appropriate in vivo assays, with adequate justification for the endpoints measured and demonstration of exposure....., are considered sufficient to demonstrate absence of significant genotoxic risk.’

Molnupiravir Genotoxicity Data from Guideline Studies

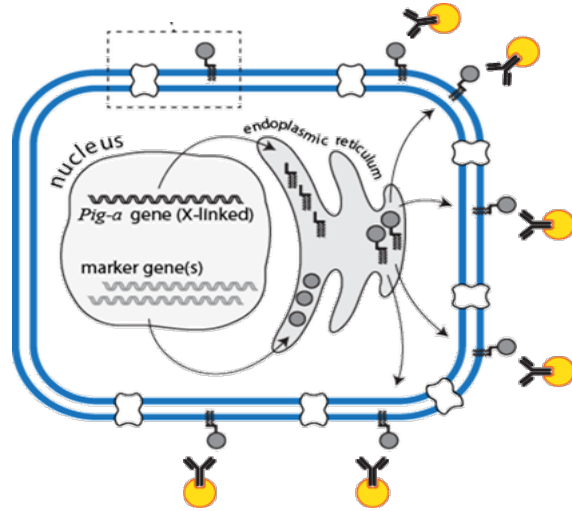
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Summarized from study reports

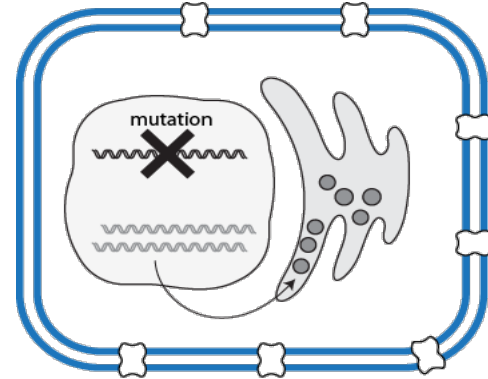
Pig-a Assay Basics: *Pig-a* gene function is necessary for Glycosylphosphatidylinositol (GPI) biosynthesis



Drawing courtesy of VN Dobrovolsky



Pig-a wild-type cell



Pig-a mutant cell

Mutations generated in nucleated erythroid precursor cells of bone marrow are measured in peripheral blood erythrocytes (reticulocytes and mature red blood cells)

Sprague-Dawley Rat *Pig-a* Assay Data for Molnupiravir



Treatment	Dose x days	No. rats	<i>Pig-a</i> mutants/10 ⁶ erythrocytes ± SD	
			Reticulocytes	Total RBCs
Vehicle control	x 28	6	4.97 ± 1.56	0.87 ± 0.26
MOV	50 mg/kg/day x 28	6	5.52 ± 1.83	1.57 ± 0.53*
	150 mg/kg/day x 28	5 ^b	7.80 ± 1.54	1.92 ± 0.53*
	^a 500 mg/kg/day x 28	5 ^c	10.98 ± 3.54*	2.63 ± 0.41*
Positive control	20 mg ENU/kg/day x 3	4	259.05 ± 56.41*	156.63 ± 26.04*

^aMTD determined from preliminary experiment.

^bOutlier RET value removed from 150 mg/kg/day group.

^cBlood from one rat had unacceptable coagulation and was not used.

*Statistically significant, p<0.05.

Summarized from study report

Analysis of *Pig-a* Assay Data for Molnupiravir

- Pairwise comparison of treated responses to control:
 - Significant increases in mutant RETs and RBCs for dosed groups
- Analysis for an increasing response trend:
 - Sponsor indicates no increasing trend with dose
- Comparison of responses to distribution of historical negative control:
 - All within negative control database distribution

Conclusion: MOV is equivocal (neither clearly positive nor clearly negative) under the conditions of the assay

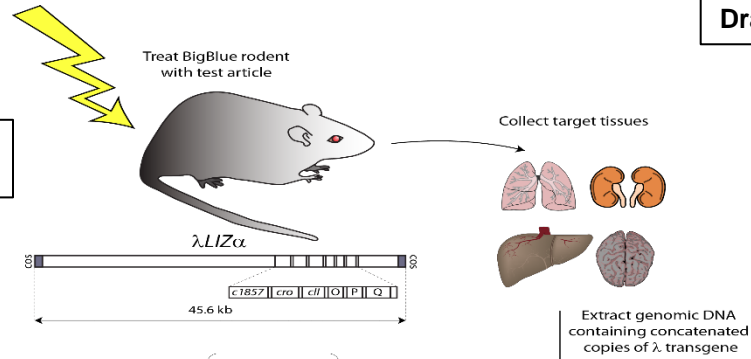
In order to resolve this equivocal call, a second in vivo assay for mutation was conducted, the Transgenic Rodent (TGR) assay

Transgenic Rodent (TGR) Assay: measures gene mutation in bacterial reporter transgenes integrated into every tissue of rats or mice

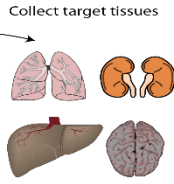


Drawing courtesy of MG Manjanatha

1. Treat TGR rodent

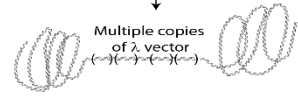


2. Recover tissues of interest

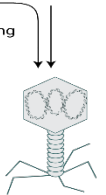


Extract genomic DNA containing concatenated copies of λ transgene

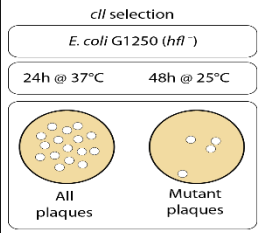
3. Extract DNA



In vitro λ packaging

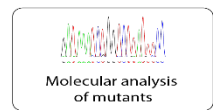


4. Package phage containing transgene



5. Infect bacteria and assay plaques under permissive (titer) and nonpermissive (mutants) conditions

Infection and positive selection of mutants



6. Sequence mutant phage (optional)

Rat TGR Assay Data for Molnupiravir

Treatment	Dose x days	No. rats	<i>cII</i> mutants/10 ⁶ phage ± SD	
			Liver	Bone marrow
Vehicle control	x 28	5	34.0 ± 1.9	33.0 ± 11.9
MOV	50 mg/kg/day x 28	5	40.8 ± 18.3	38.8 ± 16.3
	150 mg/kg/day x 28	5	35.7 ± 17.1	24.4 ± 6.0
	^a 500 mg/kg/day x 28	5	34.1 ± 9.3	39.1 ± 12.3
Positive control	20 mg ENU/kg/day x 6	5	221.7 ± 45.5*	434.2 ± 61.6*

^aMTD determined from preliminary experiment.

*Statistically significant (One-Way ANOVA) p<0.001.

Summarized from study report

Analysis of TGR Assay of Molnupiravir

- Pairwise comparison of treated responses to control:
 - None significant
- Trend:
 - No increasing trend
- Comparison of responses to distribution of historical negative control:
 - All within negative control database distribution
- Evidence for tissue exposure (from a separate experiment)

Conclusion: MOV clearly negative under conditions of the assay

Excerpt from CDER Genetic Toxicology Committee Consult on *in vivo* Mutagenic Potential of Molnupiravir (Conducted in March 2021)

After consulting with colleagues from the Pharmacology/Toxicology Genotoxicity Subcommittee (Drs. Robert Heflich and Mugimane Manjanatha at NCTR), Dr. Robison provided the following conclusions:

- (1) the *in vitro* bacterial reverse mutation assay would be considered positive based upon the response in the *E. coli* strain;
- (2) a Transgenic Rodent (TGR) study (not the *Pig-a* assay) is the primary assay for follow-up of an Ames-positive active pharmaceutical ingredient (API);
- (3) the results of the Big Blue rat study suggest that the compound is not an *in vivo* mutagen; and
- (4) given the negative response in the Big Blue rat assay, it would seem that neither parent pro-drug nor the initial metabolite NHC are *in vivo* mutagens, suggesting that the level of concern for mutagenicity in the clinical setting would be low.

Additional Study

- Zhou et al. have recently published a non-guideline study indicating that molnupiravir is mutagenic in CHO-K1 cells following 32 days of treatment + 13 days expression; 50K cells selected *Hprt* mutation (no unselected c.e. control, n = 3, 2 noncytotoxic doses (J Infect Dis 2021:224).
- Experimental protocol might be considered optimized for detecting the mutagenicity of a drug like molnupiravir (but two similar antivirals, ribavirin and favipiravir were negative—also Ames negative)

My analysis—these data don't affect the Committee conclusions:

- MOV was previously shown to be an *in vitro* mutagen in the Ames test—this reinforces that conclusion (with an assay performed in mammalian cells, albeit a cell line with known deficiencies in DNA damage response mechanisms)
- Doesn't alter the conclusion from the TGR assay that molnupiravir is not an *in vivo* mutagen in rodents



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FDA Clinical Virology Review of Molnupiravir

Assessment of MOV-associated SARS-CoV-2 Changes in Clinical Trials

Antimicrobial Drugs Advisory Committee Meeting
November 30, 2021

Patrick R. Harrington, Ph.D.
Senior Clinical Virology Reviewer

Eric F. Donaldson, Ph.D.
Senior Clinical Virology Reviewer

Jules O'Rear, Ph.D.
Clinical Virology Team Leader

Division of Antivirals
FDA/CDER/OND/OID

Background

- Molnupiravir (MOV) is a prodrug of N⁴-Hydroxycytidine (NHC), which is a nucleoside analogue that inhibits SARS-CoV-2 replication by causing the accumulation of nucleotide errors in the RNA genome.
- MOV-associated mutagenesis can occur anywhere in the SARS-CoV-2 genome, potentially resulting in amino acid changes in proteins targeted by therapeutics or the immune response.
- The SARS-CoV-2 spike protein is the major functional target for antibody responses to infection, and the target of vaccines and therapeutic anti-SARS-CoV-2 monoclonal antibodies.
- Analyses were conducted to explore whether MOV treatment is associated with amino acid changes in the viral spike protein.

Analysis Approach

- In MOV clinical trials, viral RNA samples from nasopharyngeal (NP) and oropharyngeal (OP) swabs, mostly collected between Baseline and Day 5/End-of-Treatment (EOT), were subjected to RT-PCR and full genome sequencing. Next generation sequencing (NGS) conducted in a central laboratory using the ION Torrent platform.
- Nucleotide and amino acid changes were reported relative to a prototypic reference isolate (Wuhan-Hu-1).
- Nucleotide mutation rates were calculated across the entire viral genome (~30,000 bases) to confirm MOV mutagenesis of SARS-CoV-2 in treated patients.
- Independent FDA analyses conducted to identify and confirm treatment-emergent amino acid changes ($\geq 5\%$ sensitivity cutoff) in SARS-CoV-2 spike protein and replicase proteins.
- Analyses of treatment-emergent AA changes conducted for **MK-4482-002 Part 1 (Outpatient/Phase 2)** and **MK-4482-001 (Hospitalized/Phase 2)**; limited available data from MK-4482-002 Part 2 (Outpatient/Phase 3).

SARS-CoV-2 Nucleotide Changes

MK-4482-002 Part 2 (Phase 3)						
Visit	Analysis Parameter	MOV 800 mg		Placebo		P Value MOV vs. PBO*
		N	Median (Range)	N	Median (Range)	
Day 5 (EOT)	Number of SARS-CoV-2 Mutations Relative to <u>Baseline</u> (NP Swab)	42	2.5 (0-46)	50	1.3 (0-30)	0.005

*Wilcoxon test. Source: FDA analysis of sponsor-reported mutations per 10,000 bases

Day 5 (EOT) Mean # Nucleotide Changes Relative to Baseline														
Treatment	N	Transition Mutations				Transversion Mutations								Other (In/Del)
		C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	
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: Sponsor report p002v02eff

- MOV treatment associated with increased rate of nucleotide changes, including mostly transition mutations, but also other types.
- Similar results in MK-4482-002, Part 1 (outpatient/Phase 2).
- Likely underestimates MOV viral mutagenic effects, e.g., replication defective genomes may not be detected.

MK-4482-002, Part 1 (Outpatient/Phase 2)

Imbalance of Tx-Emergent Changes in **Spike Protein**

- Greater proportion of participants in MOV Arms with tx-emergent amino acid changes.
- Emergence of multiple changes at positions under immune selective pressure, and where changes present in some key SARS-CoV-2 variants.
- Additional analyses conducted for 7 (6%) MOV-treated participants with tx-emergent changes of particular interest (in green):
 - Detected as minority variants (~5-20%).
 - Spike protein N-terminal domain (NTD) deletions/insertions confirmed in raw NGS data, not obviously attributed to artifacts.
- Several other emergent Spike protein amino acid changes detected in individual participants (MOV- or Placebo-treated), of unknown significance.

	# Participants in MOV Arms (pooled, n=113)	# Participants in Placebo Arm (n=39)
Any AA change	38 (34%)	9 (23%)
Total number of AA changes	72 (1-7 per participant)	9 (1 per participant)
AA Positions with ≥ 2 participants with change		
NTD aa 139-145	5	0
Δ P139-Y145	1	
P139S	1	
Δ L141-Y144	1	
Δ L141-Y144, Fins	1	
Δ Y145	1	
G261I/V	2	0
S297L	1	1
T385I	2	0
E484K	2	0
P681H	2	0
S884F	1	1
A1022T	2	0



MK-4482-001 (Hospitalized/Phase 2)

Imbalance of Tx-Emergent Changes in Spike Protein

- Greater proportion of participants in MOV Arms with tx-emergent amino acid changes.
- Emergence of multiple changes at positions under immune selective pressure, and where changes present in some key SARS-CoV-2 variants.

	# Participants in MOV Arms (pooled, n=89)	# Participants in Placebo Arm (n=27)
Any AA change	31 (35%)	5 (19%)
AA Positions <u>with ≥2 participants with change</u>		
del_L141-Y144	2	0
G142V	1	0
ΔY145	2	1
A262S	1	1
P681H	2	0

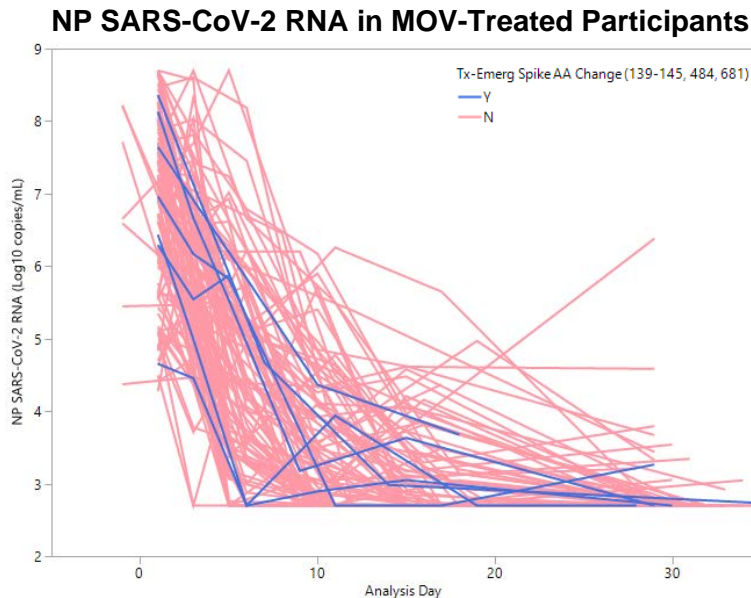
Source: FDA analysis

MK-4482-002, Part 1 (Outpatient/Phase 2)

Clinical/Virologic Outcomes for Participants with Spike Changes

No clear evidence that MOV tx-emergent spike protein changes affected virologic or clinical outcomes:

- For the 7 participants with key spike protein changes of interest (139-145, E484K, P681H), viral RNA shedding patterns comparable to those without these changes.
 - Note: Sequence data not available after Day 5.
- Few participants (and none of these 7) with cell culture infectious virus detected in a Post-Baseline sample.
- None of these 7 participants reached the clinical endpoint of hospitalization or death.
- Similar findings when considering participants with any spike amino acid change.



Source: FDA analysis

Conclusions

- Molnupiravir treatment may increase the rate of detection of SARS-CoV-2 populations with amino acid changes in the viral spike protein, consistent with its viral RNA mutagenic mechanism of action.
- No evidence that the emergence of spike protein amino acid changes affected virologic or clinical outcomes in outpatients with COVID-19 in MK-4482-002, Part 1.

MOV-Associated Spike Protein Changes

Questions and Uncertainties

Are all spike protein changes clearly attributed to MOV?

- MOV causes transition mutations (C↔U, G↔A), but many of the spike protein changes were not due to transition mutations.
- Other types of mutations (transversions, deletions, insertions) increased in MOV-treated participants, and could be enriched if they confer a selective advantage.

Are these changes substantially affecting SARS-CoV-2 evolution?

- SARS-CoV-2 spike protein is under evolutionary pressure, with or without MOV.
- Spike protein evolution could also be facilitated by natural immunity, vaccines and other treatments.

Are the MOV-associated SARS-CoV-2 spike protein variants transmissible?

- Most changes detected as minority variants and only in one postbaseline sample.
(note: 38% in P002, Part 1 had only one postbaseline sample analyzed; no data after Day 5/EOT)
- Emergence of spike changes occurred while viral RNA shedding declined.
- MOV antiviral activity linked directly to its mutagenicity; i.e., ↑mutations ↓fitness.
- Transmissibility could depend on other factors (e.g., immune deficiency, susceptibility of close contacts).



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Charge to the Committee:

Antimicrobial Drugs Advisory Committee Meeting
November 30, 2021

Debra Birnkrant, MD
Director, Division of Antivirals
OID, OND, CDER, FDA



Molnupiravir EUA

- Treatment of mild to moderate COVID-19 in patients at high risk for progression to severe disease
- Seeking advice on authorized use based on known and potential benefits and risks

- Consider the following:
 - Interim results from Part 2 of Trial MK-4482-002 where molnupiravir appeared safe and well-tolerated among high-risk outpatient adults and showed 48% relative risk reduction in all-cause hospitalization or death; recent final data with ~ 30% relative risk reduction in all cause hospitalization or death in approximately 700 + patients. Final data still under review.
 - In vitro mutagenicity with negative in vivo findings; 5-day treatment course
 - Nonclinical studies demonstrating bone and cartilage toxicity during embryo-fetal development and in chronic toxicity studies
 - Implications for pregnant women and individuals of childbearing potential
 - Increased rate of viral mutations involving the spike protein among participants receiving molnupiravir
 - Also, note that molnupiravir is an oral drug compared to other products that are authorized for the same indication



Molnupiravir EUA

Discussion point #1 - Please discuss the potential use of molnupiravir during pregnancy – both in terms of risk and benefit.

- Comment if you think molnupiravir should be accessible for use in pregnancy in certain scenarios, and if so, please describe what those scenarios might be.
- Do the concerns regarding the use of molnupiravir during pregnancy extend to the use of molnupiravir in individuals of childbearing potential? If so, are there mitigation strategies that should be considered?



Molnupiravir EUA

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



Molnupiravir EUA

Voting question #1 - Do the known and potential benefits of molnupiravir outweigh the known and potential risks of molnupiravir when used for the treatment of mild-moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death?

- a. If yes, please describe the appropriate authorized population such as risk factors for disease progression and pregnant individuals.

Please comment on the proposed risk mitigation strategies and if additional risk mitigation strategies are needed.

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

EUA Considerations

- FDA's authorization of a medical product under EUA is not the same as the Agency's approval or licensure of a product.
- For an EUA, the Agency authorizes a Health Care Provider Fact Sheet and a Patient Fact Sheet. These are similar to Prescribing Information and Patient Labeling or a Medication Guide for approved products.
- As part of its authorization, FDA will establish, to the extent practicable, conditions in the EUA that it finds necessary to protect the public health.
- FDA will periodically review the circumstances and appropriateness of the EUA .



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